frontiers | Research Topics

Efficacy and mechanism of herbal medicines and their functional compounds in preventing and treating cardiovascular diseases and cardiovascular disease risk factors, volume II

Edited by
Qing Yong He, Yu-Qing Zhang, Zhongfeng Li, Chen Huei Leo, Jie Wang, Kuo Gao and Jian Zhang

Coordinated by
Tiantian Menghang

Published in
Frontiers in Pharmacology

ISSN 1664-8714
ISBN 978-2-8325-7298-6
DOI 10.3389/978-2-8325-7298-6

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Efficacy and mechanism of herbal medicines and their functional compounds in preventing and treating cardiovascular diseases and cardiovascular disease risk factors, volume II

Topic editors

Qing Yong He — Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China

Yu-Qing Zhang — McMaster University, Canada

Zhongfeng Li — Capital Normal University, China

Chen Huei Leo — National University of Singapore, Singapore

Jie Wang — Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China

Kuo Gao — Beijing University of Chinese Medicine, China

Jian Zhang — Tianjin Medical University, China

Topic coordinator

Tiantian Meng — Guang'anmen Hospital, China Academy of Chinese Medical Sciences, China

Citation

He, Q. Y., Zhang, Y.-Q., Li, Z., Leo, C. H., Wang, J., Gao, K., Zhang, J., eds. (2026). *Efficacy and mechanism of herbal medicines and their functional compounds in preventing and treating cardiovascular diseases and cardiovascular disease risk factors, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-7298-6

Table of contents

frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 09 December 2025
DOI 10.3389/fphar.2025.1742260

OPEN ACCESS

EDITED BY
Javier Echeverria,
University of Santiago, Chile

REVIEWED BY
Luca Rastrelli,
University of Salerno, Italy

*CORRESPONDENCE
Qingyong He,
heqingyongg@163.com
Kuo Gao,
515123134@qq.com
Jian Zhang,
zhangjian_tina@163.com

RECEIVED 08 November 2025
ACCEPTED 20 November 2025
PUBLISHED 09 December 2025

CITATION
Meng T, Zhang Y, Wang J, Leo CH, Li Z, Zhang J, Gao K and He Q (2025) Editorial: Efficacy and mechanism of herbal medicines and their functional compounds in preventing and treating cardiovascular diseases and cardiovascular disease risk factors-Volume II. *Front. Pharmacol.* 16:1742260. doi: 10.3389/fphar.2025.1742260

Editorial: Efficacy and mechanism of herbal medicines and their functional compounds in preventing and treating cardiovascular diseases and cardiovascular disease risk factors-Volume II

Tiantian Meng[1,2], Yuqing Zhang[3,4], Jie Wang[2], Chen Huei Leo[5], Zhongfeng Li[6], Jian Zhang[7]*, Kuo Gao[8]* and Qingyong He[2]*

[1]Department of Rehabilitation, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China, [2]Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [3]Department of Oral and Maxillofacial Surgery/Pharmacology, School of Dental Medicine, University of Pennsylvania, Philadelphia, PA, United States, [4]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada, [5]Department of Science, Mathematics and Technology, Singapore University of Technology and Design, Singapore, Singapore, [6]Department of Chemistry, Capital Normal University, Beijing, China, [7]Shanghai Frontiers Science Center of Optogenetic Techniques for Cell Metabolism, Shanghai Key Laboratory of New Drug Design, School of Pharmacy, East China University of Science and Technology, Shanghai, China, [8]School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China

KEYWORDS

cardiovascular diseases, cardiovascular disease risk factors, herbal medicine, therapeutic mechanisms, clinical efficacy

Editorial on the Research Topic
Efficacy and mechanism of herbal medicines and their functional compounds in preventing and treating cardiovascular diseases and cardiovascular disease risk factors-Volume II

Introduction

According to the latest statistics, cardiovascular diseases (CVDs) continue to be the primary cause of morbidity and death globally (Li et al., 2025; Mensah et al., 2023). Despite significant advancements in conventional pharmacotherapy and interventional strategies, the global burden of CVDs and their associated risk factors—such as diabetes, hypertension, and dyslipidemia—continues to rise (Global Burden of Cardiovascular Diseases Collaborators, 2025). Between 2025 and 2050, projections suggest a 90.0% increase in CVD prevalence, a 73.4% rise in the crude mortality rate, with deaths expected to reach 35.6 million, highlighting the critical requirement for alternative or complementary therapeutic strategies (Chong et al., 2025). Herbal medicines, with a history of

thousands of years in traditional medical systems, have emerged as promising candidates for their multi-component, multi-target characteristics, and relatively favorable safety profiles compared to certain synthetic drugs (Yan et al., 2023).

In recent decades, increasing evidence from preclinical and clinical studies has illuminated the efficacy of herbal medicines and their bioactive compounds in modulating key pathological processes underlying CVDs, such as inflammation, oxidative stress, endothelial dysfunction, and myocardial remodeling (Cao et al., 2024; Huang et al., 2025; Yan et al., 2023; Zhang et al., 2025). Nonetheless, systematic integration of these fragmented findings and a thorough investigation of their molecular mechanisms are crucial for translating traditional knowledge into evidence-based clinical practice. To address this gap, we organized the Research Topic.

A total of 76 manuscripts were received, and after a rigorous peer-review process, this Research Topic successfully compiled 14 high-quality articles, encompassing original research studies and comprehensive reviews.

Dyslipidemia

Dyslipidemia, commonly referred to as hyperlipidemia, is primarily defined by elevated levels of total cholesterol (TC, ≥200 mg/dL), triglycerides (TG, ≥150 mg/dL), and low-density lipoprotein cholesterol (LDL-C, ≥160 mg/dL) in the bloodstream, or by reduced levels of high-density lipoprotein cholesterol (HDL-C, <40 mg/dL in male or <50 mg/dL in female). This condition is recognized as a significant risk factor for CVDs (Zeljkovic et al., 2024).

Shi et al. performed a meta-analysis of 33 randomized controlled trials (RCTs) to evaluate the clinical efficacy of red yeast rice-containing Chinese polyherbal preparations in the treatment of dyslipidemia. The pooled results indicated that the combined preparations significantly reduced TC, TG, and LDL-C, while increasing HDL-C compared to statin therapy alone. Tian et al. reviewed the clinical efficacy and mechanisms of action of the classic traditional Chinese medicine (TCM) prescription Erchen decoction in treating hyperlipidemia. Previous clinical studies have shown that Erchen decoction and its modified formulations can reduce the levels of TG, TC, and LDL-C. Mechanistically, Erchen decoction primarily enhances lipid metabolism, regulates oxidative stress, and suppresses inflammation. Its active components mainly include β-sitosterol, *Poria cocos* polysaccharides, glycyrrhetinic acid, gingerol, oleanolic acid, and ursolic acid. Tang et al. systematically investigated the active ingredients and mechanisms of the BuShao Tiaozhi capsule for hyperlipidemia treatment. The findings indicated that BuShao Tiaozhi capsule effectively alleviates lipid metabolism disorders by blocking the Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/Akt) pathway.

Hypertensive heart disease

Hypertensive heart disease (HHD) is a secondary cardiac condition characterized by pathological alterations in cardiac structure and function, resulting from prolonged exposure to hypertension. It represents one of the most prevalent forms of target organ damage of hypertension and may eventually progress to heart failure (Díez and Butler, 2023).

An SR conducted by Hui et al. encompassed 21 RCTs, aiming to evaluate the clinical efficacy of specific TCM interventions designed to replenish qi and activate blood circulation as adjunctive treatments for hypertensive heart disease. The findings revealed that the combination of TCM and western medicine outperforms western medicine alone in enhancing cardiac function and alleviating adverse left ventricular remodeling. Notably, Danshen, Chuanxiong, Gegen, Huangqi, and Puhuang are the five most frequently utilized Chinese herbal medicines.

Coronary heart disease

Coronary heart disease (CHD), commonly referred to as ischemic heart disease, includes acute coronary syndrome (such as unstable angina pectoris and myocardial infarction) and chronic coronary syndrome. It represents the leading cause of age-standardized mortality globally (Virani et al., 2023; Rao et al., 2025).

Six systematic reviews (SRs) have examined the effectiveness of herbal medicines in treating CHD. Wang et al.'s SR found that the modified Danggui Sini decoction, as an adjunct treatment, can shorten the duration of angina pectoris attacks, lower N-terminal pro-B-type natriuretic peptide levels, and improve the Seattle Angina Questionnaire scores in patients with CHD. Dai et al. performed a network meta-analysis comparing the clinical efficacy of ten different Danshen class injections for treating CHD. Their findings revealed that the combination of Danshen class injections with western medicine outperformed the use of western medicine alone. Specifically, Danshenduofensuanyan injection and Danshenchuanxiongqin injection demonstrated superior anti-inflammatory effects, while Danhong injection exhibited greater antioxidative properties. An SR by Chen et al. reported the efficacy of Salvianolate for injection, a Danshen-derived metabolite, as an adjunctive therapy for acute myocardial infarction. The pooled results from 30 RCTs involving 3,931 cases indicated that the combined use of Salvianolate for injection alongside western medicine could significantly decrease major adverse cardiac events incidence. An SR by Zhou et al., including 113 RCTs and 10,779 cases, aimed to evaluate the clinical efficacy of four TCM injections for tonifying qi in treating acute myocardial infarction. Findings indicated that combining these injections with conventional treatment decreased mortality and malignant arrhythmia risk in such patients, while also demonstrating enhanced safety. In a separate SR, Yu et al. compared the efficacy of the Guanxinshutong capsule alongside western medicine against western medicine alone for the treatment of stable angina pectoris. The results indicated that combining the Guanxinshutong capsule with western medicine can enhance electrocardiogram readings, left ventricular ejection fraction, and TC levels in individuals suffering from stable angina pectoris. Additionally, Mao et al. conducted a SR that included 28 preclinical studies to evaluate the efficacy and mechanism of Hydroxysafflor yellow A for ischemic heart disease.

The results showed that Hydroxysafflor yellow A can reduce the area of myocardial infarction, lower the level of myocardial enzymes, and improve cardiac function. Its mechanisms may involve anti-inflammatory effects, anti-apoptosis, autophagy regulation, antioxidation, promotion of angiogenesis, and improvement of microcirculation.

Myocardial ischemia-reperfusion injury

Myocardial ischemia-reperfusion injury (MIRI) is defined as the cellular damage that occurs when blood flow is restored to the ischemic heart, rather than facilitating functional recovery (Heusch, 2024).

Yang et al. conducted a meta-analysis of 32 animal experiments, demonstrating that salvianolic acid B can improve MIRI through mechanisms such as anti-inflammatory effects, antioxidation, reduction of apoptosis, regulation of vascular function, and promotion of angiogenesis. However, the efficacy of traditional therapies is often limited by suboptimal drug bioavailability, primarily attributable to poor target specificity. The review by Shi et al. summarized the integration of plant-derived secondary metabolites with nanotechnology as an innovative therapeutic strategy for MIRI. It highlights that nanocarriers, including liposomes, polylactic acid/glycolic acid nanoparticles, and mesoporous silica nanoparticles, enhance the stability, targeting precision, and bioavailability of plant-derived secondary metabolites, such as notoginsenosides, curcumin, and puerarin. This enhancement amplifies their antioxidant, anti-inflammatory, and anti-apoptotic effects, thereby mitigating myocardial damage associated with MIRI.

Heart failure

Heart failure is characterized by impaired cardiac pumping function and represents the terminal stage of CVDs, serving as one of the leading causes of death (Bozkurt et al., 2025; Heidenreich et al., 2022).

In both cellular models, specifically angiotensin II-induced hypertrophic H9c2 cells, and animal models, such as a rat model of transverse aortic constriction-induced heart failure, Xu et al. demonstrated that the combined administration of Astragalus mongholicus and Salvia miltiorrhiza can enhance the prognosis of heart failure by inhibiting ferroptosis. The mechanisms underlying this effect may be linked to elevated levels of dihydroorotate dehydrogenase, ferroptosis suppressor protein 1, and glutathione peroxidase 4.

Oxylipins

Oxylipins, which are bioactive lipid mediators oxidized from polyunsaturated fatty acids, are key regulators of inflammation, platelet aggregation, and vascular endothelial dysfunction—core processes driving cardiovascular pathologies such as atherosclerosis and hypertension (Ağagündüz et al., 2024).

A review by Li et al. systematically investigated oxylipins as critical biomarkers and mediators in CVDs, detailing their dysregulation in conditions such as hypertension, myocardial infarction, and heart failure. It further elucidated how TCMs modulate these oxylipin profiles; for example, they upregulate cardioprotective epoxyeicosatrienoic acids while downregulating pro-inflammatory hydroxyeicosatetraenoic acids, thus providing cardioprotection.

Conclusion

This Research Topic successfully compiles 14 high-quality studies that advance our understanding of herbal medicines in addressing CVDs and their risk factors. Covering key conditions—from dyslipidemia and hypertensive heart disease to heart failure and MIRI—this Research Topic integrates SRs, meta-analyses, and mechanistic investigations to validate efficacy (e.g., improved lipid profiles, enhanced cardiac function) and unravel critical mechanisms, such as PI3K/Akt pathway modulation, ferroptosis suppression, and the use of nanotechnology to enhance bioavailability. Notably, the exploration of oxylipins as therapeutic indicators offers a novel perspective on the molecular mechanisms of TCMs' cardioprotection. These findings lay a solid foundation for translating traditional herbal wisdom into evidence-based practice, while highlighting the need for future large-scale clinical trials and mechanistic studies. We extend our gratitude to all authors, reviewers, and the editorial team of *Frontiers in Pharmacology* for their invaluable contributions to this Research Topic.

Author contributions

TM: Writing – review and editing, Writing – original draft, Conceptualization, Visualization, Validation. YZ: Writing – review and editing. JW: Writing – original draft. CL: Writing – original draft. ZL: Writing – original draft. JZ: Supervision, Writing – review and editing, Validation. KG: Validation, Writing – review and editing, Supervision. QH: Supervision, Writing – review and editing, Validation.

Funding

The authors declare that financial support was received for the research and/or publication of this article. This work is supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (No. 2024ZD0528200), the Scientific and technological innovation project of China Academy of Chinese Medical Sciences (No. C12023D004), the National Natural Science Foundation of China (No. 81903950, No. 82370068), the Fundamental Research Funds for the Central Universities (No. 2024-BUCMXJKY-051, No. 2025-JYB-XJSJJ-038), and the National High Level Chinese Medicine Hospital Clinical Research Funding (No. DFGZRA-2024GJRC005).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Ağagündüz, D., Yeşildemir, Ö., Koçyiğit, E., Koçak, T., Özen Ünaldı, B., Ayakdaş, G., et al. (2024). Oxylipins derived from PUFAs in cardiometabolic diseases: mechanism of actions and possible nutritional interactions. *Nutrients* 16, 3812. doi:10.3390/nu16223812

Bozkurt, B., Ahmad, T., Alexander, K., Baker, W. L., Bosak, K., Breathett, K., et al. (2025). HF STATS 2024: heart failure epidemiology and outcomes statistics an updated 2024 report from the heart failure society of America. *J. Card. Fail.* 31, 66–116. doi:10.1016/j.cardfail.2024.07.001

Cao, L., Ni, H., Gong, X., Zang, Z., and Chang, H. (2024). Chinese herbal medicines for coronary heart disease: clinical evidence, pharmacological mechanisms, and the interaction with gut microbiota. *Drugs* 84, 179–202. doi:10.1007/s40265-024-01994-w

Chong, B., Jayabaskaran, J., Jauhari, S. M., Chan, S. P., Goh, R., Kueh, M. T. W., et al. (2025). Global burden of cardiovascular diseases: projections from 2025 to 2050. *Eur. J. Prev. Cardiol.* 32, 1001–1015. doi:10.1093/eurjpc/zwae281

Díez, J., and Butler, J. (2023). Growing heart failure burden of hypertensive heart disease: a call to action. *Hypertension* 80, 13–21. doi:10.1161/hypertensionaha.122.19373

Global Burden of Cardiovascular Diseases Collaborators (2025). Global, regional, and national burden of cardiovascular diseases and risk factors in 204 countries and territories, 1990-2023. *J. Am. Coll. Cardiol.* doi:10.1016/j.jacc.2025.08.015

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., et al. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation* 145, e895–e1032. doi:10.1161/cir.0000000000001063

Heusch, G. (2024). Myocardial ischemia/reperfusion: translational pathophysiology of ischemic heart disease. *Med* 5, 10–31. doi:10.1016/j.medj.2023.12.007

Huang, M., Xie, X., Yuan, R., Xin, Q., Ma, S., Guo, H., et al. (2025). The multifaceted anti-atherosclerotic properties of herbal flavonoids: a comprehensive review. *Pharmacol. Res.* 211, 107551. doi:10.1016/j.phrs.2024.107551

Li, J., Pandian, V., Davidson, P. M., Song, Y., Chen, N., and Fong, D. Y. T. (2025). Burden and attributable risk factors of non-communicable diseases and subtypes in 204 countries and territories, 1990-2021: a systematic analysis for the global burden of disease study 2021. *Int. J. Surg.* 111, 2385–2397. doi:10.1097/js9.0000000000002260

Mensah, G. A., Fuster, V., Murray, C. J. L., Roth, G. A.Global Burden of Cardiovascular Diseases and Risks Collaborators (2023). Global burden of cardiovascular diseases and risks, 1990-2022. *J. Am. Coll. Cardiol.* 82, 2350–2473. doi:10.1016/j.jacc.2023.11.007

Rao, S. V., O'Donoghue, M. L., Ruel, M., Rab, T., Tamis-Holland, J. E., Alexander, J. H., et al. (2025). 2025 ACC/AHA/ACEP/NAEMSP/SCAI guideline for the management of patients with acute coronary syndromes: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. *Circulation* 151, e771–e862. doi:10.1161/cir.0000000000001309

Virani, S. S., Newby, L. K., Arnold, S. V., Bittner, V., Brewer, L. C., Demeter, S. H., et al. (2023). 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American heart association/American college of cardiology joint committee on clinical practice guidelines. *Circulation* 148, e9–e119. doi:10.1161/cir.0000000000001168

Yan, Z., Zhong, L., Zhu, W., Chung, S. K., and Hou, P. (2023). Chinese herbal medicine for the treatment of cardiovascular diseases-targeting cardiac ion channels. *Pharmacol. Res.* 192, 106765. doi:10.1016/j.phrs.2023.106765

Zeljkovic, A., Vekic, J., and Stefanovic, A. (2024). Obesity and dyslipidemia in early life: impact on cardiometabolic risk. *Metabolism* 156, 155919. doi:10.1016/j.metabol.2024.155919

Zhang, L. Y., Yin, H. Y., Song, X. Z., Du, R., He, Z. M., and Pei, H. Y. (2025). Mechanisms of action of traditional Chinese medicine in the treatment of myocardial injury: a comprehensive review. *Phytomedicine* 147, 157195. doi:10.1016/j.phymed.2025.157195

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 04 June 2024
DOI 10.3389/fphar.2024.1375795

OPEN ACCESS

EDITED BY
Michael Heinrich,
University College London, United Kingdom

REVIEWED BY
Lin Zhu,
The Chinese University of Hong Kong, China
Tao Yi,
Hong Kong Baptist University, Hong Kong SAR, China
Chunxiang Liu,
Tianjin University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Yabin Zhou,
yabzhou@163.com
Jianfei Yang,
yangjianfei119@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 24 January 2024
ACCEPTED 09 May 2024
PUBLISHED 04 June 2024

CITATION
Wang H, Liu C, Guo X, Yang J and Zhou Y (2024), Effects of modified Danggui Sini Decoction as adjuvant therapy for angina pectoris in coronary heart disease: a systematic review and meta-analysis based on randomised controlled trials. *Front. Pharmacol.* 15:1375795.
doi: 10.3389/fphar.2024.1375795

Effects of modified Danggui Sini Decoction as adjuvant therapy for angina pectoris in coronary heart disease: a systematic review and meta-analysis based on randomised controlled trials

He Wang[1†], Changxing Liu[2†], Xinyi Guo[3†], Jianfei Yang[1*] and Yabin Zhou[1*]

[1]The First Hospital of Heilongjiang University of Chinese Medicine, Harbin, China, [2]First Clinical College of Medicine, Heilongjiang University of Chinese Medicine, Harbin, China, [3]Clinical College of Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu, China

Introduction: This systematic review evaluates the efficacy of the Chinese herbal formula modified Danggui Sini Decoction as an adjunctive treatment for angina pectoris in patients with coronary heart disease.

Methods: We conducted a comprehensive search for randomized controlled trials that investigated the effects of modified Danggui Sini Decoction in combination with conventional Western medication on angina pectoris in coronary artery disease, published up to July 2023 across eight databases, including China Knowledge International Literature screening and data extraction were performed by two researchers following predefined inclusion and exclusion criteria. The quality of included studies was assessed using the Cochrane Handbook version 5.1, and meta-analysis was executed via RevMan 5.4 software.

Results: Thirteen studies encompassing 1,232 participants were incorporated. The meta-analysis revealed that combining modified Danggui Sini Decoction with conventional Western medication significantly enhanced overall clinical efficacy, reduced the duration of angina attacks, decreased the Chinese medicine syndrome score, improved inflammatory markers and cardiac function, lowered serum NT-proBNP levels, and elevated the Seattle Angina Questionnaire scores compared to the control group.

Conclusion: Modified Danggui Sini Decoction, when used alongside conventional Western medications, shows promise in treating coronary artery disease patients with angina pectoris and may serve as a beneficial adjunctive therapy in clinical settings. Nonetheless, due to the limited quantity and quality of the included studies, further high-caliber research is essential to substantiate these findings.

Systematic Review Registration: https://inplasy.com/? s=202390078, identifier INPLASY 202390078.

KEYWORDS

modify Danggui Sini Decoction, conventional western medicine, angina pectoris, meta-analysis, systematic review

1 Introduction

Coronary arteriosclerotic heart disease, also known as coronary heart disease (CHD), is a cardiac condition caused by atherosclerotic lesions in the coronary arteries. This leads to narrowing and blockage of the vessel lumen, resulting in myocardial ischemia or necrosis (Guo Z. et al., 2023). Angina pectoris, characterized by transient myocardial ischemia and chest pain, is the most common clinical manifestation of CHD and can progress to acute myocardial infarction with a high mortality rate (Wang and Chen, 2018). A global burden of disease study in 2017 reported 126.45 million cases of ischemic heart disease worldwide, including 10.6365 million new cases, leading to 8.9304 million deaths and making it the leading cause of mortality globally (Dalys and Collaborators, 2018; GBD Causes of Death Collaborators, 2018). Further research has indicated that the ratio of years lived with disability (YLD) to years of life lost (YLL) due to CHD in China is 14.2:1, with the burden of CHD ranking second and an absolute value increase of 122.0% (China Cardiovascular Health and Disease Report, 2021 Coronary Heart Disease Section, 2022; Buyiman et al., 2023). Consequently, there is a pressing need to develop early, safe, and cost-efficient interventions to improve patient daily functioning, enhance their quality of life, and alleviate the economic burden on individuals and society.

Currently, the treatment goals for CHD aim to reduce the frequency and severity of angina attacks, and prevent cardiovascular events such as acute myocardial infarction (AMI), sudden cardiac death, and heart failure (Xiaoping and Zhao, 2023). Antiplatelet aggregating drugs are commonly used in Western medicine, with severe cases possibly requiring percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (Yassen et al., 2023). However, despite significant improvements from interventional therapies and conventional Western medicine, the long-term efficacy in improving survival rates and decreasing recurrence rates of CHD remains unclear, with considerable side effects (Guo J. et al., 2023). CHD not only threatens the health and life of patients but also imposes a significant economic burden on society and families. Among cardiovascular diseases, the recurrence rate of coronary angina is notably high, severely affecting patients' normal life and work (Jia-Yi and Xi-Ping, 2023). Therefore, an increasing number of researchers are turning their focus to complementary and alternative medicine.

In traditional Chinese medicine (TCM), CHD and angina pectoris are categorized under "chest impediment" and "heartache." The etiology of these conditions is attributed to deficiencies in Qi, blood, Yin, and Yang as underlying factors, complemented by Qi and blood stasis, cold coagulation in the blood vessels, and phlegm obstruction as primary manifestations (Liu et al., 2023). The modified Danggui Sini Decoction, derived from the "Shang Han Lun," is reputed to nourish and activate blood, warm meridians, and disperse cold. Recently, this decoction has demonstrated promising clinical outcomes in treating CHD (Zhang and Wang, 2017; Lu et al., 2019; Zifeng, 2019; Chen et al., 2020; Jia, 2020; Qi-Min, 2020; Zhang, 2020; Cui et al., 2021; Wang, 2021; Wang et al., 2021; Du et al., 2022; Li, 2022; Hui and Qian, 2023). However, the research conducted to date predominantly features small sample sizes and single-center clinical trials, highlighting a lack of comprehensive, high-quality systematic reviews. Consequently, this study utilizes an evidence-based medicine approach to systematically assess the efficacy of the modified Danggui Sini Decoction alongside conventional Western medicine in treating CHD and angina pectoris, aiming to provide objective, evidence-based recommendations for clinical treatment and drug guidance.

2 Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (as detailed in Supplementary Material S1). Additionally, this review was registered with PROSPERO (registration number INPLASY202390078).

2.1 Literature search

Search terms in Chinese for the modified Danggui Sini Decoction included "Danggui Sini Tang," "Coronary atherosclerosis," "Coronary heart disease," "Coronary atherosclerotic heart disease," "Angina pectoris," and "Myocardial ischaemia." English search terms comprised "modified Danggui Sini Decoction," "Coronary atherosclerosis," "Coronary heart disease," "Myocardial ischemia," and "Angina pectoris." These terms were utilized in databases such as the China Knowledge Information Network (CNKI), WanFang Database, VIP Database, Chinese Biomedical Literature Database (CBM), PubMed, Embase, Web of Science. Searches were conducted by title, keywords, subject terms, and free word combinations. The search period extended from the inception of each database up to July 2023. Refer to the supplementary document for a detailed search strategy (Supplementary Table S1).

2.2 Inclusion criteria

2.2.1 Literature type

Included were publicly published RCTs both within China and internationally, in both Chinese and English, with no requirement for blinding.

2.2.2 Study subjects

The diagnostic criteria for UA were based on the Guidelines for the Diagnosis and Treatment of Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction, and the Guidelines for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes (2016 Edition) (Lei, 2012; Chinese Medical Association and Division of Cardiovascular Diseases, 2017). Similarly, the diagnosis of Stable Angina (SA) adhered to criteria set forth in the Guidelines for the Diagnosis and Treatment of Chronic Stable Angina (Chinese Medical Association Cardiovascular Disease Branch and Chinese Journal of Cardiovascular Disease Editorial Committee, 2007).

2.2.3 Intervention measures

The control group received conventional Western medicines, while the experimental group was treated with modified Danggui Sini Decoction in addition to the standard treatment.

2.2.4 Outcome measures

The primary efficacy outcomes encompassed the clinical effective rate (including angina pectoris effective rate, electrocardiogram effective rate, nitroglycerin dosage reduction rate, and traditional Chinese medicine syndrome effective rate). Secondary outcomes entailed the traditional Chinese medicine syndrome score [as specified in the "Guidelines for Clinical Research of New Chinese Medicines" (Zheng, 2002)], cardiac function indicators [cardiac output (CO), left ventricular ejection fraction (LVEF), and left ventricular end-diastolic diameter (LVEDD)], angina pectoris episodes (frequency and duration of angina attacks), Seattle Angina Questionnaire (SAQ) score, and inflammatory factors [interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and high-sensitivity C-reactive protein (hs-CRP)].

2.3 Exclusion criteria

Exclusions included duplicate publications, reviews, conference papers, animal studies, case reports, studies with incomplete data or lacking outcome indicators, and studies whose interventions did not align with the inclusion criteria.

2.4 Literature screening and data extraction

Two researchers independently conducted literature screening and data extraction based on the inclusion and exclusion criteria. Discrepancies were resolved through discussion or consultation with a third researcher. Extracted data covered authors, publication year, title, sample sizes of test and control groups, demographics (sex, age, disease duration), interventions, treatment duration, and outcome measures.

2.5 Quality assessment of included literature

Quality was assessed using the Cochrane Handbook 5.1 "Risk of Bias Assessment" tool, examining six dimensions: random sequence generation, allocation concealment, blinding implementation, data completeness, selective reporting, and other sources of bias. Outcomes were categorized as "low risk," "high risk," or "unclear risk" of bias.

2.6 Evidence quality evaluation

Use GRADEprofiler 3.6 for evidence quality evaluation, divided into four levels: high (A), medium (B), low (C), and extremely low (D). Whether to downgrade during the evaluation process mainly considers five aspects: research limitations, inconsistency, indirectness, imprecision, and publication bias.

2.7 Statistical methods

Meta-analysis was conducted using RevMan 5.4 software. For count data, odds ratios (OR) or risk ratios (RR) were used, while mean difference (MD) or standardized mean difference (SMD) were employed for continuous data, with 95% confidence intervals (CI) calculated. Heterogeneity was assessed by the I^2 statistic; a fixed-effects model was applied if $p > 0.10$ and $I^2 \leq 50\%$, and a random-effects model for $p \leq 0.10$ and $I^2 > 50\%$, with subgroup or sensitivity analysis as appropriate. Publication bias was evaluated with a funnel plot for studies including more than 10 outcome measures.

3 Results

3.1 Results of literature screening

A total of 432 pieces of literature were retrieved. After removing duplicates using Endnote software, 219 remained and were assessed according to the inclusion and exclusion criteria, ultimately including 13 studies (Zhang and Wang, 2017; Lu et al., 2019; Zifeng, 2019; Chen et al., 2020; Jia, 2020; Qi-Min, 2020; Zhang, 2020; Cui et al., 2021; Wang, 2021; Wang et al., 2021; Du et al., 2022; Li, 2022; Hui and Qian, 2023). The literature screening process is depicted in Figure 1. In accordance with the "Type A extract" definition from the ConPhyMP consensus statement (Peng et al., 2023), a summary table was compiled to describe the botanical drug components reported in the original studies. As a Type A extract, modified Danggui Sini Decoction comprises six botanical drugs, aimed at warming meridians, dispelling cold, nourishing blood, and unblocking meridians. The core prescription in all studies was modified Danggui Sini Decoction, with additional botanical drugs like Angelica sinensis (Oliv.) Diels (Umbelliferae; *Angelicae sinensis* Radix) (Danggui), *Asarum heterotropoides* F. Schmidt (Aristolochiaceae Juss.) (Xixin), *Cynanchum otophyllum* Schneid. (Contortae.) (Baishao), *Glycyrrhiza uralensis* Fisch. (Fabaceae Lindl.) (Gancao), *Cinnamomum cassia* (L.) D. (DonRamulus Cinnamomi) (Guizhi), *Tetrapanax papyrifer* (Hook.) K. Koch (*Tetrapanax papyriferus*) (Tongcao), adjusted according to syndrome differentiation. The composition of these prescriptions is detailed in Supplementary Table S2.

3.2 Basic information of included studies

The review included 13 RCTs, encompassing 1,232 patients—616 in the treatment group and 616 in the control group. Baseline characteristics across studies were comparable, with detailed features presented in Table 1.

3.3 Quality assessment of included studies

The quality of the studies was assessed using the Cochrane Handbook 5.1 "Risk of Bias Assessment" tool. Ten studies (Lu et al., 2019; Chen et al., 2020; Jia, 2020; Qi-Min, 2020; Cui et al., 2021; Wang, 2021; Wang et al., 2021; Du et al., 2022; Li, 2022; Hui and Qian, 2023) utilized the randomized numeric table method for randomization. Three studies (Zhang and Wang, 2017; Zifeng, 2019; Zhang, 2020) did not clearly specify their randomization techniques; none disclosed details on allocation concealment or blinding, hence were considered at unknown risk. All studies

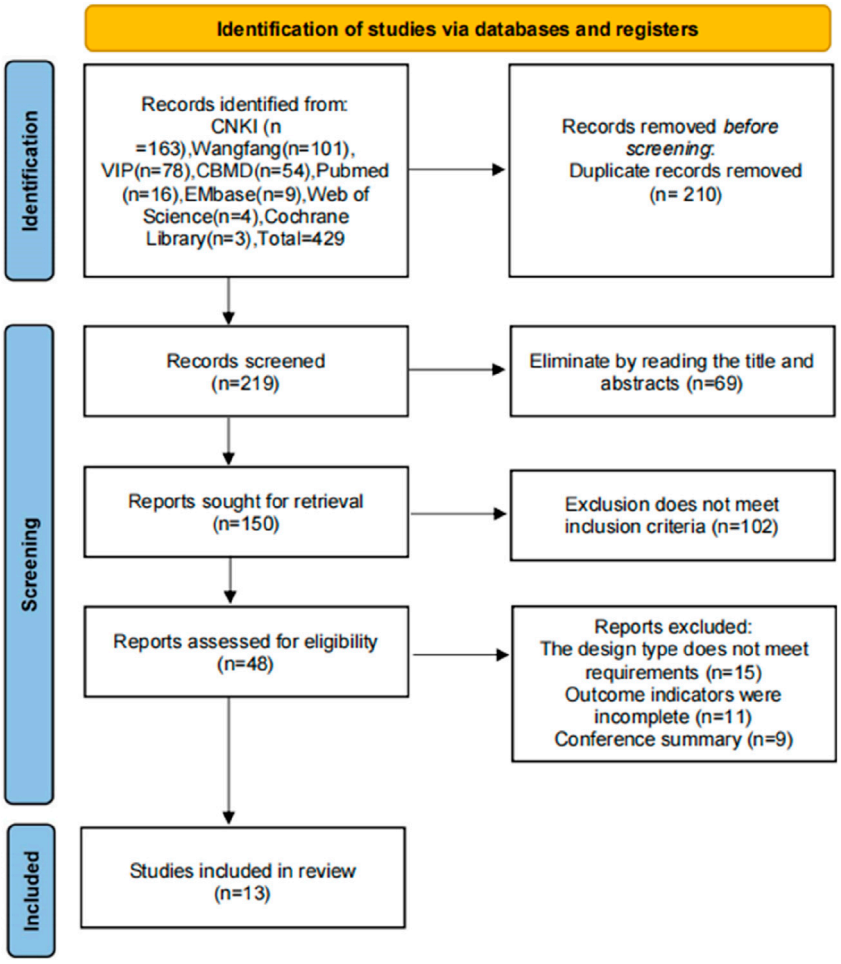


FIGURE 1
Literature screening process.

reported complete outcomes, with no evidence of selective outcome reporting or other biases, classifying them at low risk (Figures 2, 3).

3.4 Meta-analysis results

3.4.1 Efficacy in angina pectoris

Eight studies (Chen et al., 2020; Jia, 2020; Qi-Min, 2020; Zhang, 2020; Cui et al., 2021; Wang, 2021; Li, 2022; Hui and Qian, 2023) involving 636 patients assessed the efficacy of treatment for angina pectoris. These studies demonstrated homogeneity ($p = 0.99$, $I^2 = 0$), and a fixed-effects model was applied for the meta-analysis. The results indicated that the experimental group experienced a significant improvement in the treatment efficacy of angina pectoris compared to the control group, with a statistically significant difference [RR = 1.23, 95% CI (1.14, 1.33), $p < 0.00001$] (Figure 4).

3.4.2 Effective rate of TCM symptoms

Seven studies (Zhang and Wang, 2017; Lu et al., 2019; Zifeng, 2019; Jia, 2020; Qi-Min, 2020; Wang et al., 2021; Du et al., 2022), totaling 728 patients, reported on the effective rate of TCM symptoms. The analysis found homogeneity among the studies ($p = 0.55$, $I^2 = 0$), and a fixed-effects model was employed. The findings revealed that, compared to the control group, the experimental group significantly improved the TCM symptomatic effective rate, with a statistically significant difference [RR = 1.19, 95% CI (1.12, 1.28), $p < 0.000\ 01$].(Figure 5).

3.4.3 Nitroglycerin usage reduction

Four studies (Lu et al., 2019; Zifeng, 2019; Qi-Min, 2020; Du et al., 2022), comprising 270 patients, examined the reduction in nitroglycerin usage. These studies showed homogeneity ($p = 0.71$, $I^2 = 0$), allowing for a fixed-effects model in the meta-analysis. The outcomes demonstrated that the experimental group significantly reduced nitroglycerin usage compared to the control group, with a statistically significant difference [RR = 1.28, 95% CI (1.11, 1.47), $p = 0.0005$]. Refer to Figure 6.

3.4.4 ECG effectiveness rate

The effectiveness of ECG improvements was reported in four studies (Lu et al., 2019; Zifeng, 2019; Qi-Min, 2020; Du et al., 2022) with a total of 270 patients. The analysis showed homogeneity ($p = 0.80$, $I^2 = 0$), and a fixed-effects model was utilized. Results indicated

TABLE 1 Basic characteristics of the included studies.

Subjects	Disease type	Sample size (m/f)		Average age/ years		Interventions		Average duration of illness/year		Treatment/ week	Outcomes
		T	C	T	C	T	C	T	C		
Hui and Qian (2023)	UA	40(23/17)	40(21/19)	62.17 ± 3.24	61.33 ± 2.97	modified Danggui Sini Decoction+C	CWM	-	-	4	①⑤⑥
Li (2022)	SA	55(30/25)	55(32/23)	67.30 ± 5.71	68.37 ± 7.20	modified Danggui Sini Decoction+C	CWM	2.56 ± 0.58	2.67 ± 0.63	12	①⑤⑦
Du et al., 2022	SA/UA	39(24/15)	39(27/12)	64.87 ± 6.51	65.81 ± 6.24	modified Danggui Sini Decoction+C	CWM	6.14 ± 2.03	6.38 ± 1.53	4	②③④⑤⑧
Cui et al. (2021)	UA	34(13/21)	34(11/24)	55.24 ± 2.21	53.03 ± 1.41	modified Danggui Sini Decoction+C	CWM	4.97 ± 0.21	4.93 ± 0.26	3	①⑤⑦
Wang (2021)	SA	45(26/19)	45(24/21)	70.16 ± 2.32	70.23 ± 2.83	modified Danggui Sini Decoction+C	CWM	5.47 ± 1.31	5.52 ± 1.28	4	①⑤⑥⑦
Wang et al. (2021)	SA/UA	132 (64/68)	132(66/66)	67.61 ± 7.81	66.13 ± 6.92	modified Danggui Sini Decoction+C	CWM	8.15 ± 0.94	8.94 ± 1.12	4	④⑤⑥
Jia (2020)	UA	30(17/13)	30(15/15)	60.23 ± 15.32	61.07 ± 14.8	modified Danggui Sini Decoction+C	CWM	3.01 ± 3.71	3.25 ± 4.2	4	①②③④
Qi-Min (2020)	SA	36(20/16)	36(19/17)	56.23 ± 15.32	58.07 ± 14.8	modified Danggui Sini Decoction+C	CWM	-	-	8	①②③④⑤⑦
Zhang (2020)	SA/UA	48(22/26)	48(25/23)	79.68 ± 9.32	78.07 ± 9.8	modified Danggui Sini Decoction+C	CWM	6.29 ± 2.71	6.04 ± 2.42	4	①⑨⑩
Chen et al. (2020)	UA	30(15/15)	30(18/12)	56.2 ± 3.6	57.4 ± 4.8	modified Danggui Sini Decoction+C	CWM	-	-	4	①⑤⑥⑨
Zifeng (2019)	SA	30(12/18)	30(16/14)	63.23 ± 5.32	64.07 ± 4.8	modified Danggui Sini Decoction+C	CWM	5.3 ± .8	5.1 ± 2.7	6	②③④⑦⑩
Lu et al. (2019)	SA	57(31/26)	57(29/28)	72.16 ± 7.21	73.07 ± 8.02	modified Danggui Sini Decoction+C	CWM	10.11 ± 2.71	9.89 ± 1.94	4	②③④⑤⑥⑧
Zhang and Wang (2017)	SA/UA	40(27/13)	40(15/25)	65.23 ± 7.76	65.15 ± 7.95	modified Danggui Sini Decoction+C	CWM	2.79 ± 1.71	3.25 ± 1.20	12	④⑤⑧

Note: T, trial group; C, control group; –, Not reported; SA, stable angina; UA, unstable angina; CWM, conventional western medicine (including antiplatelet agents, statin lipid-lowering drugs, β-blockers, nitrates, etc.); ①Angina pectoris effective rate; ②Ecg response rate; ③Nitroglycerin reduction and discontinuation rate; ④TCM, symptom Effective rate; ⑤Episodes of angina pectoris (Number of angina attacks, Duration of angina pectoris); ⑥Cardiac function index (CO, LVEF, LVEDD); ⑦TCM, syndrome score; ⑧SAQ, score; ⑨NT-ProBNP; ⑩Inflammatory factors.

that the trial group significantly improved ECG efficiency in patients compared to the control group, with a statistically significant difference [RR = 1.27, 95% CI (1.06, 1.51), p = 0.008] (Figure 7).

3.4.5 Number of angina attacks

Ten studies (Zhang and Wang, 2017; Lu et al., 2019; Chen et al., 2020; Qi-Min, 2020; Cui et al., 2021; Wang, 2021; Wang et al., 2021; Du et al., 2022; Li, 2022; Hui and Qian, 2023), involving 1,016 patients, reported on the number of angina episodes. There was significant heterogeneity among the studies ($p < 0.00001$, I^2 = 96%); thus, a random-effects model was adopted, which revealed that the trial group effectively reduced the number of angina episodes compared with the control group, with a statistically significant difference (MD = −1.87, 95% CI [−2.63, −1.10], $p < 0.00001$) (Figure 8).

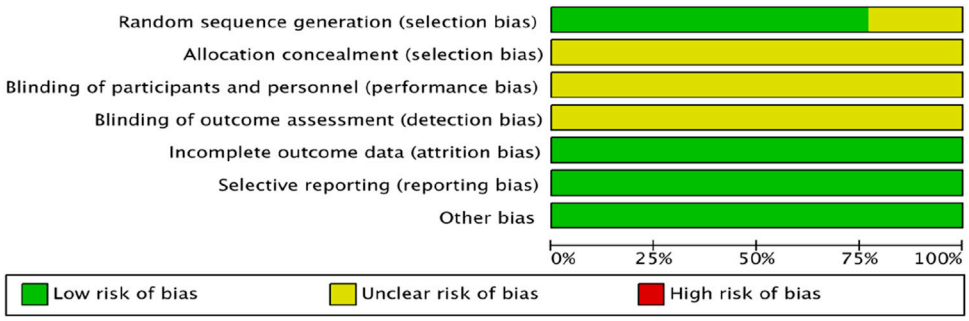


FIGURE 2
Summary of the risk of bias in the included literature.

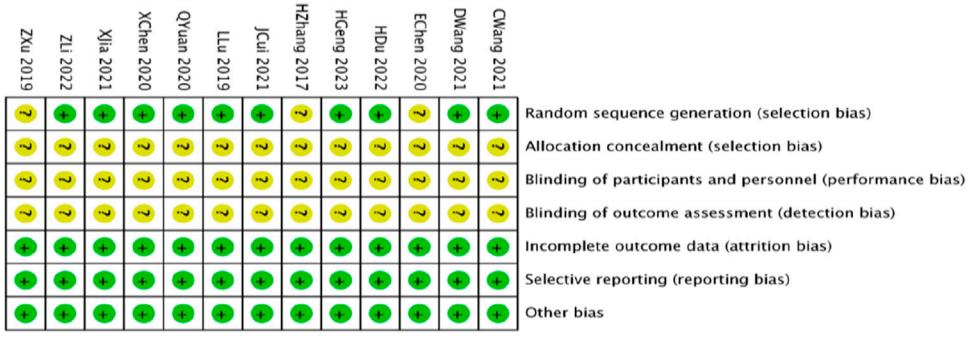


FIGURE 3
Risk of bias proportional to the risk of inclusion in the literature.

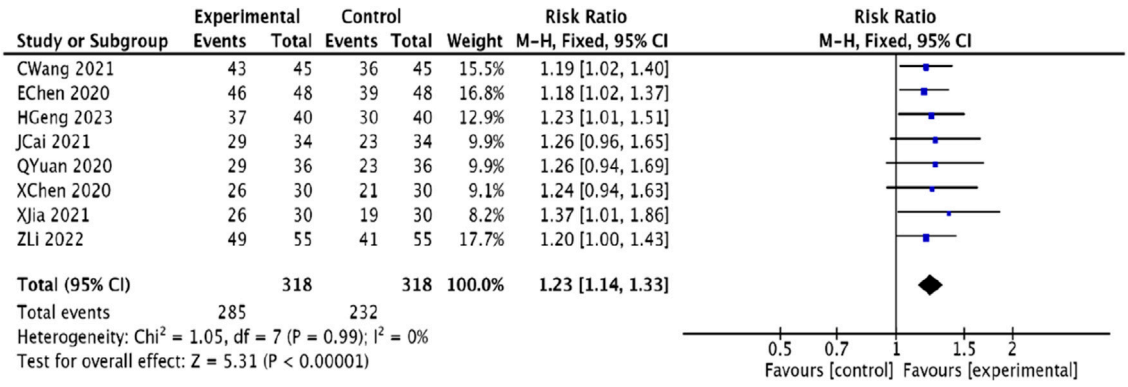


FIGURE 4
Meta-analysis of the effective rate of angina pectoris in patients with coronary heart disease angina pectoris treated with modified Danggui Sini Decoction in combination with conventional western drugs.

3.4.6 Duration of angina pectoris

Ten studies (Zhang and Wang, 2017; Lu et al., 2019; Chen et al., 2020; Qi-Min, 2020; Cui et al., 2021; Wang, 2021; Wang et al., 2021; Du et al., 2022; Li, 2022; Hui and Qian, 2023), encompassing 1,016 patients, reported on the duration of angina pectoris. Significant heterogeneity was observed among the studies ($p < 0.00001$, $I^2 = 89\%$), prompting the use of a random-effects model. The meta-analysis revealed that the trial group significantly reduced the duration of angina pectoris compared to the control group, with a statistically significant difference [MD = −1.78, 95% CI (−2.16, −1.39), $p < 0.00001$] (Figure 9).

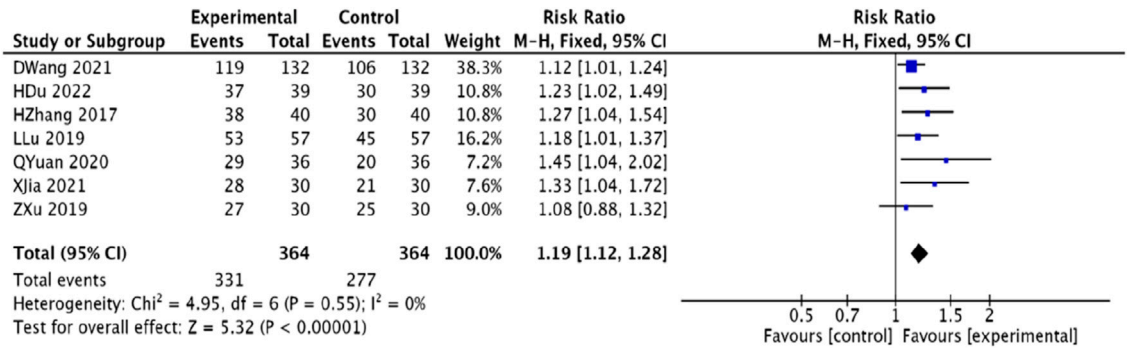


FIGURE 5
Meta-analysis of the effective rate of Chinese medicine syndromes in patients with coronary heart disease angina pectoris treated with modified Danggui Sini Decoction combined with conventional western medicine.

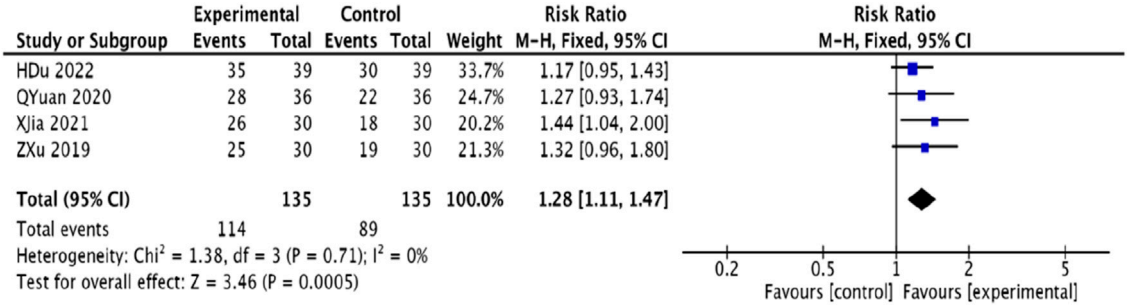


FIGURE 6
Meta-analysis of the rate of nitroglycerin reduction in patients with coronary heart disease angina pectoris treated with modified Danggui Sini Decoction in combination with conventional western medicines.

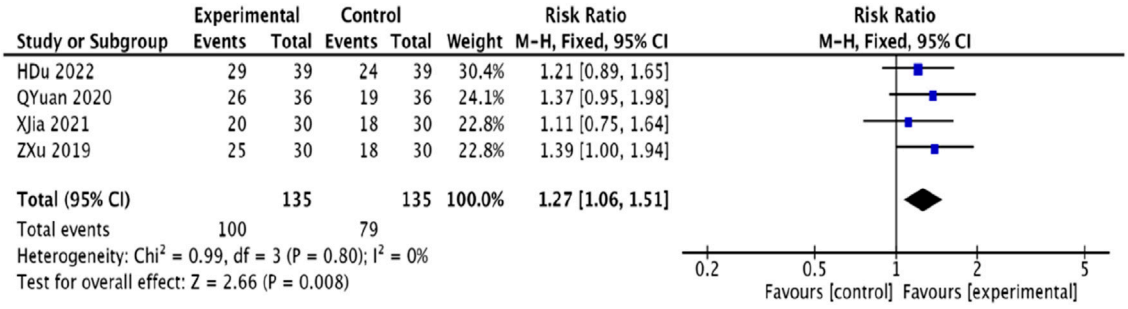


FIGURE 7
Meta-analysis of the ECG efficiency of modified Danggui Sini Decoction combined with conventional western drugs in the treatment of patients with angina pectoris in coronary artery disease.

3.4.7 Indicators of cardiac function

Five studies (Lu et al., 2019; Chen et al., 2020; Wang, 2021; Wang et al., 2021; Hui and Qian, 2023) evaluated CO and LVEF indices, while three studies (Chen et al., 2020; Wang et al., 2021; Hui and Qian, 2023) examined LVEDD. Due to heterogeneity among the findings, a random-effects model was employed for the meta-analysis. The results indicated improvements in CO [MD = 0.92, 95% CI (0.72, 1.11), $p < 0.00001$], LVEF [MD = 6.14, 95% CI (3.41, 8.87), $p < 0.0001$], and LVEDD [MD = −8.32, 95% CI (−9.92, −6.73), $p < 0.00001$], demonstrating that the experimental group significantly enhanced cardiac function compared to the control group (Figure 10).

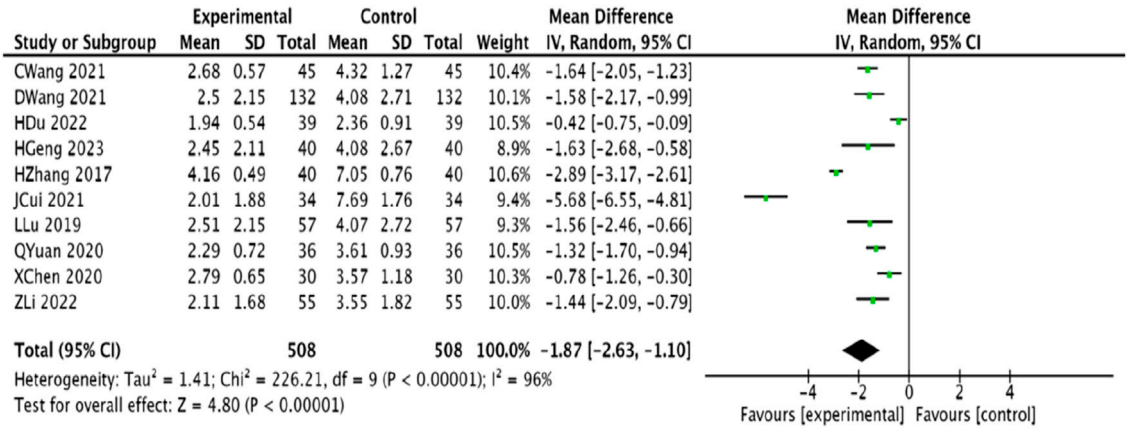


FIGURE 8
Meta-analysis of the combination of modified Danggui Sini Decoction with conventional western drugs to reduce the number of angina pectoris in patients with coronary heart disease angina pectoris.

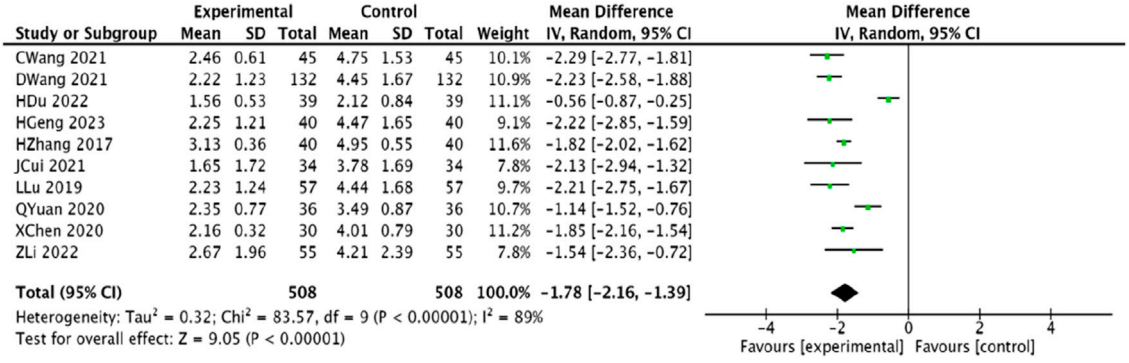


FIGURE 9
Meta-analysis of the combination of modified Danggui Sini Decoction with conventional western drugs to shorten the duration of angina in patients with coronary angina pectoris.

3.4.8 TCM symptom score

Five studies (Zifeng, 2019; Jia, 2020; Cui et al., 2021; Wang, 2021; Li, 2022), involving 392 patients, assessed TCM symptom scores. The studies showed homogeneity ($p = 0.84$, $I^2 = 0$), leading to the application of a fixed-effect model. The analysis showed that the experimental group significantly reduced TCM syndromic scores compared to the control group, with a statistically significant difference [MD = −2.90, 95% CI (−3.47, −2.34), $p < 0.00001$] (Figure 11).

3.4.9 Seattle angina questionnaire

Three studies (Zhang and Wang, 2017; Lu et al., 2019; Du et al., 2022), comprising 272 patients, referenced the Seattle Angina Questionnaire. Given the homogeneity of these studies, a random-effects model was conducted for meta-analysis. The findings highlighted significant improvements in the limitation of physical activity [MD = 7.50, 95% CI (4.82, 10.18), $p < 0.00001$], stability of angina [MD = 9.18, 95% CI (7.25, 11.11), $p < 0.00001$], frequency of anginal attacks [MD = 7.23, 95% CI (3.99, 10.47), $p < 0.00001$], treatment satisfaction [MD = 7.35, 95% CI (5.90, 8.79), $p < 0.0001$], and disease awareness (MD = 9.47, 95% CI (7.42, 11.51), $p < 0.00001$), demonstrating the experimental group's effectiveness in improving patient symptoms of angina compared to the control group (Figure 12).

3.4.10 NT-proBNP

Two studies (Chen et al., 2020; Zhang, 2020) assessed NT-proBNP levels in 156 patients. Given the homogeneity observed among the studies ($p = 0.42$, $= 0$), a fixed-effects model was employed for the meta-analysis. The results demonstrated that, compared to the control group, the experimental group significantly reduced NT-ProBNP levels, with a statistically significant difference [MD = −333.63, 95% CI (−362.00, −305.25), $p < 0.00001$] (Figure 13).

3.4.11 Inflammatory factors

Two studies (Zifeng, 2019; Zhang, 2020) examined IL-6, TNF-α, and hs-CRP levels. After testing for homogeneity, a fixed-effects model was applied for the meta-analysis. The findings indicated significant reductions in IL-6 [MD = −5.25, 95% CI (−5.88, −4.61),

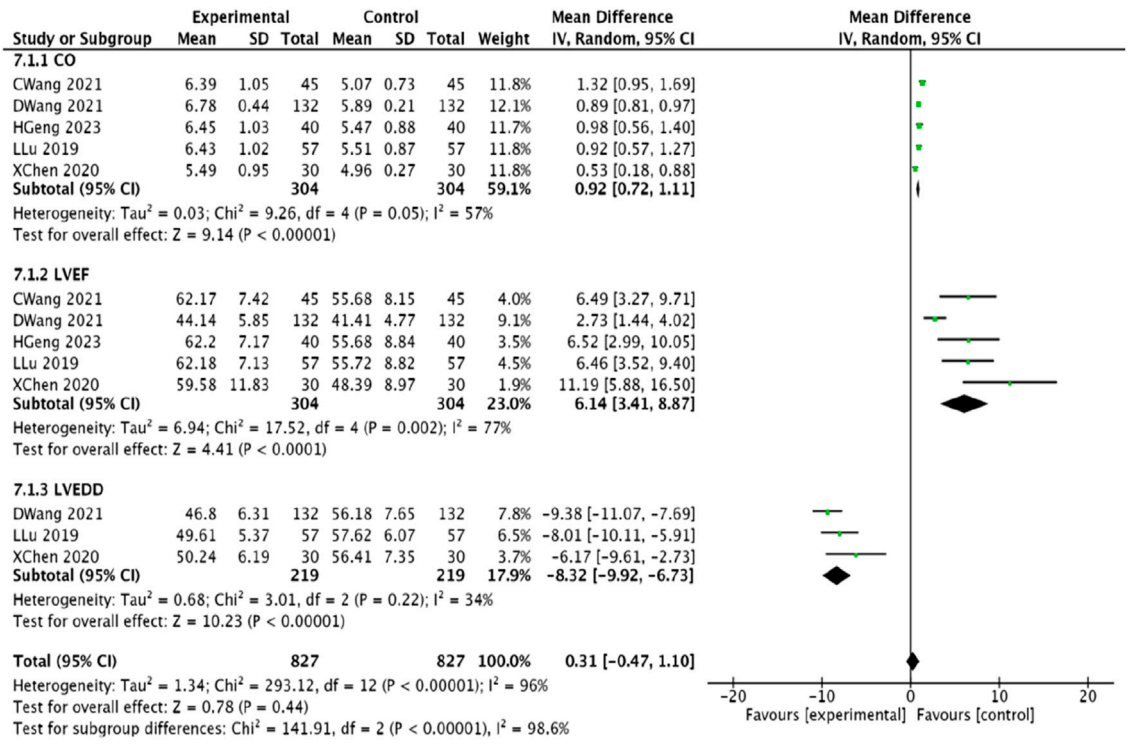


FIGURE 10
Meta-analysis of modified Danggui Sini Decoction combined with conventional western drugs to improve cardiac function in patients with coronary angina pectoris.

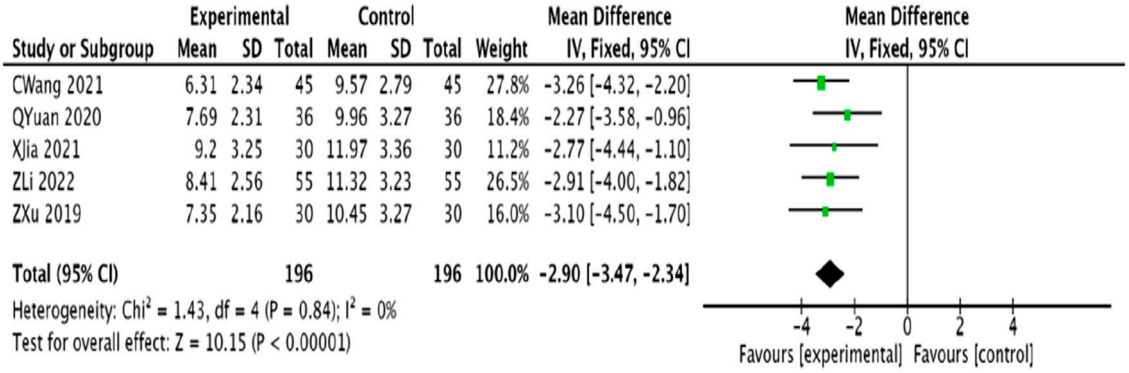


FIGURE 11
Meta-analysis of the improvement of TCM symptom scores in patients with angina pectoris of coronary artery disease by combining modified Danggui Sini Decoction with conventional western drugs.

$p < 0.00001$], TNF-α (MD = −8.33, 95% CI (−10.25, −6.41), $p < 0.00001$), and hs-CRP [MD = −5.30, 95% CI (−6.02, −4.57), $p < 0.00001$] in the experimental group compared to the control group, effectively reducing inflammatory markers (Figure 14).

3.4.12 Adverse events rates

Two studies (Zhang, 2020; Wang et al., 2021) reported on adverse events, noting that two patients in the experimental group experienced thirst, while 10 patients in the control group suffered from decreased appetite, diarrhea, and gastrointestinal symptoms. The homogeneity test showed consistency among the studies. The meta-analysis results [OR = 0.23, 95% CI (0.06, 0.92), $p = 0.04$] indicated that the experimental group had a better safety profile than the control group. These results are depicted in Figure 15.

3.4.13 Risk of publication bias assessment

A funnel plot was used to evaluate the risk of publication bias for the outcome indicators concerning the number of angina episodes and the duration of angina. The left-right asymmetry observed in the plot of each study point suggests a potential for publication bias (Figures 16A,B).

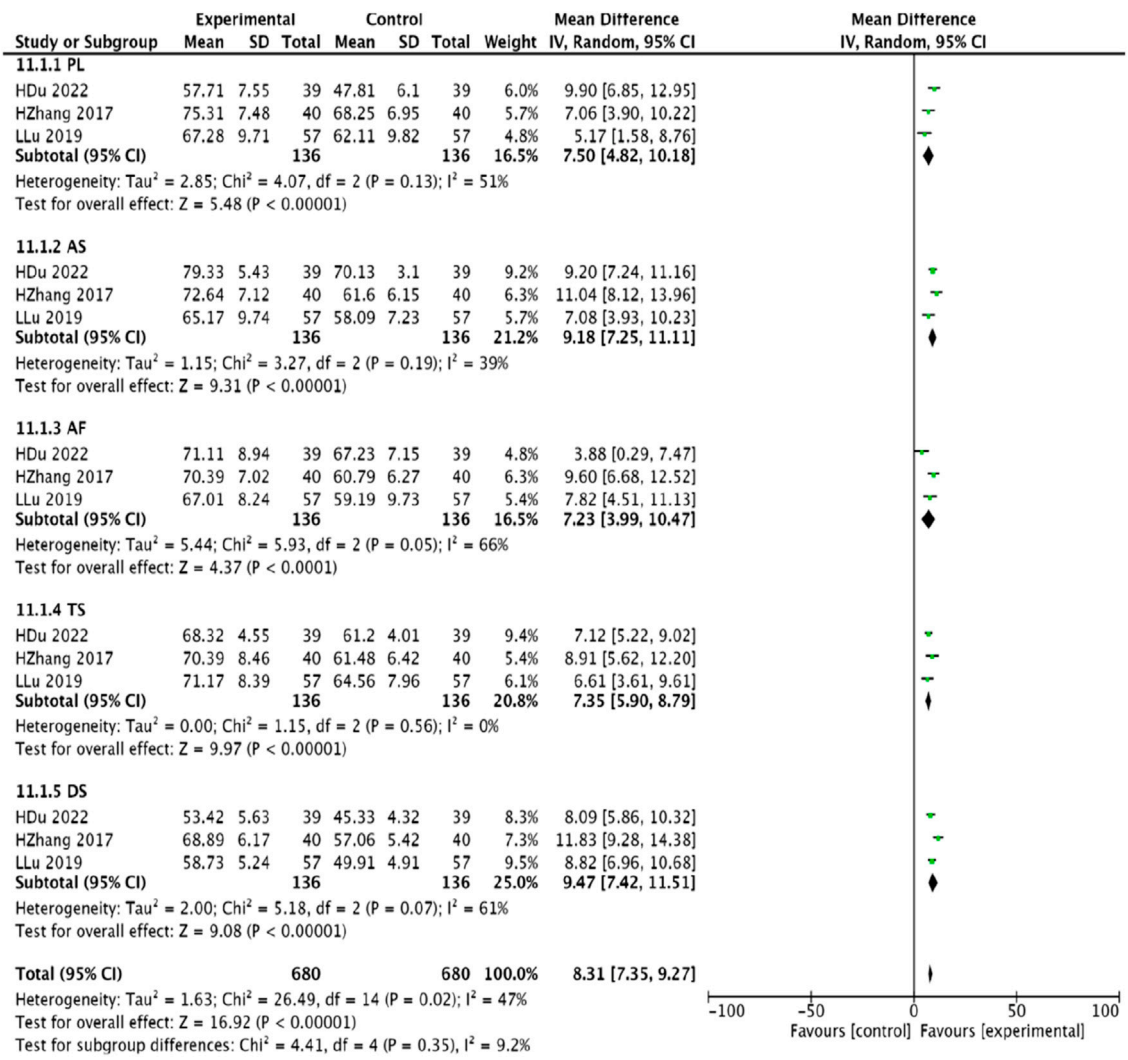


FIGURE 12
Meta-analysis of the improvement of SAQ scores in patients with coronary angina pectoris by combining modified Danggui Sini Decoction with conventional western drugs.

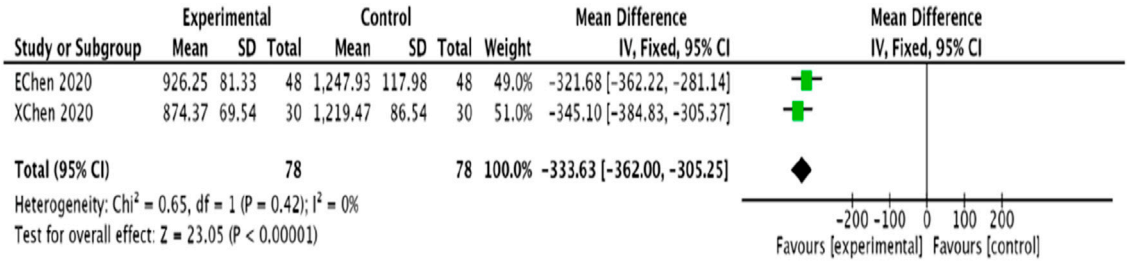


FIGURE 13
Meta-analysis of modified Danggui Sini Decoction combined with conventional western drugs to improve NT-ProBNP in patients with coronary angina pectoris.

3.5 Evidence quality evaluation

The GRADE evaluation results of the evidence of Danggui Sini Tang in assisting the treatment of coronary heart disease angina pectoris patients can be found in Supplementary Material S2. The main reasons for the downgrading of bias risk include bias caused by missing blinding and insufficient allocation concealment in the included studies; The main reason for the inconsistency degradation is that there is significant

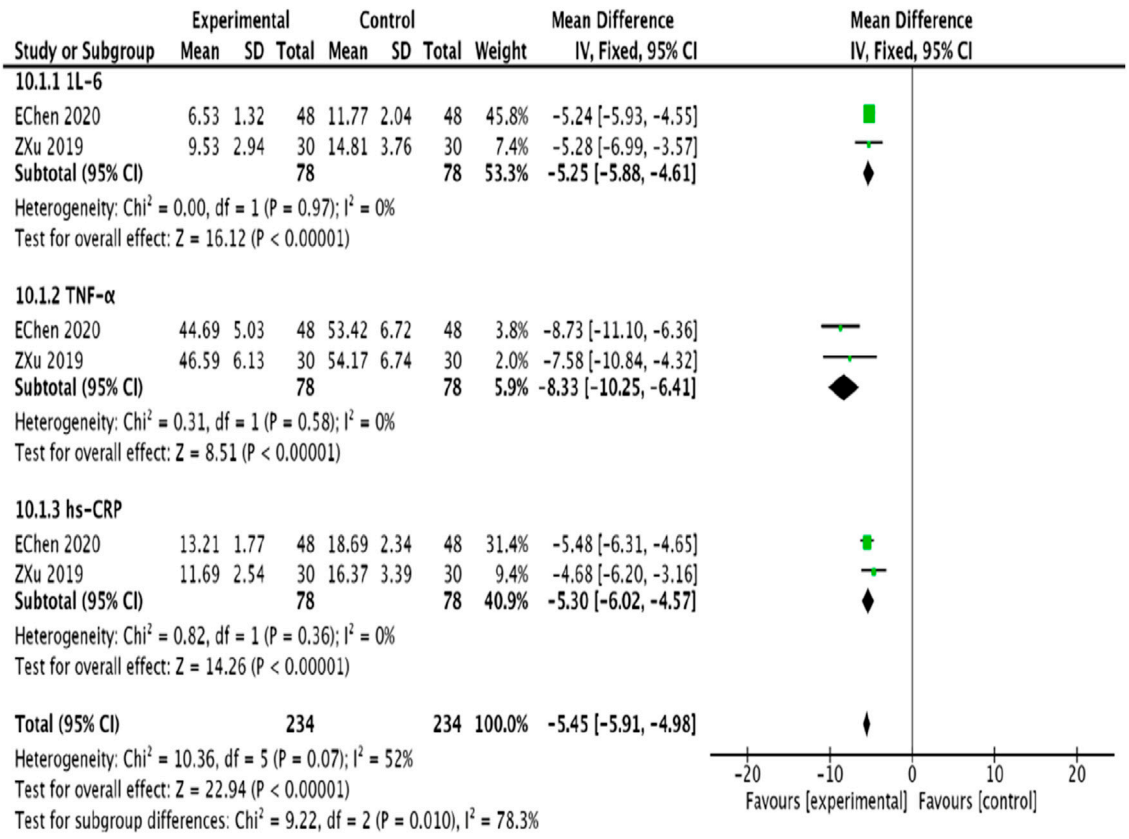


FIGURE 14
Meta-analysis of the improvement of inflammatory factors in patients with coronary heart disease angina pectoris by combining modified Danggui Sini Decoction with conventional western medicines.

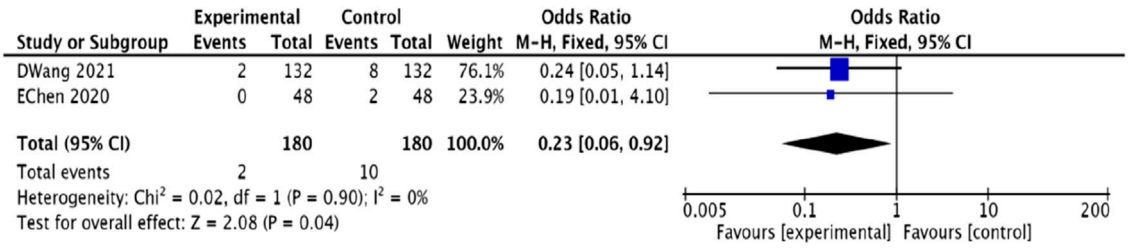


FIGURE 15
Meta-analysis of the improvement of adverse events rates in patients with coronary heart disease angina pectoris by combining modified Danggui Sini Decoction with conventional western medicines.

heterogeneity among some studies without reasonable explanations, which may affect the scientific validity of research methods and the reliability of research results; The main reason for the degradation of imprecision is that the confidence interval is too large, which affects the accuracy of the evidence.

4 Discussion

According to the China Cardiovascular Health and Disease Report 2019, cardiovascular disease affects approximately 330 million individuals in China, with the burden of disease on the rise (Layang, 2016). Among these, around 11 million are currently suffering from CHD, highlighting the growing focus on the prevention and treatment of CHD. Angina pectoris, a significant subtype of CHD, is noted for its high prevalence, mortality rate, treatment costs, and generally poor prognosis (Wang et al., 2023). Consequently, there is an increasing interest in traditional medicines, with the integration of Chinese and Western medicine in CHD treatment emerging as a 21st-century focal point. This approach has shown substantial progress in enhancing physical activity tolerance and symptom relief and is gaining acceptance

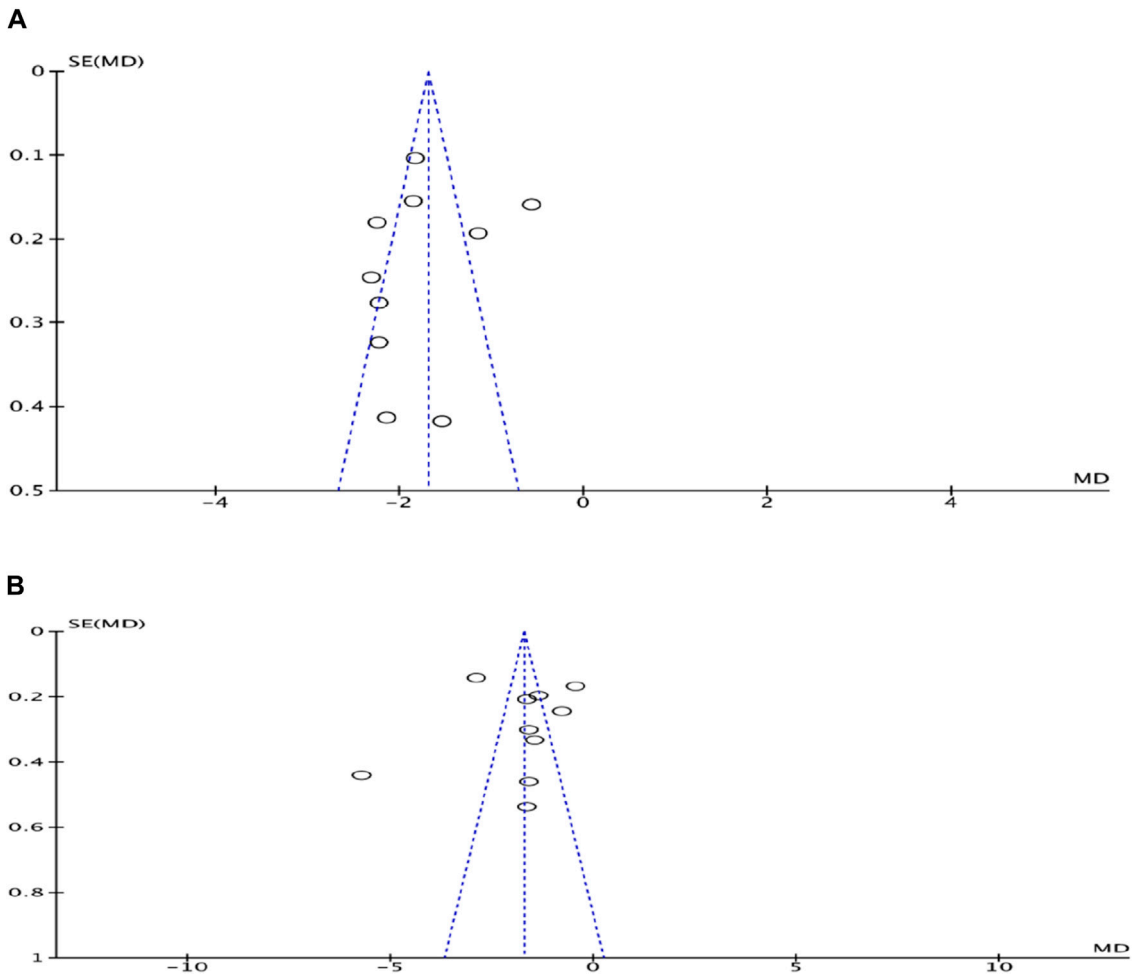


FIGURE 16
(A) Funnel plot of the number of episodes of angina pectoris in coronary artery disease treated with modified Danggui Sini Decoction combined with conventional western drugs. **(B)** Funnel plot of duration of angina pectoris in coronary artery disease treated with modified Danggui Sini Decoction in combination with conventional western drugs.

among healthcare professionals and patients (Yafang et al., 2019). Thus, exploring and understanding the trends and patterns in the combined use of traditional Chinese and Western medicines for CHD treatment is essential.

Coronary artery disease, resulting from coronary atherosclerosis or thrombosis, leads to myocardial ischemia and hypoxia due to the narrowing or blockage of the artery lumen. The inflammatory response and abnormal platelet activation are pivotal in thrombosis, forming the pathological basis of coronary artery thrombosis (Ruddox et al., 2017). Percutaneous coronary intervention (PCI), a primary treatment, does not alter the underlying pathology, hence the risk of in-stent thrombosis and coronary in-stent restenosis (ISR) remains, potentially causing adverse cardiovascular events (Wan, 2023). Post-PCI, antiplatelet therapy is essential, with dual antiplatelet therapy comprising aspirin and clopidogrel recommended for managing coronary artery disease. Clopidogrel, an adenosine diphosphate (ADP) receptor antagonist, together with aspirin, which does not inhibit ADP-induced platelet aggregation alone, can prevent thrombin and platelet activation when combined. Nonetheless, clopidogrel resistance often necessitates increased dosages, the addition of a third antiplatelet drug (aspirin, clopidogrel, cilostazol), P2Y12 receptor antagonists, or the incorporation of TCM (Liu et al., 2013; Yu and Wang, 2014; Zhou and Wang, 2014). Notably, the China Food and Drug Administration has endorsed over 200 proprietary Chinese medicines for adjunctive or complementary angina pectoris treatments, significantly contributing to the reduction of primary end-stage events, anginal episodes, and improvement in electrocardiograms (Quan et al., 2004).

Modified Danggui Sini Decoction, originally detailed in Zhang Zhongjing's "Shang Han Lun," comprises Angelicae Sinensis Radix, Ramulus Cinnamomi, Asarum sieboldii Miq, Tetrapanax papyriferus, and Paeonia lactiflora Pall. It is recognized for its ability to warm Yang, activate the veins, promote blood circulation, and eliminate blood stasis (Xiong et al., 2015). Modern research has identified that Angelica sinensis contains diverse components such as volatile oils, terpenes, organic acids, polysaccharides, flavonoids, alkaloids, trace elements, and amino acids (Yi et al., 2005; Yi et al., 2007a; Yi et al., 2007b). Recent studies have isolated "ferulic acid" from Angelica sinensis, highlighting its vascular protective properties and capacity to inhibit platelet aggregation (Li et al., 2006). Additionally, the volatile

oil from Angelica sinensis has been found effective in alleviating vasospasm and expanding blood vessels (Quan et al., 2004). Cinnamaldehyde, derived from Cinnamomum cassia, inhibits collagen- and thrombin-induced platelet aggregation both *in vitro* and *in vivo* (Huang et al., 2006). Compounds such as caffeic acid, isochlorogenic acid C, chlorogenic acid, and wild baicalin from Cynanchum officinale exhibit vasodilatory and smooth muscle relaxing properties, besides inhibiting thrombosis *in vivo* (CHEN et al., 2010). The primary active constituents of Paeonia lactiflora, mainly terpenes and terpene glycosides, act on vascular endothelium to dilate vascular smooth muscle, enhancing myocardial blood flow and oxygen and blood supply (Yan et al., 2023). Pharmacological studies have demonstrated that extracts from Tongzhi exhibit significant antithrombotic and anti-inflammatory activities, effectively preventing thrombus formation (Xue et al., 2019). Ginger has been shown to improve blood lipids, facilitate cholesterol excretion, reduce arteriosclerosis (AS) progression, and inhibit platelet aggregation through the activation of signaling pathways such as PI3K-Akt, IL-17, HIF-1, and p53, and the regulation of genes like TP53, MAPK3, MAPK1, AKT1, ESR1, and JUN, thereby mitigating hypoxia-induced cardiac muscle injury and aiding in the management of angina pectoris (Jiang et al., 2023). Various studies confirm that Angelica Siwei Tang possesses anticoagulant and antithrombotic effects, enhances vascular perfusion, and offers anti-inflammatory and analgesic benefits, thereby protecting cardiomyocytes and improving clinical outcomes.

This study was informed by the integration of Chinese and Western medicinal theories, adopting an evidence-based approach to demonstrate that modified Danggui Sini Decoction, in conjunction with conventional Western medications, can effectively enhance clinical outcomes for patients with coronary heart disease coexisting with angina pectoris. This includes improvements in inflammatory markers, cardiac function, and frequency of angina episodes, thereby contributing to disease progression control. Nonetheless, this study is subject to certain limitations. Firstly, among the 13 included RCTs, 3 (Zhang and Wang, 2017; Zifeng, 2019; Zhang, 2020) did not clearly detail their randomization methods; none of the studies disclosed the concealment of allocation schemes or the application of blinding. Secondly, the dosage and treatment duration of modified Danggui Sini Decoction varied across the studies. Thirdly, the geographical location of all included RCTs being in China introduces potential geographic bias, all of which could influence the outcomes. These conclusions warrant confirmation through high-quality research.

5 Conclusion

Drawing from the existing evidence, fthe combination of modified Danggui Sini Decoction and conventional Western medicines significantly enhances clinical efficiency, cardiac function, and the management of angina episodes and inflammatory markers, alongside notably improving SAQ scores compared to control treatments, thus offering increased safety. This provides substantiated evidence for its adjunctive use in treating this condition. However, due to several limitations, these findings require further validation through more rigorous clinical studies and foundational research in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

HW: Writing–original draft, Writing–review and editing. CL: Writing–original draft, Writing–review and editing. XG: Writing–original draft, Writing–review and editing. JY: Funding acquisition, Supervision, Validation, Writing–review and editing. YZ: Funding acquisition, Supervision, Validation, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported through funding to State Administration of Traditional Chinese Medicine project [No. HED(2022)75].

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1375795/full#supplementary-material

References

Buyiman, B., Sarawati, K., Nie, Y., Yang, Z., and Zhang, L. (2023). Analysis of coronary heart disease mortality trends in China from 2006 to 2020 based on age-period-cohort model. *Mod. Prev. Med.* 50 (02), 193–198.

Chen, X., Li, L., Zhao, M., and Xue, R. (2020). Study on the effect and mechanism of Angelica sinensis Sibiru Tang in the adjuvant treatment of coronary atherosclerotic heart disease. *Mod. J. Integr. Chin. West. Med.* (07), 698–701.

Chen, X., Wenmin, X. U., Wenli, L. I., et al. (2010). Clinical efficacy observation on the treatment of acute coronary syndromes in the elderly with dengzhanxiaoxin. *Chin. J. Traditional Chin. Med.* 28 (11), 2261–2262.

China Cardiovascular Health and Disease Report 2021 (Coronary Heart Disease Section) (2022). *J. Cardiopulm. Vasc. Dis.* 41 (12), 1205–1211.

Chinese Medical Association Cardiovascular Disease Branch, Chinese Journal of Cardiovascular Disease Editorial Committee (2007). Guidelines for the diagnosis and treatment of chronic stable angina. *Chin. J. Cardiovasc. Dis.* 35 (3), 195–206.

Chinese Medical Association, Division of Cardiovascular Diseases (2017). Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes (2016). *Chin. J. Cardiovasc. Dis.* 45 (5), 359–376.

Cui, J., Wang, C., and Yaru, L. (2021). Clinical observation on the treatment of microvascular angina pectoris (cold condensation of heart vein syndrome) by adding Angelica sibirica soup. *China TCM Emergencies* (11), 1987–1990.

Dalys, G. B. D., and Collaborators, H. (2018). Global, regional, and national disability-adjusted life-years(DALYs)for 359 diseases and injuries and healthy life expectancy(HALE) for 195 countries and territories, 1990-2017:a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392 (10159), 1859–1922. doi:10.1016/S0140-6736(18)32335-3

Du, H., Lei, R., Zhang, H., Mou, H., and Yu, Y. (2022). Clinical observation on the treatment of unstable angina pectoris of coronary heart disease (yin-cold stagnation certificate) by adding flavour of Angelica sinensis Si Reverse Soup. *China TCM Emergencies* (05), 875–877.

GBD Causes of Death Collaborators (2018). Global, regional, and national age-sex-specific mortality for 282 causes of death in195 countries and territories, 1980-2017:a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392 (10159), 1736–1788. doi:10.1016/S0140-6736(18)32203-7

Guo, J., Wang, H., Li, Y., Zhu, S., Hu, H., and Gu, Z. (2023b). Nanotechnology in coronary heart disease. *Acta Biomater.* 171, 37–67. doi:10.1016/j.actbio.2023.09.011

Guo, Z., Wu, Y., Feng, Q., Wang, C., Wang, Z., Zhu, Y., et al. (2023a). Circulating HDAC4 reflects lipid profile, coronary stenosis and inflammation in coronary heart disease patients. *Biomark. Med.* 17, 41–49. [published online ahead of print, 2023 Apr 4]. doi:10.2217/bmm-2022-0797

Huang, J., Luo, X., Wang, S., Luo, H., and Wang, T. (2006). Characteristics of cinnamaldehyde against platelet aggregation and thrombosis. *China Clin. Rehabil.* 10 (31), 34–36.

Hui, G., and Qian, Wu (2023). Study on the effect of adding and subtracting Angelica sinensis Si Reverse Tang in the adjuvant treatment of angina pectoris of coronary heart disease in the elderly. *Chin. J. Drug Abuse Prev. Control* (05), 874–876+888.

Jia, X. (2020). *Clinical observation on the treatment of stable angina pectoris of coronary heart disease with yin-cold stagnation certificate by adding flavour of Angelica sinensis Sihui Tang* (Changsha, China: Hunan University of Traditional Chinese Medicine).

Jiang, J., Kunpeng, Y. A. O., and Yun, LONG (2023). Exploring the mechanism of action of Gui Zhi Zhen Ginger Hovenia Tang in the treatment of unstable angina pectoris in coronary heart disease based on network pharmacology. *Chin. Med. Sci.* 13 (10), 24–27.

Jia-Yi, X. U., and Xi-Ping, T. O. P. (2023). Progress in the application of nitrates and other drugs in elderly patients with coronary angina. *Chin. J. Evidence-Based Cardiovasc. Med.* 15 (04), 510–512.

Layang, Z. (2016). *On the doctrine of blood stasis and coronary heart disease* (Nanning, China: Guangxi University of Traditional Chinese Medicine).

Lei, L. (2012). Update of the US "Guidelines for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *World Clin. Drugs* 33 (8), 511.

Li, Z. (2022). Clinical efficacy of Angelica sinensis four reverse soup plus flavour formula in the treatment of angina pectoris (cold congealed heart pulse evidence). *Inn. Mong. Tradit. Chin. Med.* (05), 41–42.

Liu, P., Yu, Y., Yang, X., and Zhang, Z. (2023). Discussion on the inflammatory mechanism of coronary heart disease and the intervention strategy of traditional Chinese medicine based on the theory of "phlegm, blood stasis and toxicity". *Chin. J. Exp. Formulas* 29 (12), 185–191.

Li, F., Li, J., Liu, Y., Du, S., Zhang, Y., and Jiang, H. (2006). Effects of Chuanxiongzine and Angelica sinensis injection on platelet function and organ blood flow in rats with DIC. *Basic Med. Clin.* 26 (8), 909–910.

Liu, Y., Yin, H., and Chen, K. (2013). Platelet proteomics and its advanced application for research of blood stasissyndrome and activated blood circulation herbs of Chinese medicine. *Sci. China Life Sci.* 56 (11), 1000–1006. doi:10.1007/s11427-013-4551-8

Lu, L., Qiu, X., and Zhenguo, W. (2019). The efficacy of danggui siwei tong plus reduction combined with musk cardioprotective pill in treating angina pectoris of coronary heart disease in the elderly and the effect on patients' electrocardiogram and serum factor levels. *Shaanxi Tradit. Chin. Med.* (05), 587–590.

Peng, S., Tian, J., Jin, L., Wang, H., Xie, C., Zheng, J., et al. (2023). Efficacy and safety of Danggui Niantong Decoction in patients with gout: a systematic review and meta-analysis. *Front. Pharmacol.* 14, 1168863. doi:10.3389/fphar.2023.1168863

Qi-Min, Y. (2020). *Clinical study on the treatment of unstable angina pectoris in coronary heart disease with yin-cold stagnation type by danggui siwei tang* (Changchun, China: Changchun University of Traditional Chinese Medicine).

Quan, X. I. A., Zhang, P., Shaoping, L. I., and Wang, T. (2004). Progress in the study of pharmacological effects of Angelica sinensis. *Shizhen Guomian Guomao* 3 (15), 164.

Ruddox, V., Sandven, I., Munkhaugen, J., Skattebu, J., Edvardsen, T., and Otterstad, J. E. (2017). Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: a systematic review and meta-analysis. *Eur. J. Prev. Cardiol.* 24 (14), 1555–1566. doi:10.1177/2047487317715769

Wan, Z. (2023). Effect of PCI combined with atorvastatin calcium on myocardial injury indexes in patients with coronary artery disease combined with renal insufficiency. *Chin. J. Gerontology* 43 (11), 2566–2569.

Wang, C. (2021). Clinical study on the treatment of angina pectoris in elderly patients with coronary artery disease by adding and subtracting Angelica sibirica. *Chin. Community Physician* (23), 96–97.

Wang, H., Li, J., Hu, C., and Zheng, T. (2023). Meta-analysis of clinical efficacy and safety of broad-chest aerosol in the treatment of angina pectoris in coronary heart disease. *J. Cardiovasc. Cerebrovasc. Dis. Chin. West. Med.* 21 (14), 2636–2640.

Wang, J., and Chen, G. (2018). Expert consensus on Chinese medicine diagnosis and treatment of stable angina in coronary heart disease. *J. Traditional Chin. Med.* 59 (5), 447–450.

Wang, D., Xi, X., Liu, J., Qin, J., and Zhang, S. (2021). Observations on the therapeutic effect of danggui sibiye tang in treating unstable angina of coronary heart disease of yin-cold stagnation type. *West. Tradit. Chin. Med.* (05), 120–121.

Xiaoping, S. H. I., and Zhao, F. (2023). Clinical study on the treatment of angina pectoris in coronary atherosclerotic heart disease with Danshen injection combined with Dio Xinguankang capsule. *Chin. Pharm. Ind.* 32 (09), 98–102.

Xiong, X. J., Wang, Z., and Wang, J. (2015). Innovative strategy in treating angina pectoris with Chinese PatentMedicines by promoting blood circulation and removing blood stasis:experience from CombinationTherapy in Chinese medicine. *Curr. Vasc. Pharmacol.* 13 (4), 540–553. doi:10.2174/1570161112666141014153735

Xue, L., Zhang, C., Jin, P., Lai, Y., and Zhai, W. (2019). Current status and prospect of the research on the Chinese medicine Xiaotongcao. *Chin. Herb. Med.* 42 (11), 2736–2739.

Yafang, D., Baohe, W., and Yuhong, H. (2019). Research progress of Chinese patent medicines in the treatment of coronary heart disease. *New Chin. Med. Clin. Pharmacol.* (04).

Yan, H., Zhang, Z., Yao, M., and Yan, L. (2023). Network pharmacological analysis of the mechanism of action of Guizhi-Bai Shao in the treatment of chronic heart failure. *China J. Basic Chin. Med.* 29 (03), 464–469. doi:10.19945/j.cnki.issn.1006-3250.2023.03.013

Yassen, M., Moustafa, A., Venkataramany, B., Schodowski, E., Royfman, R., and Eltahawy, E. (2023). Clinical outcomes of transcatheter aortic valve replacement with and without percutaneous coronary intervention - an updated meta-analysis and systematic review. *Curr. Probl. Cardiol.* 48, 101980. [published online ahead of print, 2023 Jul 18]. doi:10.1016/j.cpcardiol.2023.101980

Yi, T., Leung, K. S., Lu, G. H., and Zhang, H. (2007a). Comparative analysis of Ligusticum chuanxiong and related umbelliferous medicinal plants by high performance liquid chromatography-electrospray ionization mass spectrometry. *Planta Med.* 73 (4), 392–398. doi:10.1055/s-2007-967139

Yi, T., Leung, K. S., Lu, G. H., Zhang, H., and Chan, K. (2005). Identification and comparative determination of senkyunolide A in traditional Chinese medicinal plants Ligusticum chuanxiong and Angelica sinensis by HPLC coupled with DAD and ESI-MS. *Chem. Pharm. Bull. (Tokyo)* 53 (11), 1480–1483. doi:10.1248/cpb.53.1480

Yi, T., Zhang, H., Xie, J., and Xue, D. (2007b). A new procedure for the preparative separation and isolation of Z-ligustilide from the roots of Angelica sinensis. *J. Sep. Sci.* 30 (12), 1973–1978. doi:10.1002/jssc.200700001

Yu, G., and Wang, J. (2014). Blood stasis syndrome of coronary heart disease:A perspective of modern medicine. *Chin. J. Integr. Med.* 20 (4), 300–306. doi:10.1007/s11655-013-1332-3

Zhang, E. (2020). Observation on clinical efficacy of adding and subtracting Angelica Sibei Tang in treating angina pectoris of coronary heart disease in the elderly. *Cap. Food Med.* (08), 198.

Zhang, H., and Wang, L. (2017). Treatment of 40 cases of stable angina pectoris of yin-cold stagnation type in the elderly by adding flavour to danggui sibiye tang. *Zhejiang J. Traditional Chin. Med.* (10), 725.

Zheng, X. (2002). *Guiding principles for clinical research of new Chinese medicines (for trial implementation) [M]*. Beijing: China Medical Science and Technology Press.

Zhou, W., and Wang, Y. (2014). A network-based analysis of the types of coronary artery disease from traditionalChinese medicine perspective:potential for therapeutics and drug discovery. *J. Ethnopharmacol.* 151 (1), 66–77. doi:10.1016/j.jep.2013.11.007

Zifeng, Xu (2019). *Clinical study on the treatment of stable angina pectoris (cold congealed heart vein type) by warming meridians and collaterals method and its effect on Lp-PLA_2[D]* (Jinan, China: Shandong University of Traditional Chinese Medicine).

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 23 July 2024
DOI 10.3389/fphar.2024.1398934

OPEN ACCESS

EDITED BY
Qing Yong He,
China Academy of Chinese Medical Sciences, China

REVIEWED BY
Xiaomo Xiong,
University of Cincinnati, United States
Lihui Zhang,
First Affiliated Hospital of Henan University of Traditional Chinese Medicine, China
Yang Zhi,
Chengdu Fifth People's Hospital, China

*CORRESPONDENCE
Junhua Zhang,
zjhtcm@foxmail.com
Fengwen Yang,
13682027022@163.com

†These authors have contributed equally to this work

RECEIVED 11 March 2024
ACCEPTED 01 July 2024
PUBLISHED 23 July 2024

CITATION
Shi M, Sun T, Zhang C, Ma Y, Pang B, Cao L, Ji Z, Yang F and Zhang J (2024), Effects of the combination of red yeast rice-containing commercial Chinese polyherbal preparation with statins for dyslipidemia: a systematic review and meta-analysis.
Front. Pharmacol. 15:1398934.
doi: 10.3389/fphar.2024.1398934

Effects of the combination of red yeast rice-containing commercial Chinese polyherbal preparation with statins for dyslipidemia: a systematic review and meta-analysis

Menglong Shi[1†], Tianye Sun[2†], Chenyao Zhang[1†], Yucong Ma[1], Bo Pang[1,3], Lujia Cao[1,3], Zhaochen Ji[1,3,4], Fengwen Yang[1,3*] and Junhua Zhang[1,3*]

[1]Evidence-Based Medicine Center, Tianjin University of Traditional Chinese Medicine, Tianjin, China, [2]Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China, [3]Haihe Laboratory of Modern Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China, [4]College of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China

Background: Significant challenges are associated with the pharmacological management of dyslipidemia, an important risk factor for cardiovascular disease. Limited reliable evidence exists regarding the efficacy of red yeast rice (RYR)-containing commercial Chinese polyherbal preparation (CCPP), despite their widespread use in China.

Purpose: We aimed to investigate the efficacy of RYR-containing CCPPs combined with statins in treating dyslipidemia.

Methods: Eight databases were searched for relevant randomized controlled trials (RCTs) from database inception date to November 2023. Outcome measures, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), clinical efficacy, and adverse reactions, were assessed. The Cochrane Handbook for Systematic Reviews of Interventions was used for quality evaluation, and the meta-analysis was conducted using RevMan 5.3 and Stata 15.1.

Results: Thirty-three studies involving 4,098 participants were included. The combination of RYR-containing CCPP, such as Xuezhikang (XZK), Zhibitai (ZBTAI), or Zhibituo (ZBTUO) with statins had a significant effect on the increase in clinical efficacy [RR:1.16, 95%CI (1.13, 1.19), $p < 0.00001$]. In addition, they also improved blood lipid profile parameters by increasing HDL-C levels [MD:0.21, 95%CI(0.17,

Abbreviations: AMSTAR-2, Modified Quality Assessment Scale for Systematic Reviews; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ASCVD, arteriosclerotic cardiovascular disease; CCPP, commercial Chinese polyherbal preparation; CVD, cardiovascular disease; GRADE, Grading of Recommendation Assessment Development and Evaluation; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MD, mean difference; M/F, male/female; PRISMA, referred Reporting Program for Systematic Review and Meta-Analysis; RCTs, randomized controlled trials; ROBIS, Risk of bias in systematic reviews tool; RYR, red yeast rice; RR, relative risk; SR, systematic review; TC, total cholesterol; TG, triglyceride; XZK, Xuezhikang capsule; ZBTAI, Zhibitai capsule; ZBTUO, Zhibituo capsule; 95%CI, 95% confidence interval.

0.25), $p < 0.00001$], and decreasing TC [MD: 0.60, 95%CI(−0.76, −0.45), $p < 0.00001$], TG [MD: 0.33, 95%CI(−0.39, −0.26), $p < 0.00001$] and LDL-C levels [MD: 0.45, 95%CI(−0.54, −0.36), $p < 0.00001$]. No significant adverse reactions was observed in the RYR-containing CCPPs. Notably, ZBTAI and XZK significantly reduced the incidence of gastrointestinal disturbances and muscular adverse reactions. However, subgroup analyses suggested that the type of CCPPs, dose, and treatment duration might affect the efficacy of RYR-containing CCPPs.

Conclusion: RYR-containing CCPPs combined with statins appears to improve lipid profiles and clinical efficacy in patients with dyslipidemia. However, due to the poor quality of the included studies, and some studied showing negative findings was unpublished. The results should be interpreted with caution until further confirmation by well-designed RCTs.

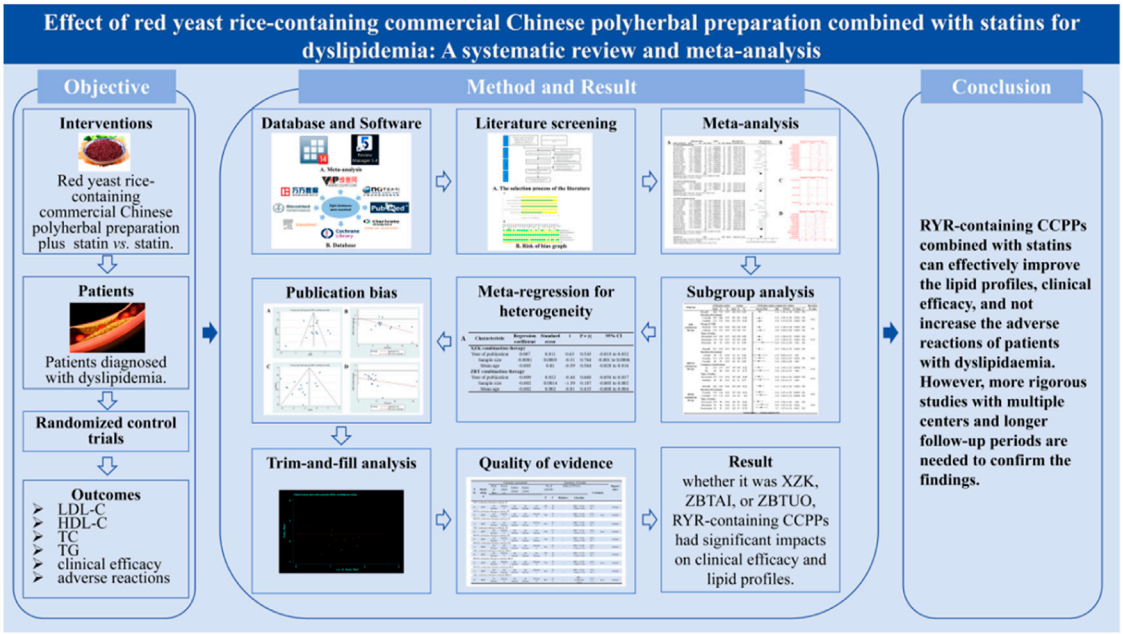
Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=487402, identifier CRD42023487402.

KEYWORDS

red yeast rice, dyslipidaemia, Xuezhikang capsule, Zhibitai capsule, Zhibituo capsule, meta-analysis

1 Introduction

Dyslipidemia, characterized by an abnormal increase in triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels, and decrease in high-density lipoprotein cholesterol (HDL-C) levels, is a common problem associated with lipid abnormalities (Townsend et al., 2015). Furthermore, dyslipidemia is an important risk factor for cardiovascular disease, which is the leading cause of morbidity and mortality worldwide (Visseren et al., 2021). Altered lipid profiles have significantly contributed to improving cardiovascular disease (CVD), with a survey in United States indicating that the death rate associated with coronary heart disease decreased by more than 40 percent from 1980 to 2000, with a reduction in TC levels being the largest contributor. Therefore, the control of dyslipidemia is the key to prevent CVDs (Ford et al., 2007). However, epidemiological studies have found that the global prevalence of dyslipidemia was 15.2% in 2019 (Zeljkovic et al., 2019). In addition, the prevalence of dyslipidemia among adults in China was 40.45% in 2012, representing a significant increase over the previous period (World Health Organization, 2020). Even among those identified with arteriosclerotic cardiovascular disease (ASCVD) or at high risk of ASCVD, only 26.6% and 42.9%, respectively, exhibited LDL-C control targets (Dai et al., 2022). Furthermore, dyslipidemia has been regarded as a major



GRAPHICAL ABSTRACT

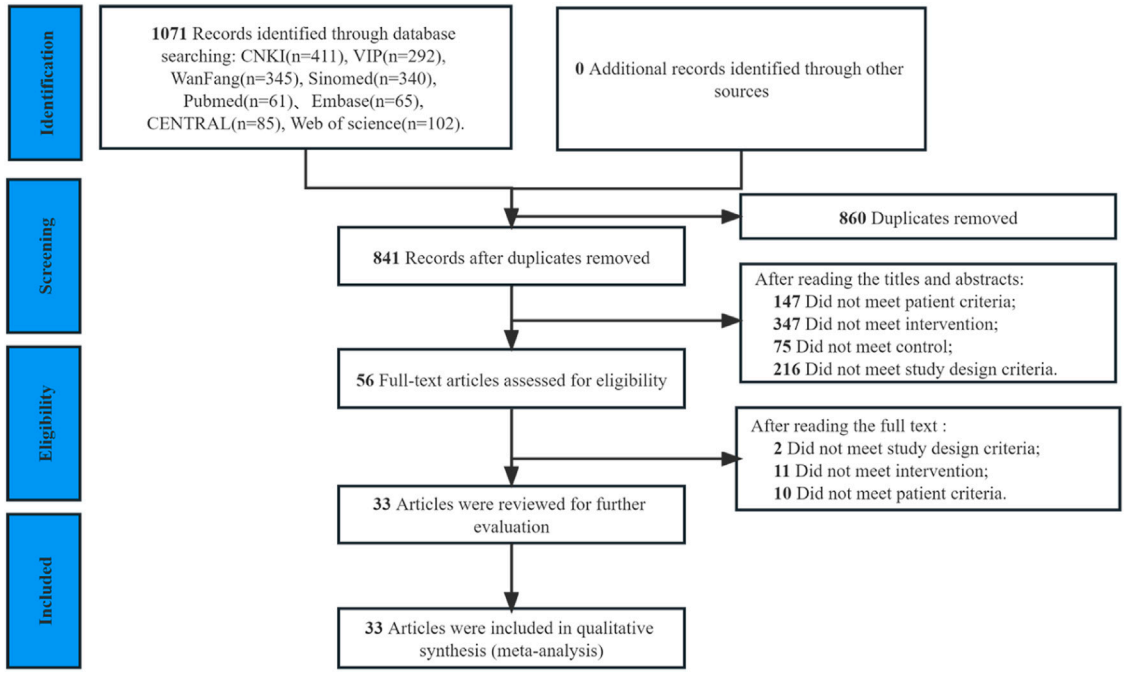


FIGURE 1
PRISMA flow diagram of study selection.

causative factor for many diseases, such as cerebral infarction, hypertension, and kidney dysfunction. In summary, it is important to manage and control blood lipid levels.

Currently, dyslipidemia management involves drug management and lifestyle changes (Gerhard-Herman, 2017; Whelton et al., 2018). Commonly prescribed medications for dyslipidemia include statins, cholesterol absorption inhibitors, absorption inhibitors, cholic acid chelating agents, fibrates, and nicotinic acid. Among these, statins are the basic drugs for the treatment of dyslipidemia (Mach et al., 2020). Although drug management has achieved positive results in lowering lipid levels, it remains a challenge due to adverse reactions such as neuropathy, gastrointestinal reaction, and related muscle complications such as myalgia, myositis, myopathy, or rhabdomyolysis (Stroes et al., 2015). Moreover, research showed that the use of statins, especially at large doses or for long durations, is related to an increased risk of myopathy, new-onset diabetes mellitus, and, probably, haemorrhagic stroke (Collins et al., 2016; Pergolizzi et al., 2020). Notably, unsatisfactory therapeutic effects and patient compliance-related issues also affect lipid management (Soppert et al., 2020). Therefore, it is necessary to explore additional therapies to achieve improved dyslipidemia treatment.

The available evidence suggests that traditional Chinese medicine, especially red yeast rice (RYR), in the treatment of dyslipidemia is increasingly recognized (Hu et al., 2022). RYR is a type of fermented rice produced by the fermentation of Monascus purpureus, and its active metabolites, including monacolin, can effectively regulate lipid levels (Jiang et al., 2021; Banach et al., 2022; Buzzelli et al., 2023). The Zhibitai capsule (ZBTAI), Zhibituo capsule (ZBTUO), and Xuezhikang capsule (XZK), which are RYR-containing CCPPs, are orally administered drugs approved by the Chinese State Food and Drug Administration (Management, 2023). Studies have confirmed that RYR-containing CCPPs can effectively reduce blood lipid levels in patients. Additionally, they can reduced the mortality rate in patients with coronary heart disease (Cicero et al., 2023). Notably, XZK is described as a medium-intensity lipid-lowering drug with proven safety that can significantly reduce LDL-C (Lu et al., 2008; Mach et al., 2020). Additionally, the results of multi-center clinical trials have demonstrated that ZBTAI combined with statins was as effective in reducing LDL-C levels as high-dose statins alone (Xu et al., 2018). The botanical drugs included and traditional effects of RYR-containing CCPPs were described in Supplementary Table S2.

The widespread use of RYR-containing CCPPs has resulted in an increase in the number of systematic reviews (SRs) to assess their efficacy (Wang et al., 2022; Zhao et al., 2023). However, these SRs was found several shortcomings such as heterogeneity and publication bias, which have not been addressed and explained. It is worth noting that there were significant differences in the interventions of the control group included in the previous systematic review, which reduced the statistical reliability. Therefore, statins, currently the basic drug for the treatment of dyslipidemia, were selected as the control group in this study, aiming to provide a new evaluation of the efficacy of RYR-containing CCPPs combined with statins in the treatment of dyslipidemia.

2 Methods

This study strictly followed the Preferred Reporting Program for Systematic Review and Meta-Analysis (PRISMA) guidelines (Page et al., 2018) and has been registered in the International Prospective Register of Systematic Reviews (registration No. CRD42023487402).

TABLE 1 Detailed information about the studies included.

Study	Subtypes of disease	Sample		Gender (M/F)		Age distribution		Treatment group	Control group	Study duration	Outcomes
		T	C	T	C	T	C				
Zou (2017)	dyslipidemia	244	244	134/110	140/104	52.6 ± 5.4	53.1 ± 5.5	XZK 0.6 g/bid + C	Atorvastatin 20 mg/qd	3 months	1,2,3,4,5,6
Shi et al. (2018)	dyslipidemia	62	62	34/28	35/27	62.13 ± 7.27	63.03 ± 7.52	XZK 0.6 g/bid + C	Fluvastatin 40 mg/qd	2 months	1,2,3,4,5,6
Zhang et al. (2017)	dyslipidemia	40	40	26/14	29/11	53.34 ± 13.64	54.62 ± 12.42	XZK 0.6 g/bid + C	Atorvastatin 40 mg/qd	1 month	1,2,3,4
Yu (2021)	dyslipidemia	38	38	20/18	20/18	58.69 ± 6.44	58.46 ± 6.28	XZK 0.6 g/bid + C	Atorvastatin 10 mg/qd	3 months	1,2,3,4,6
Wang (2012)	dyslipidemia	39	39	NR	NR	NR	NR	XZK 0.6 g/bid + C	Atorvastatin 10 mg/qd	3 months	1,2,3,4,5,6
Liu et al. (2018)	dyslipidemia	52	52	29/23	27/25	58.7 ± 3.8	58.5 ± 4.1	XZK 0.6 g/bid + C	Atorvastatin 20 mg/qd	2 months	1,2,3,4,5,6
Tian et al. (2022)	dyslipidemia	30	30	17/13	12/18	63.49 ± 3.05	64.02 ± 3.11	XZK 0.6 g/bid + C	Pitavastatin 2–4 mg/qd	3 months	1,2,3,4,5
Zhang and Tang (2010)	dyslipidemia	182	180	89/93	88/92	57.2 ± 10.8	56.5 ± 11.4	XZK 0.6g/bid + C	Simvastatin 10 mg/qd	2 months	1,2,3,4,5,6
Sun et al. (2018)	dyslipidemia	48	48	28/20	27/21	63.34 ± 7.29	63.39 ± 7.64	XZK 1.2g/bid + C	Simvastatin 20 mg/qd	3 months	1,2,3,4,5
Fu (2017)	dyslipidemia	75	75	36/39	38/37	63.2 ± 9.3	61.8 ± 9.3	XZK 0.6g/bid + C	Atorvastatin 10 mg/qd	3 months	1,2,3,4,5,6
Ma and Deng. (2019)	hypertriglyceridemia	76	74	NR	NR	NR	NR	XZK 0.6g/bid + C	Atorvastatin 40 mg/qd	6 months	1,2,3,4,6
Jiang and Chen. (2012)	dyslipidemia	85	85	42/43	40/45	61.7 ± 6.9	61.1 ± 7.4	XZK 1.2g/bid + C	Simvastatin 10 mg/qd	3 months	1,3,4,5
Qu et al. (2020)	dyslipidemia	39	39	22/17	25/14	50.08 ± 4.19	51.08 ± 4.27	XZK 0.6g/bid + C	Pitavastatin 2–4 mg/qd	3 months	1,2,3,4
Zhou (2010)	dyslipidemia	39	39	21/18	22/17	52.4 ± 5.5	53.2 ± 4.9	XZK 1.2g/bid + C	Simvastatin 10 mg/qd	1 month	1,2,3,4,5
Su (2021)	dyslipidemia	50	50	36/14	30/20	54.1	60.2	ZBTUO 1.05g/bid + C	Atorvastatin 20 mg/qd	1 month	1,2,3,4,5,6
Feng (2015)	dyslipidemia	60	60	36/24	34/26	67.3 ± 5.8	66.8 ± 5.6	ZBTUO 1.05 g/bid + C	Atorvastatin 10 mg/qd	3 months	1,2,3,4,5
Zhang et al. (2013)	dyslipidemia	85	85	46/39	45/40	63.76 ± 10.32	64.02 ± 9.05	ZBTUO 1.05 g/bid + C	Atorvastatin 10 mg/qd	2 months	1,2,3,4,5
Ji and Yi (2011)	dyslipidemia	66	66	NR	NR	NR	NR	ZBTUO 1.05 g/bid + C	Lovastatin 20 mg/qd	2 months	1,2,3,4,5,6
Li (2023)	dyslipidemia	55	55	29/26	27/28	70.92 ± 5.53	70.64 ± 5.2	ZBTAI 0.24 g/bid + C	Rosuvastatin 5 mg/qd	3 months	1,2,3,4,5,6
Yuan et al. (2023)	dyslipidemia	29	29	14/15	13/16	52.46 ± 3.89	52.24 ± 3.75	ZBTAI 0.24 g/bid + C	Atorvastatin 20 mg/qd	2 months	1,2,3,4,6
Chen et al. (2022)	dyslipidemia	60	60	37/23	39/21	63.94 ± 6.89	64.27 ± 6.76	ZBTAI 0.24g/bid + Statin	Atorvastatin 20 mg/qd	2 months	1,2,3,4,6
Tan et al. (2021)	dyslipidemia	60	60	34/26	35/25	83.05 ± 1.52	84.25 ± 0.75	ZBTAI 0.24 g/bid + C	Rosuvastatin 20 mg/qd	1 month	1,2,3,4,6
Xiong (2019)	dyslipidemia	45	45	25/20	27/18	66.32 ± 2.21	66.28 ± 2.18	ZBTAI 0.48 g/bid + C	Simvastatin 20 mg/qd	2 months	1,2,3,4,6
Tan (2020)	dyslipidemia	30	30	20/10	22/8	61.5 ± 18.5	62.5 ± 19.5	ZBTAI 0.24 g/bid + C	Atorvastatin 10 mg/qd	2 months	1,2,3,4,6
Li et al. (2016)	dyslipidemia	60	60	30/30	34/26	67.1 ± 2.3	67.5 ± 2.4	ZBTAI 0.24 g/bid +C	Rosuvastatin 10 mg/qd	2 months	1,2,3,4

(Continued on following page)

10.3389/fphar.2024.1398934

TABLE 1 (*Continued*) Detailed information about the studies included.

Study	Subtypes of disease	Sample		Gender (M/F)		Age distribution		Treatment group	Control group	Study duration	Outcomes
		T	C	T	C	T	C				
Liu ZK et al. (2019)	dyslipidemia	43	50	NR	NR	NR	NR	ZBTAI 0.24 g/bid + C	Rosuvastatin 10 mg/qd	2 months	1,2,3,4,5
He (2020)	dyslipidemia	80	80	45/35	48/32	54.86 ± 10.08	55.01 ± 11.32	ZBTAI 0.48g/bid + C	Pitavastatin 2 mg/qd	2 months	1,2,3,4
Ma and Feng. (2018)	dyslipidemia	29	28	NR	NR	NR	NR	ZBTAI 0.24 g/bid + C	Rosuvastatin 5 mg/qd	2 months	1,2,3,4
Chen et al. (2020)	dyslipidemia	63	63	31/32	33/30	70.1 + 7.6	71.2 ± 8.1	ZBTAI 0.24 g/bid + C	Atorvastatin 10 mg/qd	3 months	1,2,3,4,5
Wang and Chen (2015)	dyslipidemia	32	32	18/14	19/13	67.5 ± 5.2	67.2 ± 4.5	ZBTAI 0.24 g/bid + C	Atorvastatin 10 mg/qd	6 weeks	1,2,3,4
Chen et al. (2016)	dyslipidemia	42	42	28/14	26/16	62.5 ± 5.6	63.5 ± 6.2	ZBTAI 0.24 g/bid + C	Atorvastatin 10 mg/qd	2 months	1,2,3,4,5
Liu Q et al. (2019)	dyslipidemia	45	45	27/18	29/16	73.9 ± 8.2	72.7 ± 8.5	ZBTAI 0.48 g/bid + C	Rosuvastatin 10 mg/qd	6 months	1,2,3,4
Shi (2019)	dyslipidemia	65	65	31/34	32/33	52.63 ± 5.42	52.59 ± 5.39	ZBTAI 0.24 g/bid + C	Simvastatin 20 mg/qd	2 months	1,2,3,4,5

Abbreviations: C, control group; M/F, male/female; NR, not reported; T, treatment group; XZK, xuezhikang capsule; ZBTAI, zhibitai capsule; ZBTUO, zhibituo capsule; Outcomes 1: total cholesterol (TC); 2: triglyceride (TG); 3: high-density lipoprotein cholesterol (HDL-C); 4: low-density lipoprotein cholesterol (LDL-C); 5: clinical efficacy; 6:adverse reaction.

2.1 Search strategy

A comprehensive search for all relevant studies was performed in China Biomedical Literature Service System, the Chinese Science and Technology Journals Database (VIP), China National Knowledge Infrastructure (CNKI), Wanfang Data, PubMed, Embase, CENTRAL, and Web of Science from database inception date to 22 November 2023 by two researchers (STY and ZCY). No language or geographical areas restrictions were put in place. Relevant keywords containing both medical subject headings and free text terms. Keywords for the intervention included "Red yeast rice", "Xurzhikang", "Zhibitai", "Zhibituo", and "Monascus", while keywords for the study population were "Dyslipidemias", "Hyperlipidemias", "Hypercholesterolemia", "Hyperlipoproteinemia", and "Hyperlipidemia, Familial Combined". Furthermore, potential missing studies were further identified by reviewing references of these studies. (The detailed search strategies are shown in Supplementary Table S3).

2.2 Inclusion criteria

2.2.1 Types of patients

Patients with dyslipidemia meeting accepted diagnostic criteria were included (Management, 2023), without age, sex, race, complications, or type of dyslipidemia restriction. Diagnostic criteria include either TC ≥ 6.2 mmol/L or TG of ≥2.3 mmol/dL, or LDL-C ≥ 4.1 mmol/L, or HDL-C < 1.0 mmol/L.

2.2.2 Intervention and control

The control group was treated with statins alone (fluvastatin, lovastatin, pitavastatin, rosuvastatin, and simvastatin). Participants in the experimental group were administered a combination of RYR-containing CCPPs and statins. The doses and statin types in the control and experimental groups were the same.

2.2.3 Outcome measures

Primary outcomes included low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) levels. Additional valuable outcomes that can help obtain accurate data were also collected. These included (1) clinical efficacy; (2) other lipid profiles, such as apolipoprotein A1 (ApoA1) levels, apolipoprotein B (ApoB) levels, and (3) adverse reactions such as muscular adverse drug reactions, kidney dysfunction, and gastrointestinal reactions.

2.2.4 Types of studies

This meta analysis included randomized controlled trials (RCTs) that compared the combination of RYR-containing CCPPs and statins against statins alone.

2.3 Exclusion criteria

(1) Non-RCTs, conferences abstracts, animal researches, and technical results; (2) studies with incomplete or inadequate data; (3) interventions involving other Chinese medicines, or therapies specific to Chinese medicine.

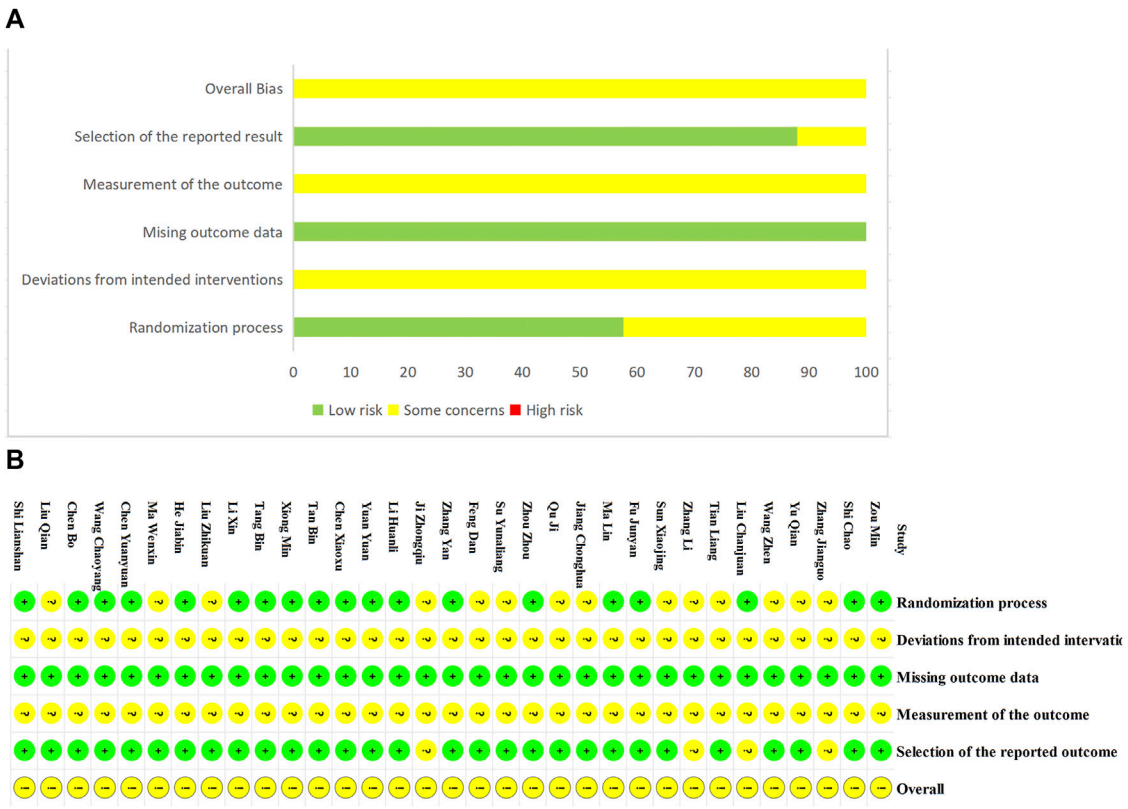


FIGURE 2
Risk of bias. **(A)** Risk of bias summary. **(B)** Risk of bias graph.

2.4 Literature screening and data extraction

Based on the inclusion and exclusion criteria, two authors (SML and PB) independently screened studies and extracted the following information: (1) sample characteristics and study design, including authors, publication year, dyslipidemia type, CCPP type, statin type, CCPP dose, and statin dose; (2) outcome information, encompassing the lipid profiles, adverse reactions, and other valuable outcomes. Disagreements were examined by a third researcher (MYC). Attempts were made to contact authors to obtain missing data.

2.5 Quality assessment

The Cochrane risk of bias tool 2.0, which includes the randomization sequence generation, deviations from intended interventions, missing outcome data, outcome measurement, and overall bias, was used to assess the quality of included studies. Two authors evaluated each domain independently, and the results were assessed by a third researcher if they were inconsistent.

2.6 Data synthesis

Meta-analysis was completed by RevMan 5.3 and Stata 15.1. Relative risk (RR) and mean difference [MD] were determined to evaluate dichotomous data and continuous variables, respectively. Confidence intervals were (CIs) set at 95% and the statistical significance was set at $p < 0.05$. Statistical heterogeneity was conducted by Q test and inconsistency index (I^2) values. If the heterogeneity was obvious (50% < I^2 and 0.1 > P), a random-effects model was used, otherwise using the fixed-effects model. Funnel plots and Egger's test were used to assess the publication bias when the number of included studies exceeded 10. Simultaneously, the influence of publication bias on the results interpretation was evaluated by trim-and-fill analysis. Pre-defined subgroup analysis was first performed to assess the influence of CCPP type on the efficacy of RYR-containing CCPPs. Then, subgroup analyses were performed for different CCPP types to evaluate the influence of some parameters (CCPP dose, statin type, and duration of treatment) on the efficacy of different RYR-containing CCPPs, respectively. Sensitivity analysis was conducted by item-by-item elimination to assess robustness of the meta-analysis. Furthermore, univariate meta-regression analyses were performed to investigate the source of heterogeneity.\

2.7 Quality of evidence and evaluation of this SR

Grading of recommendation, assessment, development, and evaluation (GRADE) guidelines to assess the certainty of the evidence for each outcome, in which five domains were evaluated:

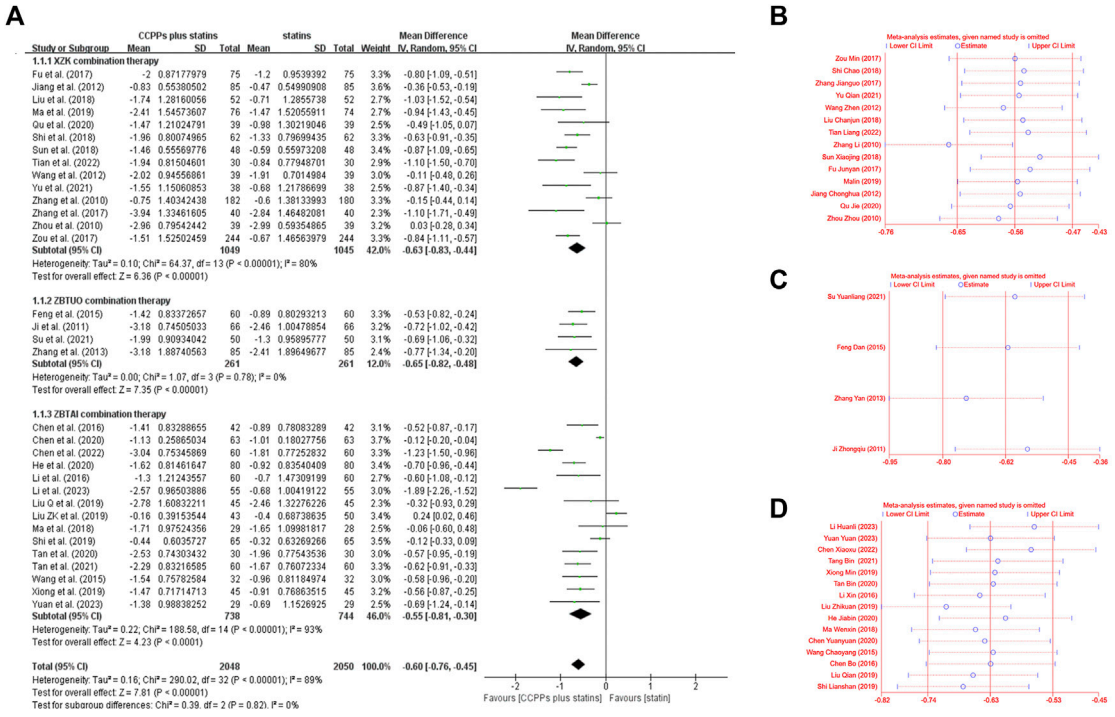


FIGURE 3
Effect of RYR-containing CCPPs on TC. **(A)** Forest plot of TC. **(B)** Sensitivity analysis of XZK on TC. **(C)** Sensitivity analysis of ZBTUO on TC. **(D)** Sensitivity analysis of ZBTAI on TC.

(1) study limitations were assessed according to RoB2.0; (2) consistency was evaluated using I^2 values and the agreement of 95% confidence and prediction intervals; (3) directness was assessed to determine whether the interventions and populations of the included studies were appropriate for the research question; (4) precision was examined by the optimal information sample size; and (5) publication bias was assessed using the funnel plot and the number of included studies (Gonzalez-Padilla and Dahm, 2021). Furthermore, the Modified Quality Assessment Scale for Systematic Reviews (AMSTAR-2) (Shea et al., 2017) and Risk of Bias in Systematic Reviews (ROBIS) tool (Whiting et al., 2016) were used to evaluate the methodological quality and risk of bias of meta-analysis by two investigators (ZP and MYY) who had no conflict of interest with this study. More importantly, meta-analysis was refined according to the review results until each domain are satisfactory.

3 Results

3.1 Study selection

Out of the 1,735 articles initially identified in the database search, 860 duplicates were removed, and an additional 785 articles were excluded after reviewing titles or abstracts. The full text of 56 trials were reviewed, and 23 were excluded (Supplementary Table S5). Ultimately, 33 RCTs including 4,098 patients (2,048 patients in experimental groups and 2,050 in control groups) (Zhang and Tang, 2010; Zhou, 2010; Ji and Yi, 2011; Jiang and Chen, 2012; Wang, 2012; Zhang et al., 2013; Feng, 2015; Wang and Chen, 2015; Chen et al., 2016; Li et al., 2016; Whiting et al., 2016; Fu, 2017; Zhang et al., 2017; Zou, 2017; Liu et al., 2018; Ma and Feng, 2018; Shi et al., 2018; Sun et al., 2018; Liu, 2019; Liu et al., 2019; Ma and Deng, 2019; Shi, 2019; Xiong, 2019; Chen et al., 2020; He, 2020; Qu et al., 2020; Tan, 2020; Su, 2021; Tan et al., 2021; Yu, 2021; Chen et al., 2022; Tian et al., 2022; Li, 2023; Yuan et al., 2023) were included in the final review (Figure 1).

3.2 Studies characteristics

The characteristics of the included studies are indicated in Table 1. All trials were conducted in China and published in Chinese between 2010 and 2023. In terms of disease subtypes, one trial recruited only patients with hypertriglyceridemia (Ma and Deng, 2019), while the remaining studies did not specify the dyslipidemia type. Patients receiving combination therapy with RYR-containing CCPPs categorized into the experimental group and those receiving statin therapy categorized into the control group. In the experimental groups, fourteen trials (Zhang and Tang, 2010; Zhou, 2010; Jiang and Chen, 2012; Wang, 2012; Fu, 2017; Zhang et al., 2017; Zou, 2017; Liu et al., 2018; Shi et al., 2018; Sun et al., 2018; Ma and Deng, 2019; Qu et al., 2020; Yu, 2021; Tian et al., 2022) with 2,094 participants focused on the XZK combination therapy, while fifteen trials (Wang and Chen, 2015; Chen et al., 2016; Li et al., 2016; Ma and Feng, 2018; Liu,

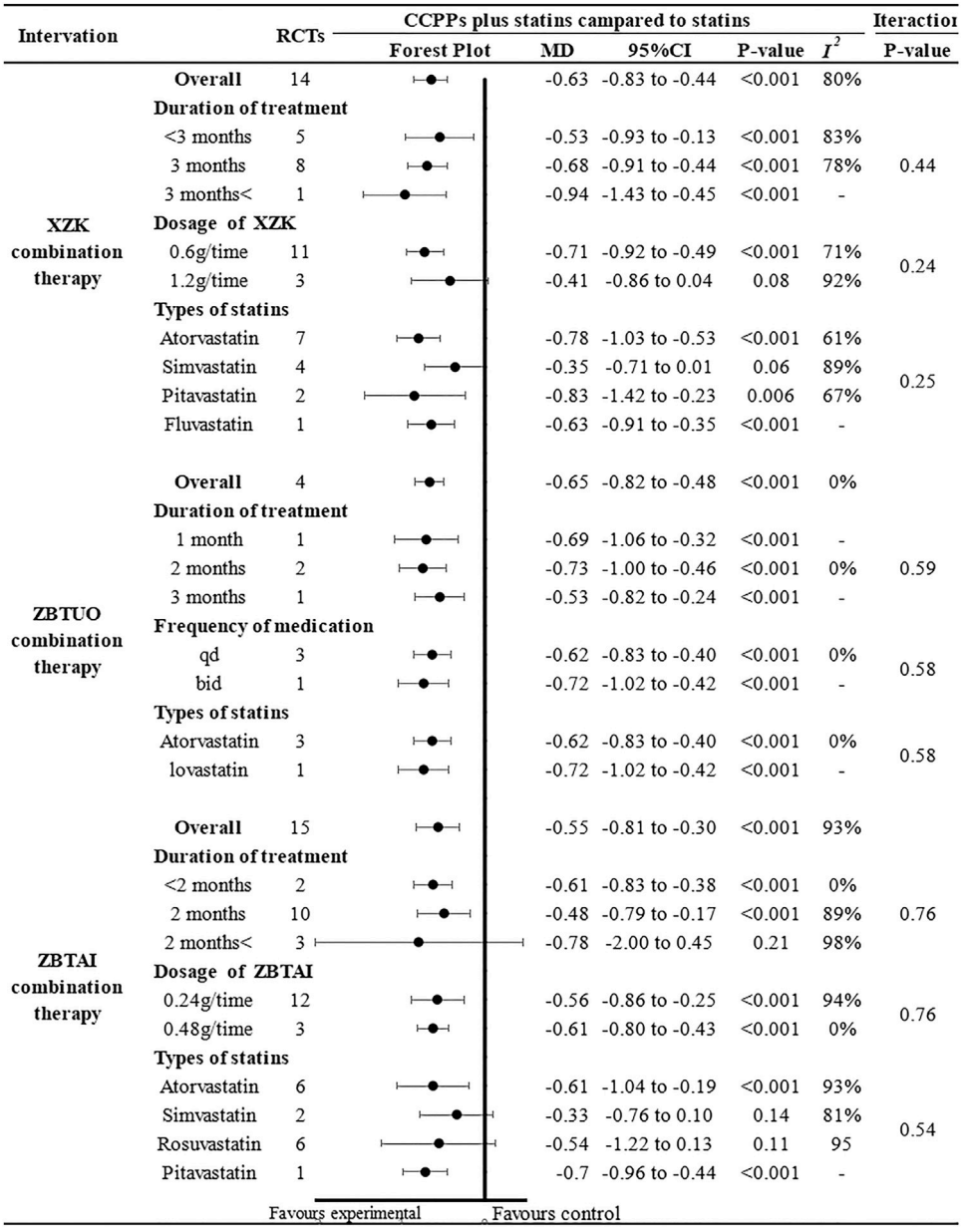


FIGURE 4
Subgroup analysis of the TC.

2019; Liu et al., 2019; Shi, 2019; Xiong, 2019; Chen et al., 2020; He, 2020; Tan, 2020; Tan et al., 2021; Chen et al., 2022; Li, 2023; Yuan et al., 2023) with 1,482 participants focused on the ZBTAI combination therapy, and four trials (Ji and Yi, 2011; Zhang et al., 2013; Feng, 2015; Su, 2021) with 522 participants focused on ZBTUO combination therapy. Furthermore, the dose of CCPPs was 0.6 g/time or 1.2 g/time for XZK, 1.05 g/time for ZBTUO, and 0.24 g/time or 0.48 g/time for ZBTAI. Notably, the duration of treatment varies from 1 to 6 months, with XZK treatment typically administered for 3 months, and ZBTAI or ZBTUO treatment administered for 2 months. In the control group, atorvastatin, fluvastatin, pitavastatin, simvastatin, lovastatin, and rosuvastatin were mainly administered during statin therapy.

3.3 Risk of bias

Nineteen RCTs (Zhou, 2010; Zhang et al., 2013; Wang and Chen, 2015; Chen et al., 2016; Li et al., 2016; Fu, 2017; Zou, 2017; Liu et al., 2018; Shi et al., 2018; Ma and Deng, 2019; Shi, 2019; Xiong, 2019; Chen et al., 2020; He, 2020; Tan, 2020; Tan et al., 2021; Chen et al., 2022; Li, 2023; Yuan et al., 2023) provided adequate randomization procedures and were assessed as low risk, while the others were deemed to have unclear risks due to the lack of specific details regarding randomization. Since none of the studies reported the information of allocation concealment, blinding, and measurement of the outcome, they were rated as unclear. All studies published complete data regarding the outcomes and were assessed as low risk. In addition, the selection of the reported results by the

A

Characteristic	Regression coefficient	Standard error	t	P > |t|	95% CI
XZK combination therapy					
Year of publication	0.007	0.011	0.63	0.543	-0.018 to 0.032
Sample size	-0.0001	0.0003	-0.31	0.764	-0.001 to 0.0006
Mean age	-0.005	0.01	-0.59	0.564	-0.028 to 0.016
ZBT combination therapy					
Year of publication	-0.009	0.022	-0.44	0.668	-0.056 to 0.037
Sample size	-0.002	0.0014	-1.39	0.187	-0.005 to 0.002
Mean age	-0.002	0.002	-0.81	0.435	-0.008 to 0.004

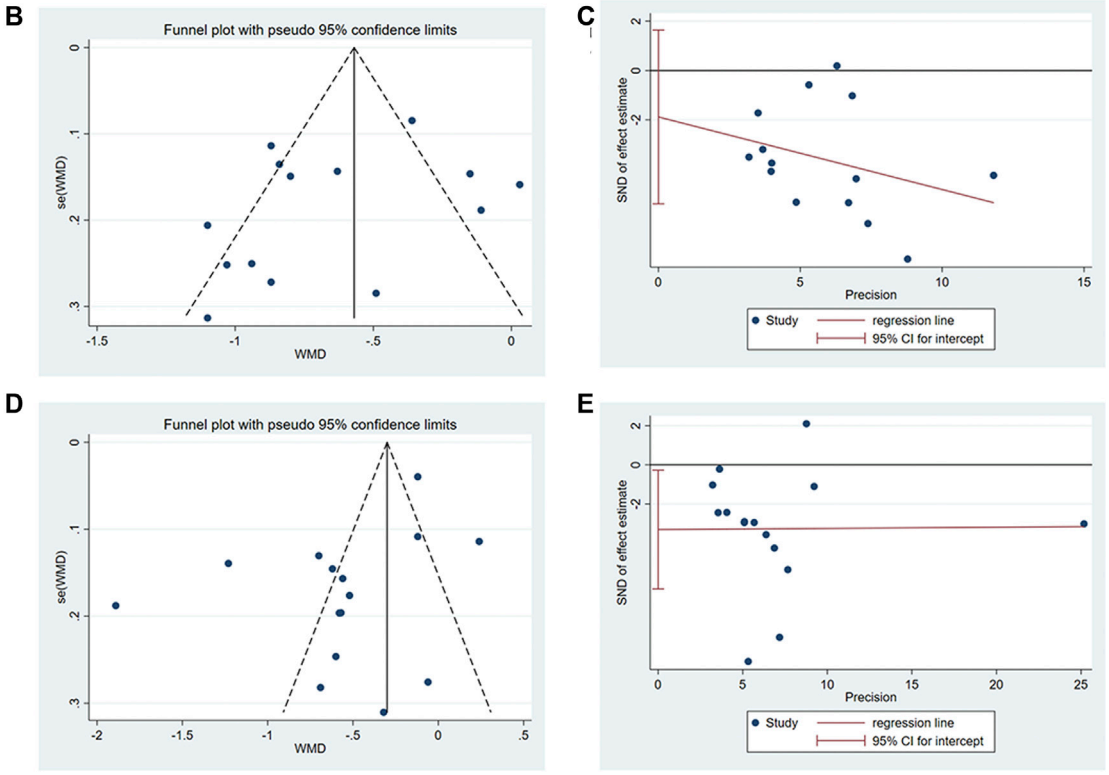


FIGURE 5
(A) Meta-regression was used to conduct the sources of heterogeneity. **(B)** Funnel plots of XZK combination therapy. **(C)** Egger's test quantified the publication bias of XZK combination therapy. **(D)** Funnel plots of ZBTAI combination therapy. **(E)** Egger's test quantified the publication bias of ZBTAI combination therapy.

four studies (Zhang and Tang, 2010; Ji and Yi, 2011; Zhang et al., 2017; Liu et al., 2018) was concerning and assessed as unclear (Figure 2).

3.4 Outcomes measures

3.4.1 Total cholesterol (TC)

Total cholesterol levels were reported in all trials, of which 14 trials focused on the XZK combination therapy, 15 trials focused on the ZBTAI combination therapy, and 4 trials focused on the ZBTUO combination therapy. Random effect model was chosen because of the strong heterogeneity (I^2 = 89%, p < 0.0001). The results showed that treatment with RYR-containing CCPPs resulted in greater reductions in TC levels compared to that with statin [MD: 0.60, 95%CI(−0.76, −0.45), p < 0.00001], regardless of whether the patients were in XZK combination therapy group [MD: 0.63, 95% CI(−0.83, −0.44), p < 0.00001, I^2 = 80%], ZBTAI combination therapy group [MD: 0.55, 95%CI(−0.8, −0.30), p < 0.00001, I^2 = 93%], or ZBTUO combination therapy group [MD: 0.65, 95% CI(−0.82, −0.48), p < 0.00001, I^2 = 0%] (Figure 3A). The results of sensitivity analyses revealed that the overall values of the analysis were consistent with each other, the conclusions were reliable (Figures 3B–D).

Further subgroup analysis was performed based on the CCPP dose, medication frequency, treatment duration, and statin type to investigate the influence of these parameters on the therapeutic effect of RYR-containing CCPPs (Figure 4). In case of ZBTUO

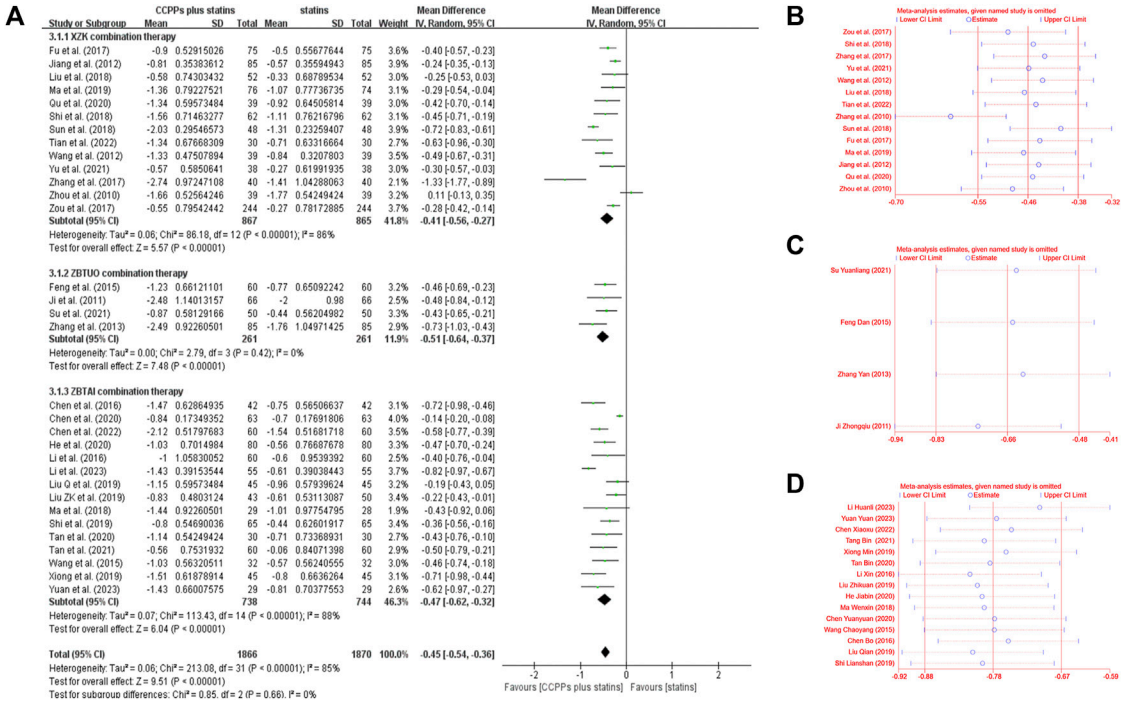


FIGURE 6
Effect of RYR-containing CCPPs on LDL-C. **(A)** Forest plot of LDL-C. **(B)** Sensitivity analysis of XZK on LDL-C. **(C)** Sensitivity analysis of ZBTUO on LDL-C. **(D)** Sensitivity analysis of ZBTAI on LDL-C.

combination therapy, the results for all the subgroups were similar to the overall conclusions. Moreover, treatment duration did not affect XZK efficacy, and the CCPP dose did not affect ZBTAI efficacy. However, XZK combination therapy did not result in significant TC reduction when the dose of XZK was 1.2 g/time [MD: 0.41, 95%CI(−0.86, 0.04), $p = 0.08$] or when XZK was combined with simvastatin [MD: 0.35, 95%CI(−0.71, 0.01), $p = 0.06$]. In the case of ZBTAI combination therapy, there was no significant positive effect in reducing TC reduction when the treatment duration exceeded 2 months [MD: 0.78, 95% CI(−2.00, 0.45), $p = 0.21$], or when ZBTAI was used in combination with simvastatin [MD: 0.33, 95%CI(−0.76, 0.10), $p = 0.14$] or rosuvastatin [MD: 0.54, 95%CI(−1.22, 0.13), $p = 0.11$].

Given the heterogeneity in both XZK combination therapies and ZBTAI combination therapies, meta-regression was performed to investigate the source of heterogeneity. Notable, no linear relationships were identified between variables and the outcome indicators, suggesting that these variables were not the source of heterogeneity (Figure 5A). Furthermore, the funnel plot and Egger's test ($P_{XZK} = 0.267$) revealed no significant publication bias in XZK combination therapy (Figures 5B, C). However, the asymmetry of the funnel plot and the results of the Egger's test ($P_{ZBTAI} = 0.035$) performed the presence of publication bias (Figures 5D, E) in ZBTAI combination therapy. Furthermore, trim-and-fill test was performed to evaluate the influence of the publication bias on the explanation of the results; and the results suggested that some studied showing negative findings was unpublished, which could influence the conclusions (Supplementary Table S6; Supplementary Figure S1).

3.4.2 Low-density lipoprotein cholesterol (LDL-C)

Thirty-two RCTs involving 4,098 patients reported LDL-C levels, of which 13 trials focused on the XZK combination therapy, 15 trials focused on the ZBTAI combination therapy, and 4 trials focused on the ZBTUO combination therapy. Random effect model was chosen because of the strong heterogeneity ($I^2 = 86\%$, $p < 0.0001$). The results showed that RYR-containing CCPPs resulted in greater reductions in the LDL-C levels compared to statin [MD: 0.45, 95% CI(−0.54, −0.36), $p < 0.00001$], regardless of whether the patients were in XZK combination therapy group [MD: 0.37, 95% CI(−0.52, −0.22), $p < 0.00001$, $I^2 = 88\%$], ZBTAI combination therapy group [MD = −0.47, 95%CI(−0.62, −0.32), $p < 0.00001$, $I^2 = 88\%$], or ZBTUO combination therapy group [MD: 0.51, 95% CI(−0.64, −0.37), $p < 0.00001$, $I^2 = 0\%$], respectively (Figure 6A). Sensitivity analyses showed that the conclusions were reliable (Figures 6B–D).

The results of subgroup analyses showed that most subgroups were consistent with the overall findings, suggesting that most parameters did not significantly affect the notable efficacy of LDL-C reduction by RYR-containing CCPPs (Figure 7). However, when the dose of XZK was 1.2g/time [MD: 0.29, 95% CI(−0.72, 0.13), $p = 0.18$], the treatment duration was less than 3 months [MD: 0.32, 95%CI(−0.74, 0.1), $p = 0.13$] or XZK combined with simvastatin [MD: 0.18, 95%CI(−0.57, 0.21), $p = 0.37$], the XZK combination therapy did not show a significant positive effect in reducing LDL-C levels. Furthermore, in case of ZBTAI combination therapy, there was no significant positive effect on reducing LDL-C when the treatment duration exceeded 2 months [MD: 0.38, 95% CI(−0.86, 0.09), $p = 0.11$].

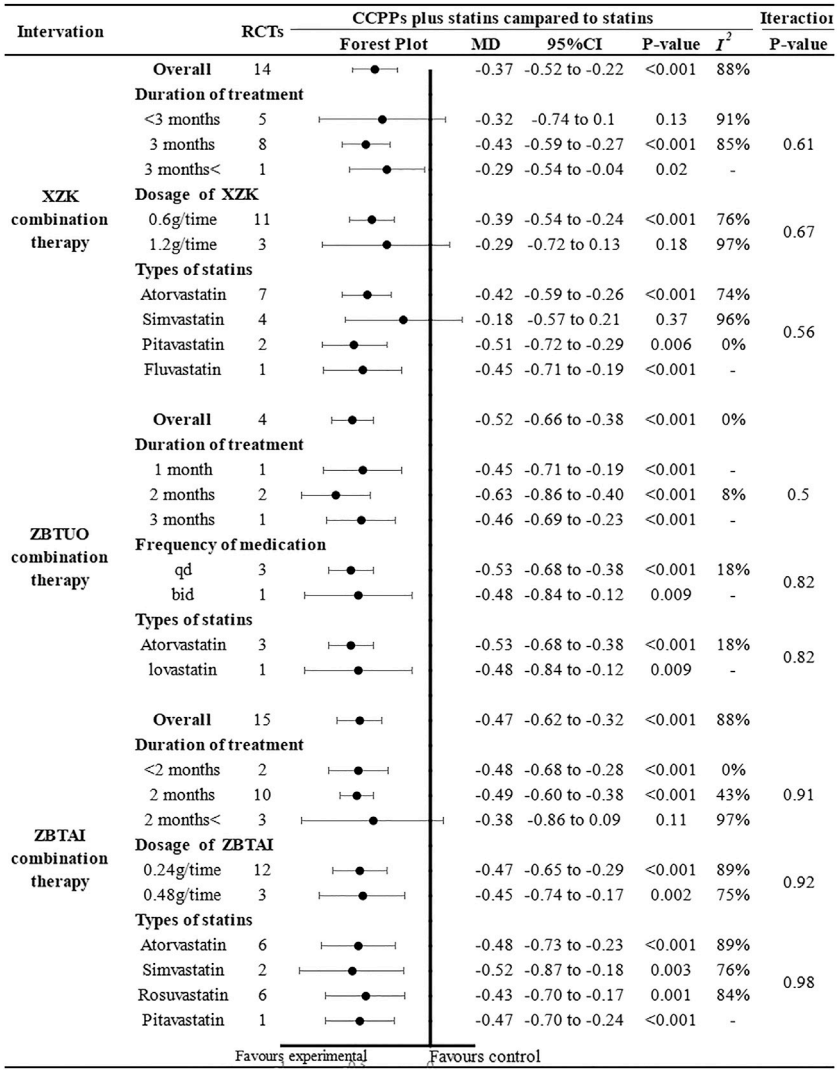


FIGURE 7
Subgroup analysis of the LDL-C.

Given the heterogeneity in ZBTAI combination therapy, the meta-regression was conducted and not found the sources of heterogeneity (Supplementary Table S7). Additionally, the funnel plot and Egger's test (P_{XZK} = 0.701) revealed that there was no significant publication bias in XZK combination therapy (Supplementary Figure S2). However, publication bias was found in ZBTAI combination therapy, and the results of trim-and-fill test suggested that publication bias could influence the conclusion (Supplementary Table S8; Supplementary Figure S3).

3.4.3 Triglyceride (TG)

Thirty-one RCTs involving 3,816 patients reported the triglyceride, of which 12 trials focused on the XZK combination therapy, 15 trials focused on the ZBTAI combination therapy, and 4 trials focused on the ZBTUO combination therapy. Random effect model was chosen because of the strong heterogeneity (I^2 = 74%, p < 0.0001). The results showed that RYR-containing CCPPs resulted in greater a reduction in TG levels compared to statin [MD: 0.33, 95% CI(−0.39, −0.26), p < 0.00001], regardless of whether the patients were in XZK combination therapy group [MD: 0.31, 95% CI(−0.41, −0.21), p < 0.00001, I^2 = 81%], ZBTAI combination therapy group [MD: 0.35, 95%CI(−0.45, −0.24), p < 0.00001, I^2 = 71%], or ZBTUO combination therapy group [MD: 0.28, 95% CI(−0.39, −0.17, p < 0.00001), I^2 = 17%] (Figure 8A). Sensitivity analyses showed that the conclusions were reliable (Figures 8B–D).

Further subgroup analyses were conducted and the results of most subgroups were consistent with the overall findings, suggesting that these parameters did not significantly influence the effect of both ZBTUO and ZBTAI on reducing the TG levels (Figure 9). However, in XZK combination therapy, there was no significant positive effect in reducing TG when the treatment duration exceeded 3 months [MD: 0.15, 95%CI(−0.32, 0.02), p = 0.09]. Notably, the high heterogeneity observed in XZK combination therapy was significantly reduced when subgroup analyses were conducted based on the statins types, suggesting that the type of statins was the source of heterogeneity. Furthermore, the difference in interaction effect among these subgroups of XZK combination therapy was highly significant ($P_{iteration}$ < 0.001) when the

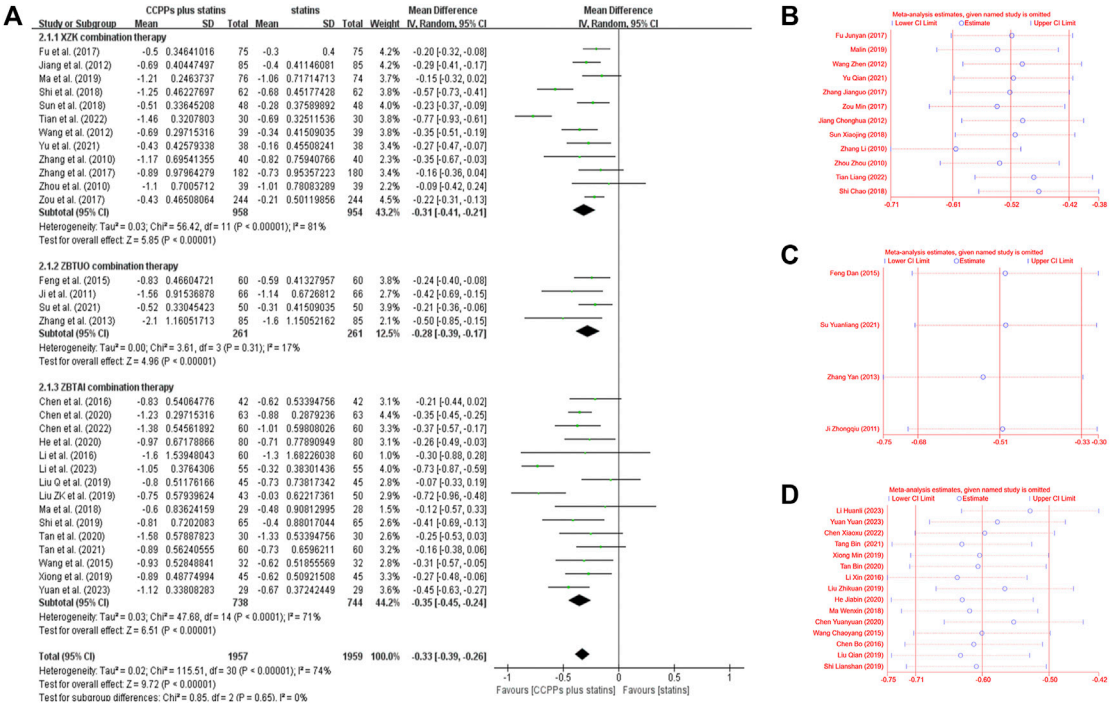


FIGURE 8
Effect of RYR-containing CCPPs on TG. **(A)** Forest plot of TG. **(B)** Sensitivity analysis of XZK on TG. **(C)** Sensitivity analysis of ZBTUO on TG. **(D)** Sensitivity analysis of ZBTAI on TG.

subgroup analyses were conducted based on the types of statins, and these results indicate that the combination of XZK with pitavastatin would be optimal for therapy.

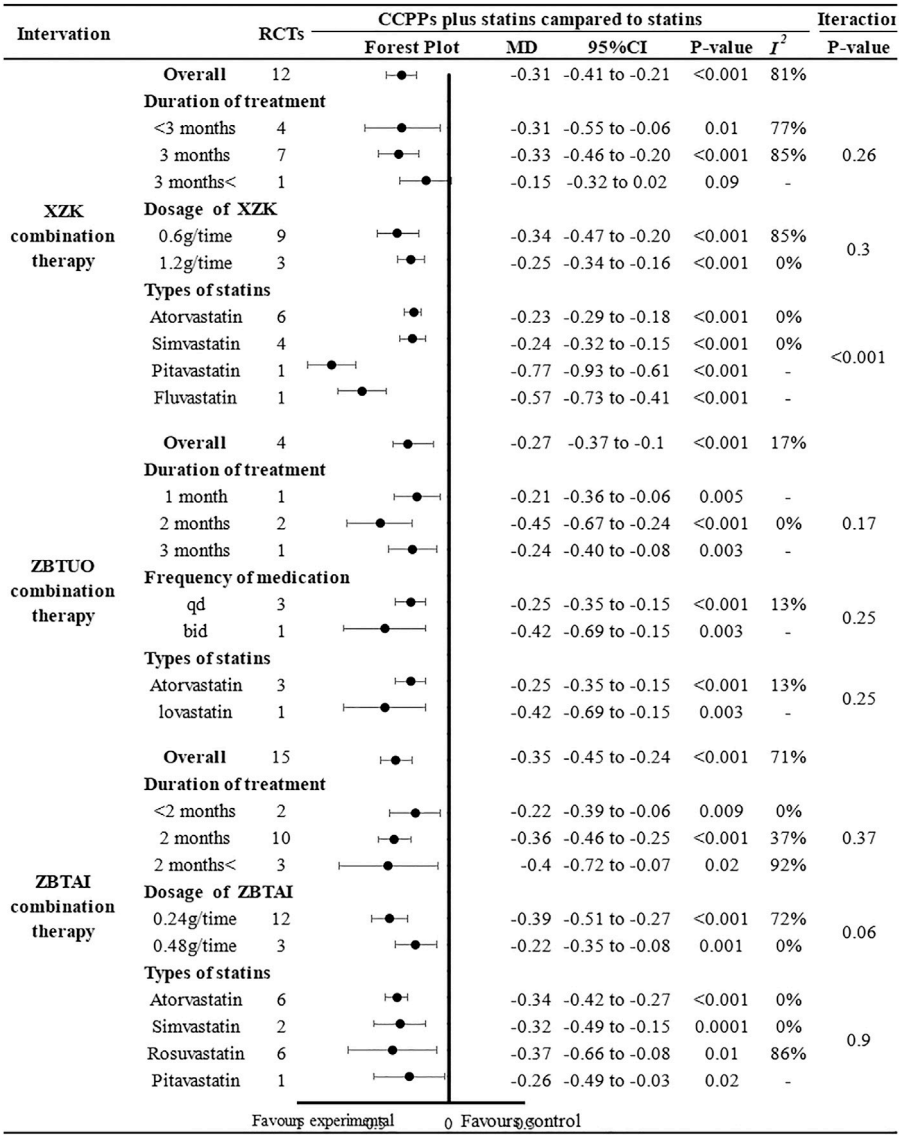
Given the heterogeneity in ZBTAI combination therapy, meta-regression was conducted and not found the sources of heterogeneity (Supplementary Table S9). Furthermore, the funnel plot and Egger's test (P_{XZK} = 0.623, P_{ZBTAI} = 0.253) revealed that there was no significant publication bias in both XZK and ZBTAI (Supplementary Figure S4).

3.4.4 High-density lipoprotein cholesterol (HDL-C)

Thirty-one RCTs reported the HDL-C levels, of which 12 trials focused on the XZK combination therapy, 15 trials focused on the ZBTAI combination therapy, and 4 trials focused on the ZBTUO combination therapy. Random effect model was chosen because of the strong heterogeneity (I^2 = 88%, p < 0.0001). The results showed that RYR-containing CCPPs resulted in greater improvements in HDL-C compared to statin [MD:0.21, 95%CI(0.17, 0.25), p < 0.00001], regardless of whether the patients were in XZK combination therapy group [MD:0.23, 95%CI(0.18, 0.29), p < 0.00001, I^2 = 79%], ZBTAI combination therapy group [MD:0.21, 95%CI(0.14, 0.28), p < 0.00001, I^2 = 88%], or ZBTUO combination therapy group [MD:0.13, 95%CI(0.02, 0.24), p < 0.00001, I^2 = 87%] (Figure 10A). Sensitivity analyses showed that the conclusions were reliable (Figures 10B–D).

Further subgroup analyses were performed to investigate the potential effects of specific parameters on the efficacy of RYR-containing CCPPs in improving HDL-C (Figure 11). (1) The results of all subgroups receiving XZK combination therapy were consistent with the overall findings. Additionally, the differences in interaction-related effects between these subgroups was highly significant ($P_{iteration}$ < 0.05) when subgroup analyses were conducted based on the XZK dose, and these results indicated an optimal treatment dose of 0.6 g/time. (2) As for ZBTAI combination therapy, it was significantly effective in improving HDL-C levels only when the treatment duration was 2 months [MD:0.17, 95% CI(0.11, 0.23), p < 0.00001]. Furthermore, there was no significant effect when ZBTAI combined with rosuvastatin [MD:0.11, 95% CI(–0.17, 0.39), p = 0.45]. It is worth noting that the difference in interaction effect between subgroups indicate an optimal treatment dose of 0.24g/time. (3) Furthermore, the differences in interaction-related effects between subgroups receiving ZBTUO combination therapy were highly significant ($P_{iteration}$<0.001) when subgroup analyses were based on the statins types or medication frequency. Furthermore, there was no significant positive effect of ZBTUO in reducing HDL-C levels when the medication frequency was bid [MD:0.01, 95%CI(–0.05, 0.07), p = 0.76], treatment duration was 2 months [MD:0.15, 95%CI(–0.13, 0.42), p = 0.29], or ZBTUO was combined with lovastatin [MD:0.01, 95%CI(–0.05, 0.07), p = 0.76].

Given the heterogeneity in ZBTAI combination therapy, ZBTUO combination therapy, and XZK combination therapy, the meta-regression was conducted, but sources of heterogeneity could not be identified (Supplementary Table S10). Additionally, the funnel plot and Egger's test (P_{ZBTAI} = 0.115) suggested that there was no significant publication bias in ZBTAI combination therapy (Supplementary Figure S5). However, publication bias was found in XZK combination therapy, and the result of trim-and-fill test suggested that publication bias could influence the conclusions (Supplementary Table S11; Supplementary Figure S6).



Intervation		RCTs	CCPPs plus statins campared to statins				Iteractior
			Forest Plot	MD	95%CI	P-value	I^2	P-value
XZK combination therapy	**Overall**	12		-0.31	-0.41 to -0.21	<0.001	81%	
	Duration of treatment							
	<3 months	4		-0.31	-0.55 to -0.06	0.01	77%	
	3 months	7		-0.33	-0.46 to -0.20	<0.001	85%	0.26
	3 months<	1		-0.15	-0.32 to 0.02	0.09	-	
	Dosage of XZK							
	0.6g/time	9		-0.34	-0.47 to -0.20	<0.001	85%	0.3
	1.2g/time	3		-0.25	-0.34 to -0.16	<0.001	0%	
	Types of statins							
	Atorvastatin	6		-0.23	-0.29 to -0.18	<0.001	0%	
	Simvastatin	4		-0.24	-0.32 to -0.15	<0.001	0%	<0.001
	Pitavastatin	1		-0.77	-0.93 to -0.61	<0.001	-	
	Fluvastatin	1		-0.57	-0.73 to -0.41	<0.001	-	
ZBTUO combination therapy	**Overall**	4		-0.27	-0.37 to -0.1	<0.001	17%	
	Duration of treatment							
	1 month	1		-0.21	-0.36 to -0.06	0.005	-	
	2 months	2		-0.45	-0.67 to -0.24	<0.001	0%	0.17
	3 months	1		-0.24	-0.40 to -0.08	0.003	-	
	Frequency of medication							
	qd	3		-0.25	-0.35 to -0.15	<0.001	13%	0.25
	bid	1		-0.42	-0.69 to -0.15	0.003	-	
	Types of statins							
	Atorvastatin	3		-0.25	-0.35 to -0.15	<0.001	13%	0.25
	lovastatin	1		-0.42	-0.69 to -0.15	0.003	-	
ZBTAI combination therapy	**Overall**	15		-0.35	-0.45 to -0.24	<0.001	71%	
	Duration of treatment							
	<2 months	2		-0.22	-0.39 to -0.06	0.009	0%	
	2 months	10		-0.36	-0.46 to -0.25	<0.001	37%	0.37
	2 months<	3		-0.4	-0.72 to -0.07	0.02	92%	
	Dosage of ZBTAI							
	0.24g/time	12		-0.39	-0.51 to -0.27	<0.001	72%	0.06
	0.48g/time	3		-0.22	-0.35 to -0.08	0.001	0%	
	Types of statins							
	Atorvastatin	6		-0.34	-0.42 to -0.27	<0.001	0%	
	Simvastatin	2		-0.32	-0.49 to -0.15	0.0001	0%	0.9
	Rosuvastatin	6		-0.37	-0.66 to -0.08	0.01	86%	
	Pitavastatin	1		-0.26	-0.49 to -0.03	0.02	-	

FIGURE 9
Subgroup analysis of the TG.

3.4.5 Clinical efficacy

Eighteen RCTs reported the clinical efficacy, of which 9 trials focused on the XZK combination therapy, 5 trials focused on the ZBTAI combination therapy, and 4 trials focused on the ZBTUO combination therapy. Fandom effect model was chosen because of the low heterogeneity ($I^2 = 0\%$, $p = 0.99$). The results showed that the RYR-containing CCPPs was superior to statin [RR:1.16, 95% CI(1.12 to 1,20, $p < 0.00001$, $I^2 = 0\%$], regardless of whether the patients were in XZK combination therapy group [RR:1.16, 95% CI(1.13, 1.19), $p < 0.00001$], ZBTAI combination therapy group [RR: 1.17, 95%CI(1.10, 1.25), $p < 0.00001$, $I^2 = 0\%$], or ZBTUO combination therapy group [RR:1.15, 95%CI(1.08, 1.23), $p < 0.00001$, $I^2 = 0\%$] (Figure 12A). Sensitivity analyses showed that the conclusions were reliable (Figures 12B–D).

Further subgroup analyses were conducted (Figure 13) and the results suggested that most subgroups were similar to the overall conclusions, indicating that the medication frequency, CCPP dose, and statin types did not significantly impact the efficacy of RYR-containing CCPPs. However, ZBTUO combination therapy did not show a significant positive effect at 1 month [RR:1.15, 95%CI(0.99, 1.33), $p = 0.07$] when considering the duration of treatment.

3.5 Adverse reactions

Eighteen RCTs reported adverse reactions. of which 8 trials focused on the XZK combination therapy, 9 trials focused on the ZBTAI combination therapy, and 1 trials focused on the ZBTUO combination therapy. Subgroup analysis (Figure 14) based on the type of adverse reaction demonstrated that XZK combination therapy was significantly better than statins in reducing the muscular adverse drug reactions [RR:0.06, 95%CI(0.02, 0.2), $p < 0.00001$, $I^2 = 30\%$] and gastrointestinal reactions [RR:0.18, 95%CI(0.08, 0.40), $p < 0.00001$, $I^2 = 62\%$]. However, there was no significant difference between the

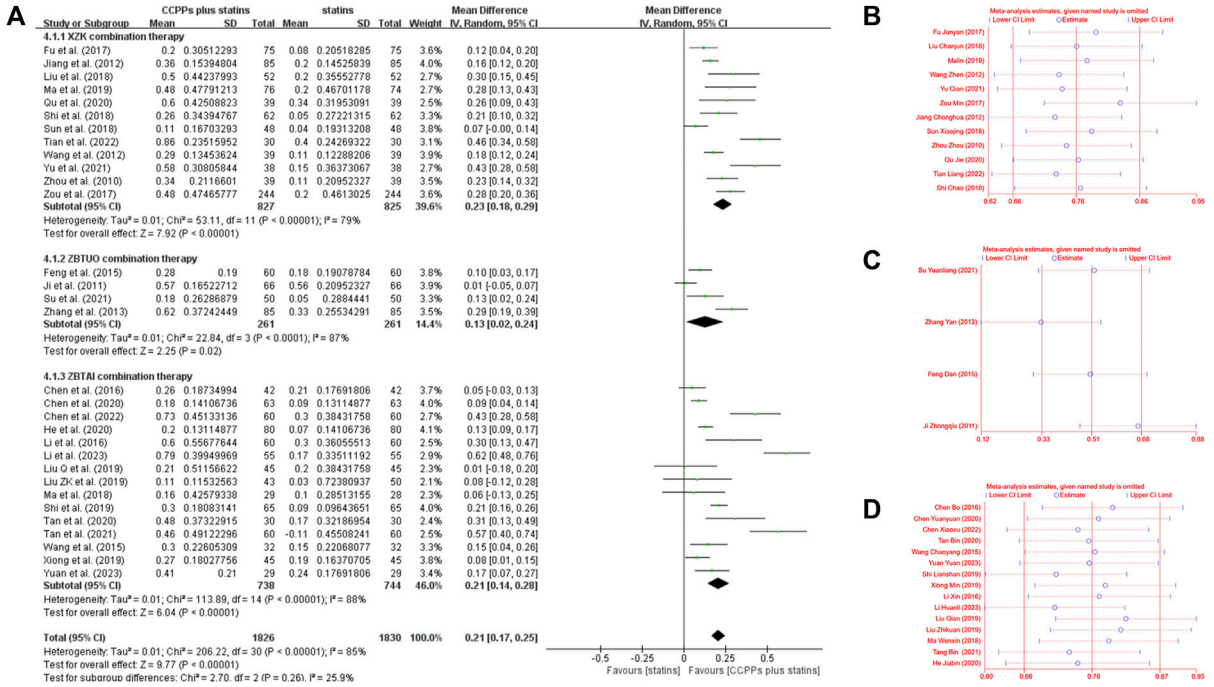


FIGURE 10
Effect of RYR-containing CCPPs on HDL-C. **(A)** Forest plot of HDL-C. **(B)** Sensitivity analysis of XZK on HDL-C. **(C)** Sensitivity analysis of ZBTUO on HDL-C. **(D)** Sensitivity analysis of ZBTAI on HDL-C.

XZK and statins in reducing liver injury. Similarly, the results indicated that there was no significant difference between the ZBTAI and statins in reducing the muscular adverse drug reactions, gastrointestinal reactions, and liver injuries. Additionally, there was no significant difference between the ZBTUO and statins in reducing the kidney injuries. Notably, for other adverse reactions such as dizziness, headache, palpitations and rashes, no significant differences were observed between the treatment group and statin group. (Details were shown in Supplementary Table S12).

3.6 Quality of evidence

The quality of outcomes were evaluated by GRADE system (Supplementary Table S13). The results showed high-quality evidence for clinical efficacy in XZK combination therapy. In addition, moderate-quality evidence was obtained with two outcome indicators (TC, LDL-C) in XZK combination therapy, three outcome indicators (TG, HDL-C, and clinical efficacy) in ZBTAI combination therapy, and four outcome indicators (TC, TG, HDL-C, and clinical efficacy) in ZBTUO combination therapy. The remaining five outcome indicators were rated as low-quality evidence. The reasons for reducing the quality of evidence included publication bias, heterogeneity among studies, and number of included RCTs.

3.7 Evaluation of SR

AMSTAR-2 and ROBIS were used to assess the methodological quality and risk of bias of this meta analysis by two investigators (ZP and MYY) who did not have conflict of interest with this research. The results (Supplementary Tables S14, S15) confirmed that the risk of bias was low, and there were no significant methodological errors.

4 Discussion

4.1 Summary of evidence

Dyslipidemia, particularly an elevated LDL-C level, is a pathogenic risk factor for ASCVD that results in disease burden on patients and significant economic implications on the nation (Mach et al., 2020). In light of existing medical management strategies, there is an urgent need to further explore and evaluate treatment modalities. This study conducted a assessment of the efficacy of RYR-containing CCPPs combined with statins for treating dyslipidemia. A total of 33 trials involving 4,098 dyslipidemia patients were included. The results demonstrated that RYR-containing CCPPs had a substantial impact on increasing HDL-C levels and clinical efficacies, and decreasing TC, TG, and LDL-C levels, regardless of whether the administration of XZK, ZBTAI, or ZBTUO combination therapies. However, apart from the clinical efficacies, all the other results mentioned above exhibit heterogeneity. Furthermore, publication bias diminished our confidence in these results. The European Food Safety Authority has issued an opinion regarding a causal relationship between RYR administration and plasma LDL-C level reduction (EFSA Panel on Dietetic ProductsNutrition and Allergies, 2011). In addition, pharmacological research has indicated that monacolins, a complex of substances and an active

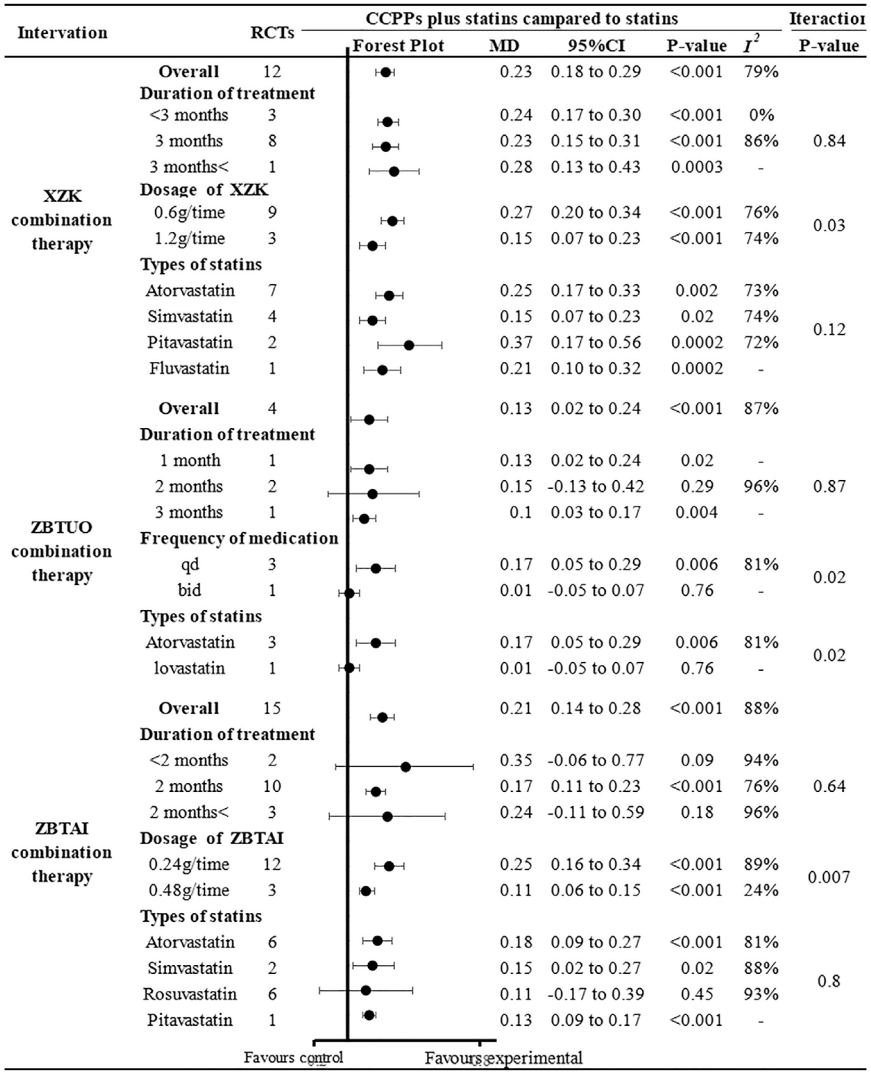


FIGURE 11
Subgroup analysis of the HDL-C.

metabolite of red yeast rice, possess a lactone form that is structurally identical to lovastatin. Monacolin K exhibits hypocholesterolemic effects by effectively and reversibly inhibiting β-hydroxyβ-methylglutaryl coenzyme A reductase (HMG-CoA), which is a crucial enzyme responsible for catalyzing the rate-limiting step in cholesterol biosynthesis, in a manner similar to that of other statins (Younes et al., 2018; Cicero et al., 2023). Notably, despite their identical structure, monacolin K and lovastatin exhibit different pharmacokinetic profiles and bioavailabilities (Banach et al., 2022; Buzzelli et al., 2023).

Moreover, increasing evidence suggests that statins have multiple adverse reactions, including liver and kidney injury, gastrointestinal reactions, and muscular adverse drug reactions. Hence, additional therapeutic options are needed to reduce the occurrence of adverse reactions (Stroes et al., 2015). Evidence from this study reveals that combining ZBTAI or XZK with statins significantly reduces the incidence of gastrointestinal disturbances and muscular adverse drug reactions. Current research also indicates that RYR-containing CCPPs do not increase the occurrence of other adverse reactions. A previous study showed that RYR demonstrates excellent tolerability even in dyslipidemia patients intolerant to statins, and these conclusions are similar to the results of this study (Cicero et al., 2017). Notably, another study revealed no significant association between monacolin K administration and an increased risk of musculoskeletal disorders (Awad et al., 2017; Fogacci et al., 2019). Moreover, a study showed that RYR exhibited a good safety profile with regard to the incidence of liver abnormalities and kidney injury (Gerards et al., 2015).

4.2 Secondary findings

Although RYR-containing CCPPs are widely used in clinical practice due to their safety and reliable efficacy, the credibility of the evidence has been diminished due to the lack of clarity regarding the optimal dose and treatment duration as well as the lack of data on drug combinations, which have posed

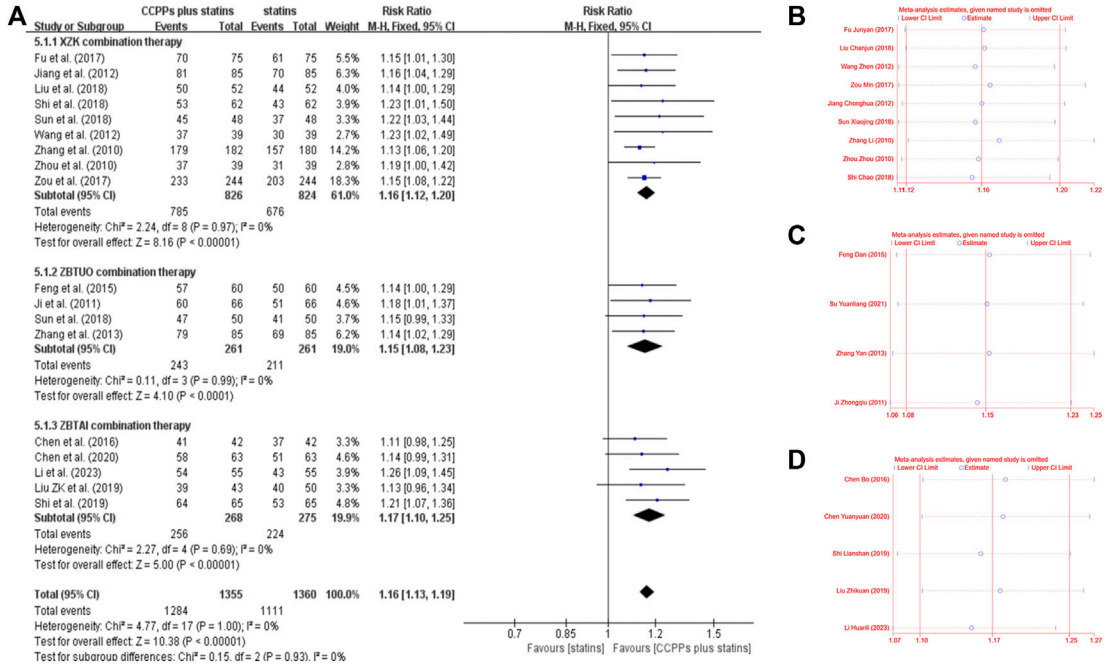


FIGURE 12
Effect of RYR-containing CCPPs on clinical efficacy. **(A)** Forest plot of clinical efficacy. **(B)** Sensitivity analysis of XZK on clinical efficacy. **(C)** Sensitivity analysis of ZBTUO on clinical efficacy. **(D)** Sensitivity analysis of ZBTAI on clinical efficacy.

challenges for clinical drug use (Ma et al., 2022). Therefore, Preplanned subgroup analysis was conducted to investigate the impact of treatment duration, statin type, and CCPP dose on the efficacy of RYR-containing CCPPs. With regard to the XZK capsule, we found that the optimal dose for improving HDL-C levels was 0.6 g/time, which aligned with the recommendations outlined in Chinese lipid management guidelines (Management, 2023). Conversely, no positive effect was observed on the reduction of LDL-C and TC levels when XZK was administered at a dose of 1.2 g/time. Furthermore, we found the source of heterogeneity among TGs was attributed to the statin types, and identified that the combination of XZK with pivastatin yielded the best therapeutic outcomes for reducing TG levels. An optimal dose of 0.24 g/time of the ZBTAI capsule, another common red yeast rice containing CCPPs, was found to improve HDL-C levels. While the number and quality of included studies may affect the credibility of these conclusions, the results can provide new ideas and directions for clinical research.

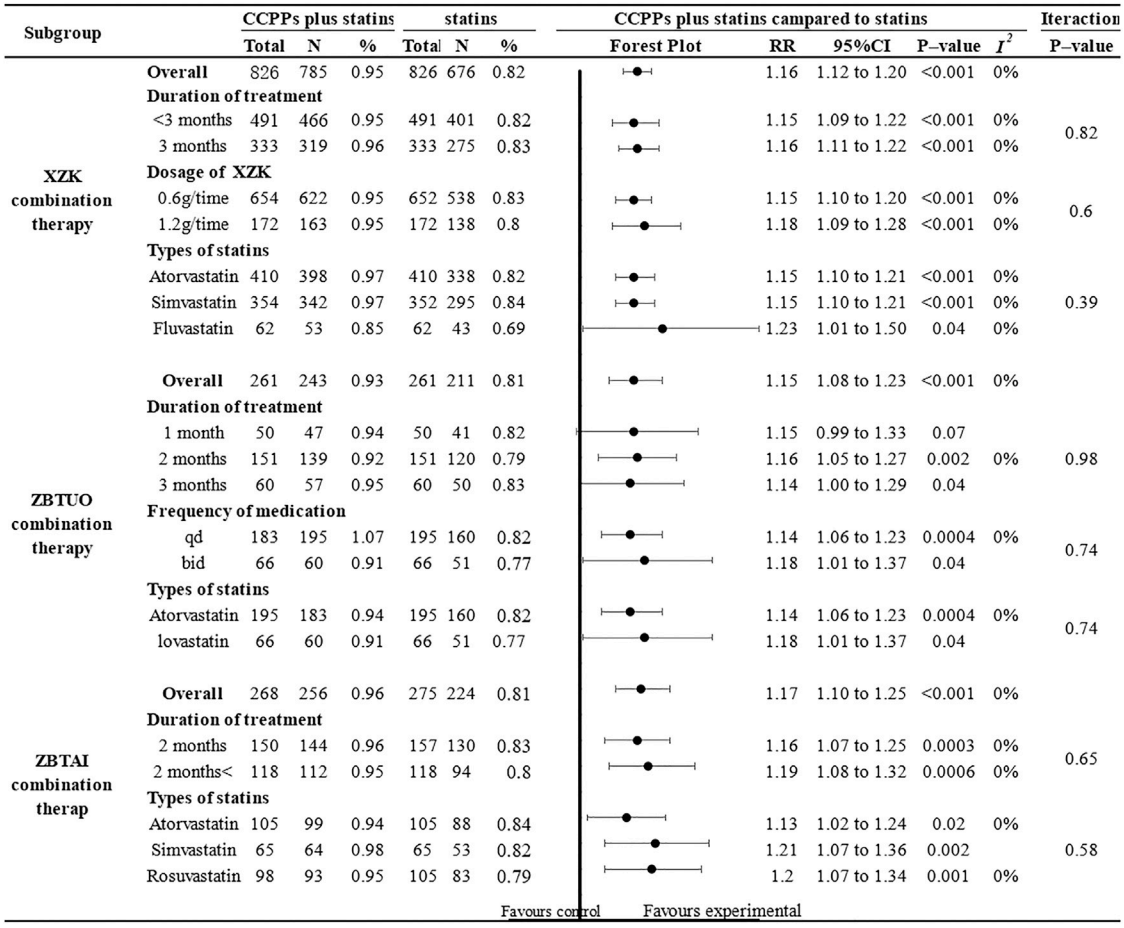
Due to the concept of "discontinue medication as soon as you observe effects" in traditional Chinese medicine theory, a clear medication course is not outlined for most CCPPs. However, long-term medication burdens the liver and kidney and results in other adverse reactions. Hence, it was necessary to assess the treatment duration (Cao et al., 2022). In this study, subgroup analysis based on CCPP treatment durations revealed that the optimal duration for XZK combination therapy was 3 months. Notably, our findings also indicated ZBTAI had a significant effect on improving blood lipid levels when the duration of treatment was 2 months. However, the above conclusions still need to be treated with caution and further research is necessary to validate them.

4.3 Quality of evidence

Given the high levels of heterogeneity of outcome indicators, meta-regression tests were used to found the sources of heterogeneity. Despite diligent efforts to mitigate heterogeneity, some outcome measures still exhibit heterogeneity, prompting cautious interpretation of conclusions. Notable, sensitivity analysis suggested the robustness of existing findings. Moreover, a trim-and-fill analysis revealed that several RCTs with negative results were unpublished. Therefore, caution must be exercised as these negative trials have the potential to overturn our current conclusions upon publication. Our assessment of the quality of evidence for outcome indicators indicated that most indicators had at least one factor leading to a downgrade. Specifically, one, nine, and five outcome indicators were rated as "high", "moderate", and "low" in terms of quality of evidence, respectively.

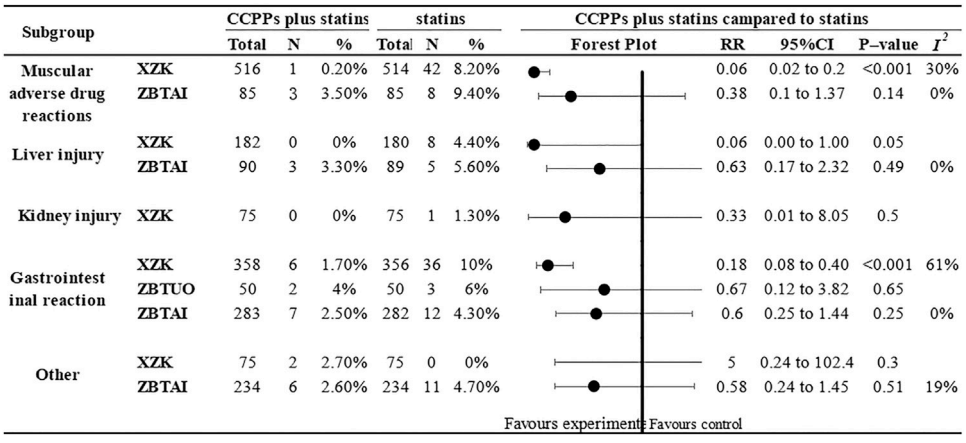
4.4 Advantages and limitations

This study provides updated evidence and has several advantages over previous research. In terms of interventions, we evaluated the efficacy of different types of RYR-containing CCPPs used for dyslipidemia treatment. Data regarding adverse reactions, categorized as liver and kidney injury, gastrointestinal reactions, and muscular adverse drug reactions, provided comprehensive evidence for assessing the safety of RYR-containing CCPPs. Meanwhile, adequate subgroup analyses of RYR-containing CCPPs were performed according to the characteristics of included studies, such as treatment duration, CCPPs dose, and drug combinations, and provided reliable evidence regarding the efficacy estimates of



Subgroup		CCPPs plus statins			statins			CCPPs plus statins campared to statins				Iteraction
		Total	N	%	Total	N	%	Forest Plot	RR	95%CI	P–value	I^2	P–value
XZK combination therapy	Overall	826	785	0.95	826	676	0.82		1.16	1.12 to 1.20	<0.001	0%	
	Duration of treatment												
	<3 months	491	466	0.95	491	401	0.82		1.15	1.09 to 1.22	<0.001	0%	0.82
	3 months	333	319	0.96	333	275	0.83		1.16	1.11 to 1.22	<0.001	0%	
	Dosage of XZK												
	0.6g/time	654	622	0.95	652	538	0.83		1.15	1.10 to 1.20	<0.001	0%	0.6
	1.2g/time	172	163	0.95	172	138	0.8		1.18	1.09 to 1.28	<0.001	0%	
	Types of statins												
	Atorvastatin	410	398	0.97	410	338	0.82		1.15	1.10 to 1.21	<0.001	0%	
	Simvastatin	354	342	0.97	352	295	0.84		1.15	1.10 to 1.21	<0.001	0%	0.39
	Fluvastatin	62	53	0.85	62	43	0.69		1.23	1.01 to 1.50	0.04	0%	
ZBTUO combination therapy	Overall	261	243	0.93	261	211	0.81		1.15	1.08 to 1.23	<0.001	0%	
	Duration of treatment												
	1 month	50	47	0.94	50	41	0.82		1.15	0.99 to 1.33	0.07		
	2 months	151	139	0.92	151	120	0.79		1.16	1.05 to 1.27	0.002	0%	0.98
	3 months	60	57	0.95	60	50	0.83		1.14	1.00 to 1.29	0.04		
	Frequency of medication												
	qd	183	195	1.07	195	160	0.82		1.14	1.06 to 1.23	0.0004	0%	0.74
	bid	66	60	0.91	66	51	0.77		1.18	1.01 to 1.37	0.04		
	Types of statins												
	Atorvastatin	195	183	0.94	195	160	0.82		1.14	1.06 to 1.23	0.0004	0%	0.74
	lovastatin	66	60	0.91	66	51	0.77		1.18	1.01 to 1.37	0.04		
ZBTAI combination therap	Overall	268	256	0.96	275	224	0.81		1.17	1.10 to 1.25	<0.001	0%	
	Duration of treatment												
	2 months	150	144	0.96	157	130	0.83		1.16	1.07 to 1.25	0.0003	0%	0.65
	2 months<	118	112	0.95	118	94	0.8		1.19	1.08 to 1.32	0.0006	0%	
	Types of statins												
	Atorvastatin	105	99	0.94	105	88	0.84		1.13	1.02 to 1.24	0.02	0%	
	Simvastatin	65	64	0.98	65	53	0.82		1.21	1.07 to 1.36	0.002		0.58
	Rosuvastatin	98	93	0.95	105	83	0.79		1.2	1.07 to 1.34	0.001	0%	

FIGURE 13
Subgroup analysis of the clinical efficacy.



Subgroup		CCPPs plus statins			statins			CCPPs plus statins campared to statins				
		Total	N	%	Total	N	%	Forest Plot	RR	95%CI	P–value	I^2
Muscular adverse drug reactions	XZK	516	1	0.20%	514	42	8.20%		0.06	0.02 to 0.2	<0.001	30%
	ZBTAI	85	3	3.50%	85	8	9.40%		0.38	0.1 to 1.37	0.14	0%
Liver injury	XZK	182	0	0%	180	8	4.40%		0.06	0.00 to 1.00	0.05	
	ZBTAI	90	3	3.30%	89	5	5.60%		0.63	0.17 to 2.32	0.49	0%
Kidney injury	XZK	75	0	0%	75	1	1.30%		0.33	0.01 to 8.05	0.5	
Gastrointestinal reaction	XZK	358	6	1.70%	356	36	10%		0.18	0.08 to 0.40	<0.001	61%
	ZBTUO	50	2	4%	50	3	6%		0.67	0.12 to 3.82	0.65	
	ZBTAI	283	7	2.50%	282	12	4.30%		0.6	0.25 to 1.44	0.25	0%
Other	XZK	75	2	2.70%	75	0	0%		5	0.24 to 102.4	0.3	
	ZBTAI	234	6	2.60%	234	11	4.70%		0.58	0.24 to 1.45	0.51	19%

FIGURE 14
Subgroup analysis of the adverse reaction.

CCPPs. Notably, trim-and-fill analysis was used to evaluate the influence of publication bias on result interpretation, and meta-regression analyses were used to identify the source of heterogeneity, while sensitivity analysis was used to confirm the robustness of conclusions. Finally, the GRADE approach was employed to assess the overall strength of the evidence for each outcome measure. ROBIS and AMSTAR-2 were used to evaluate this study, which enhanced the credibility of the results.

However, this study is associated with several weaknesses. First of all, although this SR conducted a comprehensive literature search, the included studies were all conducted in China, and most of the studies were small sample studies, which may lead to low efficiency of statistical test. Second, our study did not evaluate the long-term efficacy of CCPPs, which is an important aspect of clinical evaluation. Third, subgroup analyses were conducted to investigate the effects of different types of dyslipidemia on the efficacy of RYR-containing CCPPs. However, only one of the included studies identified the types of dyslipidemia, which hindered the further evaluation of efficacy. Fourth, the majority of the included RCTs did not report about allocation concealment and blinding, which could affect the accuracy and reliability of the analysis results. Finally, although sensitivity analyses confirmed the robustness of these conclusions, existing conclusions need to be treated with caution due to heterogeneity and publication bias. In particular, the trim-and-fill analysis showed that some RCTs with negative results were not published, which would affect the reliability of the study results.

4.5 Implications for practice

Several invaluable suggestions were proposed for future research based on the findings and limitations of this study. Given the inconsistent results of subgroup analyses, further investigations are needed to explore the optimal dose and duration. Additionally, this study did not outline definitive conclusions regarding the effect of disease subtypes on treatment efficacy, which could be clinically significant. Therefore, future studies should identify the types of dyslipidemia and investigate the most effective treatments for each subtype. Considering the high incidence of dyslipidemia, long-term efficacy should be included as an outcome indicator in future trials. Furthermore, a trim-and-fill analysis revealed that some unpublished studies with negative findings would potentially impact existing conclusions. Hence, it is crucial to avoid selective reporting bias in future studies. In terms of clinical study more large-sample, multi-center, long-period RCTs should be conducted, and strictly follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines to standardize research reports and make research more transparent. Moreover, it is crucial to conduct reasonable sample size estimation and implement random allocation, allocation concealment, and blinding methods in future studies. In summary, due to the limitations of this study, the results should be interpreted with caution until further confirmation of well-designed RCTs.

5 Conclusion

The combination of red yeast rice-containing CCPPs with statins appears to improve lipid profiles and clinical efficacy in patients with dyslipidemia, and has certain safety. However, due to the poor quality of the included studies, and some studied showing negative findings was unpublished. The results should be interpreted with caution until further confirmation by rigorous designs RCTs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

MS: Conceptualization, Data curation, Formal Analysis, Validation, Writing–original draft, Writing–review and editing. TS: Conceptualization, Formal Analysis, Writing–original draft. CZ: Data curation, Writing–original draft. YM: Methodology, Conceptualization, Writing–original draft. BP: Conceptualization, Formal Analysis, Writing–review and editing. LC: Conceptualization, Writing–review and editing. ZJ: Conceptualization, Formal Analysis, Writing–original draft. FY: Conceptualization, Writing–review and editing. JZ: Conceptualization, Resources, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by National Multidisciplinary Innovation Team of Traditional Chinese Medicine (ZYYCXTD-D-202204), National Natural Science Foundation of China (82074583), the Science and Technology Program of Haihe Laboratory of Modern Chinese Medicine in China (22HHZYJC00006).

Acknowledgments

The authors thank all the colleagues who contributed to this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1398934/full#supplementary-material

References

Awad, K., Mikhailidis, D. P., Toth, P. P., Jones, S. R., Moriarty, P., Lip, G., et al. (2017). Efficacy and safety of alternate-day versus daily dosing of statins: a systematic review and meta-analysis. *Cardiovasc Drugs Ther.* 31, 419–431. doi:10.1007/s10557-017-6743-0

Banach, M., Catapano, A. L., Cicero, A., Escobar, C., Foger, B., Katsiki, N., et al. (2022). Red yeast rice for dyslipidaemias and cardiovascular risk reduction: a position paper of the International Lipid Expert Panel. *Pharmacol. Res.* 183, 106370. doi:10.1016/j.phrs.2022.106370

Buzzelli, L., Segreti, A., Di Gioia, D., Lemme, E., Squeo, M. R., Nenna, A., et al. (2023). Alternative lipid lowering strategies: State-of-the-art review of red yeast rice. *FITOTERAPIA* 172, 105719. doi:10.1016/j.fitote.2023.105719

Cao, J., Li, X., Li, C., Xue, C., Chen, S., Gao, S., et al. (2022). Expert consensus on clinical application of Chinese patent medicine(first edition). *Chin. Pharm. J.* 57, 502–506. doi:10.11669/cpj.2022.06.012

Chen, B., Luo, J., and Wang, C. (2016). Effect of Zhibitai capsule on blood lipids and hypersensitive C-reactive protein in patients with hyperlipidemia. *Chin. J. Integr. Med. Cerebrovasc. Dis.* 14, 420–422. doi:10.3969/j.issn.1672-1349.2016.04.028

Chen, X., Ma, L., Guo, F., and Hao, L. (2022). Influence of zhebitai combined with atorvastatin on hsCRP level and IMTin patients with coronary heart disease complicated with hyperlipidemia. INNER Mongolia. *Med. J.* 54, 1305–1308. doi:10.16096/J.cnki.nmgyxzz.2022.54.11.006

Chen, Y., Liu, Q., Chen, Q., and Zhou, J. (2020). Clinical effect of Zhibitai capsule in the treatment of senile hyperlipidemia patients with phlegm and blood stasis syndrome. *Chin. J. Prim. Med. Phar* 27, 733–737. doi:10.3760/cma.j.issn.1008-6706.2020.06.020

Cicero, A., Colletti, A., Bajraktari, G., Descamps, O., Djuric, D. M., Ezhov, M., et al. (2017). Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Nutr. Rev.* 75, 731–767. doi:10.1093/nutrit/nux047

Cicero, A., Fogacci, F., Stoian, A. P., and Toth, P. P. (2023). Red yeast rice for the improvement of lipid profiles in mild-to-moderate hypercholesterolemia: a narrative review. *NUTRIENTS* 15, 2288. doi:10.3390/nu15102288

Collins, R., Reith, C., Emberson, J., Armitage, J., Baigent, C., Blackwell, L., et al. (2016). Interpretation of the evidence for the efficacy and safety of statin therapy. *LANCET* 388, 2532–2561. doi:10.1016/S0140-6736(16)31357-5

Dai, N., Zhao, F. F., Fang, M., Pu, F. L., Kong, L. Y., and Liu, J. P. (2022). Gynostemma pentaphyllum for dyslipidemia: a systematic review of randomized controlled trials. *Front. Pharmacol.* 13, 917521. doi:10.3389/fphar.2022.917521

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) (2011). Scientific opinion on the substantiation of health claims related to monacolin K from red yeast rice and maintenance of normal blood LDL cholesterol concentrations (ID 1648, 1700) pursuant to Article 13 (1) of Regulation (EC) No 1924/2006. *EFSA J.* 9, 2304. doi:10.2903/j.efsa.2011.2304

Feng, D. (2015). Effect of lipids and hypersensitive C-reactive protein in elderly patients with dyslipidemia. *Chin. Prat. Med.* 10, 151–152. doi:10.14163/j.cnki.11-5547/r.2015.15.102

Fogacci, F., Banach, M., Mikhailidis, D. P., Bruckert, E., Toth, P. P., Watts, G. F., et al. (2019). Safety of red yeast rice supplementation: a systematic review and meta-analysis of randomized controlled trials. *Pharmacol. Res.* 143, 1–16. doi:10.1016/j.phrs.2019.02.028

Ford, E. S., Ajani, U. A., Croft, J. B., Critchley, J. A., Labarthe, D. R., Kottke, T. E., et al. (2007). Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N. Engl. J. Med.* 356, 2388–2398. doi:10.1056/NEJMsa053935

Fu, Y. (2017). Effect of Xuezhikang capsule combined with atorvastatin calcium on hyperlipidemia. *Zhongguo Xiangcun Yiyao* 24, 52–53. doi:10.3969/j.issn.1006-5180.2017.24.029

Gerards, M. C., Terlou, R. J., Yu, H., Koks, C. H., and Gerdes, V. E. (2015). Traditional Chinese lipid-lowering agent red yeast rice results in significant LDL reduction but safety is uncertain - a systematic review and meta-analysis. *ATHEROSCLEROSIS* 240, 415–423. doi:10.1016/j.atherosclerosis.2015.04.004

Gerhard-Herman, M. D. (2017). 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (vol 135, pg e686, 2017). *CIRCULATION* 135, E790. doi:10.1161/CIR.0000000000000501

Gonzalez-Padilla, D. A., and Dahm, P. (2021). Evidence-based urology: understanding GRADE methodology. *Eur. Urol. FOCUS* 7, 1230–1233. doi:10.1016/j.euf.2021.09.014

He, J. (2020). Efficacy and safety of Pivastatin in the treatment of dyslipidemia. *Chin. J. Integr. Med. Cerebrovasc. Dis.* 18, 3266–3269. doi:10.12102/j.issn.1672-1349.2020.19.031

Hu, Y., Chen, X., Hu, M., Zhang, D., Yuan, S., Li, P., et al. (2022). Medicinal and edible plants in the treatment of dyslipidemia: advances and prospects. *Chin. Med.* 17, 113. doi:10.1186/s13020-022-00666-9

Ji, Z., and Yi, Z. (2011). On the effect of lovastatin combined with Zhibituo in treating 132 patients of hyperlipemia. *J. Clin. Med. Pract.* 15, 74–75. doi:10.3969/j.issn.1672-2353.2011.03.024

Jiang, C., and Chen, Y. (2012). Clinical effect of Xuezhikang capsule combined with simvastatin in the treatment of hyperlipidemia Clinical effect of Xuezhikang capsule combined with simvastatin in the treatment of hyperlipidemia. *Strait Pharm. J.* 24, 140–141. doi:10.3969/j.issn.1006-3765.2012.11.075

Jiang, Y., Dong, Y., Zhou, F., Chen, J., Zhou, Y., Tian, C., et al. (2021). Research progress on chemical constituents, pharmacological action and clinical application of Fermentum Rubrum. *Chin. Tra Herb. Drug* 52, 7379–7388. doi:10.7501/j.issn.0253-2670.2021.23.034

Li, H. (2023). Effectiveness of Zhibitai capsule in the treatment of senile hyperlipidemia with phlegm-stasis interjunction and its influence on blood lipids and hemorheology. *ZHONGHUA YANGSHENG BAOJIAN* 41, 44–46. doi:10.3969/j.issn.1009-8011.2023.12.013

Li, X., Wang, Y., and Shao, C. (2016). Clinical efficacy and safety of Lipbitar combined with Rosuvastatin in the treatment of elderly patients with atherosclerotic heart disease complicated with dyslipidemia. *Chin. J. Pharm. Econ.* 11, 67–68. doi:10.12010/j.issn.1673-5846.2016.06.024

Liu, C., Xu, W., and Wang, J. (2018). Effect research on the hyperlipidemia patients treated by hematopoeia and atorvastatin calcium tablets. *Chin. case* 19, 92–94. doi:10.3969/j.issn.1672-2566.2018.10.033

Liu, Q., Tao, T., Wang, N., and Cai, R. (2019). Effect of Zhibitai combined with rosuvastatin on patients with dyslipidemia of coronary heart disease. *Clin. Med. Res. Pract.* 4, 29–30. doi:10.19347/j.cnki.2096-1413.201924012

Liu, Z. (2019). Clinical observation of Rosuvastatin and lipbitar in the treatment of type 2 diabetes mellitus with hyperlipidemia. *Guide Chin. Med.* 17, 122–123. doi:10.15912/j.cnki.gocm.2019.28.098

Lu, Z., Kou, W., Du, B., Wu, Y., Zhao, S., Brusco, O. A., et al. (2008). Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am. J. Cardiol.* 101, 1689–1693. doi:10.1016/j.amjcard.2008.02.056

Ma, J., Gao, X., Shi, Q., Fan, S., Chen, P., Cheng, J., et al. (2022). Application rationality of traditional Chinese medicine injections in our hospital from the perspective of adjuvant drug management. *Eval. Anal. Drug-Use Hosp. Chin.* 22, 750–753. doi:10.14009/j.issn.1672-2124.2022.06.025

Ma, L., and Deng, X. (2019). Observation on clinical efficacy of Xuezhikang combined with atorvastatin in the treatment of UA with elevated TG. *Chin. Prat. Med.* 14, 1–3. doi:10.14163/j.cnki.11-5547/r.2019.35.001

Ma, W., and Feng, X. (2018). Clinical effect of Zhibitai on hyperlipidemia of phlegm-stasis interjunction type. *Chin. J. Integr. Med. Cerebrovasc. Dis.* 16, 3341–3343. doi:10.12102/j.issn.1672-1349.2018.22.032

Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., et al. (2020). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur. HEART J.* 41, 111–188. doi:10.1093/eurheartj/ehz455

Management, J. C. O. T. (2023). Chinese guidelines for lipid management (2023). *Chin. Circ. J.* 38, 237–271. doi:10.3969/j.issn.1000-3614.2023.03.001

Page, M. J., Shamseer, L., and Tricco, A. C. (2018). Registration of systematic reviews in PROSPERO: 30,000 records and counting. *Syst. Rev.* 7, 32. doi:10.1186/s13643-018-0699-4

Pergolizzi, J. J., Coluzzi, F., Colucci, R. D., Olsson, H., LeQuang, J. A., Al-Saadi, J., et al. (2020). Statins and muscle pain. *Expert Rev. Clin. Pharmacol.* 13, 299–310. doi:10.1080/17512433.2020.1734451

Qu, J., Ren, Y., and Zhang, X. (2020). Effect of Xuezhikang capsule combined with pitavastatin in the treatment of coronary heart disease complicated with hyperlipidemia and its influenceson glucose and lipid metabolism and cardiac function. *Clin. Med. Res. Pract.* 5, 28–30. doi:10.19347/j.cnki.2096-1413.202033011

Shea, B. J., Reeves, B. C., Wells, G., Thuku, M., Hamel, C., Moran, J., et al. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ-BRIT Med. J.* 358, j4008. doi:10.1136/bmj.j4008

Shi, C., Wang, X., and Zhu, H. (2018). Clinical therapeutic effect of the Xuezhikang capsule combined with fluvastatin sodium on hyperlipidemia. *World Clin. Drug* 39, 43–46. doi:10.13683/j.wph.2018.01.009

Shi, L. (2019). Comparative analysis of simvastatin and Zhibitai capsules in the treatment of simple hyperlipidemia. *Guide Chin. Med.* 17, 96–97. doi:10.15912/j.cnki.gocm.2019.06.083

Soppert, J., Lehrke, M., Marx, N., Jankowski, J., and Noels, H. (2020). Lipoproteins and lipids in cardiovascular disease: from mechanistic insights to therapeutic targeting. *Adv. Drug Deliv. Rev.* 159, 4–33. doi:10.1016/j.addr.2020.07.019

Stroes, E. S., Thompson, P. D., Corsini, A., Vladutiu, G. D., Raal, F. J., Ray, K. K., et al. (2015). Statin-associated muscle symptoms: impact on statin therapy-European

atherosclerosis society consensus Panel statement on assessment, aetiology and management. *Eur. HEART J.* 36, 1012–1022. doi:10.1093/eurheartj/ehv043

Su, Y. (2021). Clinical observation of Zhibituo capsule combined with atorvastatin calcium treatment of hyperlipidemia. *Chin. Sci. Tech. J. database Med. Health*, 46–47.

Sun, X., Liu, X., and He, S. (2018). Effect of Xuezhikang Capsule combined with simvastatin on lipid regulating and excretion of urine albumin and endothelin-1 level in 24 hours. *Drug Eval. Res.* 41, 1094–1097. doi:10.7501/j.issn.1674-6376.2018.06.029

Tan, B. (2020). Effect of atorvastatin combined with Zhibitai on coronary heart disease complicated with hyperlipidemia. *Contemp. Med.* 26, 9–11. doi:10.3969/j.issn.1009-4393.2020.03.004

Tan, B., Wu, Y. J., and Yu, B. (2021). Clinical effect of rosuvastatin calcium tablets combined with zhibitai in the treatment of hyperlipidemia. *Chin. Mod. Med.* 28, 64–66. doi:10.3969/j.issn.1674-4721.2021.13.017

Tian, L. (2022). Clinical observation of Xuzhikang capsule combined with Pivastatin in the treatment of coronary heart disease (CHD) with hyperlipidemia. *Chin. Sci. Tech. J. database Med. Health*, 208–210.

Townsend, N., Nichols, M., Scarborough, P., and Rayner, M. (2015). Cardiovascular disease in Europe--epidemiological update 2015. *Eur. HEART J.* 36, 2696–2705. doi:10.1093/eurheartj/ehv428

Visseren, F., Mach, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Back, M., et al. (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur. HEART J.* 42, 3227–3337. doi:10.1093/eurheartj/ehab484

Wang, C., and Chen, H. (2015). Influence of zhibitai capsule combined with atorvastatin calcium tablet on blood lipid and inflammatory factors in elder patients with dyslipidemia. *Her. Med.* 34, 1047–1049. doi:10.3870/yydb.2015.08.015

Wang, C., Pang, W., Du, X., Zhai, J., Zhong, M., Zhuang, M., et al. (2022). Efficacy and safety of zhibitai in the treatment of hyperlipidemia: a systematic review and meta-analysis. *Front. Pharmacol.* 13, 974995. doi:10.3389/fphar.2022.974995

Wang, Z. (2012). Curative effect of Xuezhikang combined with atorvastatin on diabetic hyperlipidemia. *J. Cnin Foreign Med. Phar Res.* 10, 16–17. doi:10.3969/j.issn.1674-6805.2012.21.009

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. J., Collins, K. J., Dennison, H. C., et al. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of cardiology/American heart association task force on clinical practice guidelines. *HYPERTENSION* 71, 1269–1324. doi:10.1161/HYP.0000000000000066

Whiting, P., Savovic, J., Higgins, J. P. T., Caldwell, D. M., Reeves, B. C., Shea, B., et al. (2016). ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *J. Clin. Epidemiol.* 69, 225–234. doi:10.1016/j.jclinepi.2015.06.005

World Health Organization (2020). WHO reveals leading causes of death and disability worldwide: 2000-2019. Available at: https://www.who.int/zh/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019 (Accessed December 28, 2023).

Xiong, M. (2019). Effect of Zhibitai capsule on blood lipid index and inflammation in patients with hyperlipidemia. *Chin. Prescr. drug* 17, 108–109. doi:10.3969/j.issn.1671-945X.2019.12.064

Xu, D., Hu, J., Wu, Q., Du, Z., Xue, Y., Zhang, X., et al. (2018). Efficacy and safety of Zhibitai in combination with atorvastatin for lipid lowering in patients with coronary heart disease. *Oncotarget* 9, 9489–9497. doi:10.18632/oncotarget.18329

Younes, M., Aggett, P., Aguilar, F., Crebelli, R., Dusemund, B., Filipic, M., et al. (2018). Scientific opinion on the safety of monacolins in red yeast rice. *EFSA J.* 16, e05368. doi:10.2903/j.efsa.2018.5368

Yu, Q. (2021). Effect analysis of Xuezhikang capsule combined with atorvastatin in the treatment of hyperlipidemia. *Electron. J. Cerebrovasc. Dis. Integr. Chin. West. Med.* 9, 64–66. doi:10.16282/j.cnki.cn11-9336/r.2021.33.001

Yuan, Y., Luo, X., Wang, M., and Li, B. (2023). Clinical effect of zhibitai capsules combined with atorvastatin in the treatment of hyperlipidemia. *J. Cnin Foreign Med. Phar Res.* 2, 72–74. doi:10.3969/j.issn.1007-1180.2023.15.024

Zeljkovic, I., Dula, K., Babacanli, A., Kruljac, I., Mustapic, V., Brkljacic, D. D., et al. (2019). High prevalence of hyperlipidaemia in patients with AV re-entry tachycardia and AV nodal re-entry tachycardia. *Sci. Rep.* 9, 11502. doi:10.1038/s41598-019-47940-9

Zhang, J., Zhu, Z., Ma, J., and Wang, L. (2017). Effect of Xuezhikang on the prognosis of patients with coronary heart disease complicated with hyperlipidemia after interventional therapy. *World Chin. Med.* 12, 1594–1596. doi:10.3969/j.issn.1673-7202.2017.07.029

Zhang, L., and Tang, M. (2010). Clinical observation of Simvastatin and Xuezhikang in the treatment of hyperlipidemia. *J. North Sichuan Med. Coll.* 25, 548–550. doi:10.3969/j.issn.1005-3697.2010.06.014

Zhang, Y., Zhang, J., Yang, H., and Tan, Z. (2013). Efficacy of zhibituo combined with atorvastatin on type 2 diabetic patients with hyperlipidemia. *Clin. Med. Chin.* 29, 942–945. doi:10.3760/cma.j.issn.1008-6315.2013.09.016

Zhao, F., Chen, L., Jiang, Y., Guo, Y., Lu, L., Lu, C., et al. (2023). Red yeast rice preparations for dyslipidemia: an overview of systematic reviews and network meta-analysis. *J. Funct. FOODS* 104, 105508. doi:10.1016/j.jff.2023.105508

Zhou, Z. (2010). Clinical observation of 39 cases of hyperlipidemia treated by combination of traditional Chinese and Western medicine. *Guid J. Tradit. Chin. Med. Pharm.* 16, 17–19. doi:10.3969/j.issn.1672-951X.2010.04.010

Zou, M. (2017). Effect of Xuezhikang capsule combined with atorvastatin in treatment of hyperlipidemia and lts influence on blood lipids and inflammatory factors. *World Chin. Med.* 12, 1824–1827. doi:10.3969/j.issn.1673-7202.2017.08.025

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 11 September 2024
DOI 10.3389/fphar.2024.1452545

OPEN ACCESS

EDITED BY
Zhongfeng Li,
Capital Normal University, China

REVIEWED BY
Lakshmi Manickavasagam Sundar,
M.S. Ramaiah University of Applied Sciences, India
Feng Zhang,
Nanjing University of Chinese Medicine, China

*CORRESPONDENCE
Kuiwu Yao,
yaokuiwu@126.com

RECEIVED 21 June 2024
ACCEPTED 29 August 2024
PUBLISHED 11 September 2024

CITATION
Yang Y, Sun Z, Sun X, Zhang J, Tong T, Zhang X and Yao K (2024) Protective effect of salvianolic acid B against myocardial ischemia/reperfusion injury: preclinical systematic evaluation and meta-analysis.
Front. Pharmacol. 15:1452545.
doi: 10.3389/fphar.2024.1452545

Protective effect of salvianolic acid B against myocardial ischemia/reperfusion injury: preclinical systematic evaluation and meta-analysis

Yuhan Yang[1], Ziyi Sun[1], Xiaoning Sun[1], Jin Zhang[1], Tong Tong[1], Xiaoxiao Zhang[1] and Kuiwu Yao[2]*

[1]Guang' anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Academic Management Service, China Academy of Chinese Medical Sciences, Beijing, China

Background: Salvianolic acid B is the most abundant water-soluble component in the traditional Chinese medicine Danshen and can reduce myocardial ischemia-reperfusion (MI/R) injury through multiple targets and pathways. However, the role of SalB in protecting the myocardium from ischemia/reperfusion injury remains unclear.

Purpose: To perform a preclinical systematic review and meta-analysis to assess the efficacy of Sal B in an animal model of myocardial infarction/reperfusion (MI/R) and to summarize the potential mechanisms of Sal B against MI/R.

Methods: Studies published from inception to March 2024 were systematically searched in PubMed, Web of Science, Embase, China National Knowledge Infrastructure Wanfang, and VIP databases. The methodological quality was determined using the SYRCLE RoB tool. The R software was used to analyze the data. The potential mechanisms are categorized and summarized.

Results: 32 studies containing 732 animals were included. The results of the meta-analysis showed that Sal B reduced myocardial infarct size ($p < 0.01$), and the cardiological indices of CK-MB ($p < 0.01$), CK ($p < 0.01$), LDH ($p < 0.01$), and cTnI ($p < 0.01$) compared to the control group. In addition, Sal B increased cardiac function indices, such as LVFS ($p < 0.01$), -dp/dt max ($p < 0.01$), +dp/dt max ($p < 0.01$), and cardiac output ($p < 0.01$). The protective effects of Sal B on the myocardium after I/R may be mediated by attenuating oxidative stress and inflammation, promoting neovascularization, regulating vascular function, and attenuating cardiac myocyte apoptosis. Publication bias was observed in all the included studies. Further studies are required to elucidate the extent of the cardioprotective effects of SalB and the safety of its use.

Conclusion: To the best of our knowledge, this is the first meta-analysis of Sal B in the treatment of MI/R injury, and Sal B demonstrated a positive effect on MI/R

injury through the modulation of key pathological indicators and multiple signaling pathways. Further studies are needed to elucidate the extent to which SalB exerts its cardioprotective effects and the safety of its use.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/.

KEYWORDS

animal model, salvianolic acid B(Sal B), myocardial ischaemia-reperfusion, metaanalysis, preclinical studies

1 Introduction

Myocardial infarction (MI) is caused by rupture or erosion of the epicardial coronary artery, coronary artery thrombosis, or atherosclerotic plaque formation, resulting in stenosis or occlusion of the coronary artery, leading to ischemia and hypoxia in the area of the myocardium supplied by the occluded artery. Severe and persistent ischemia and hypoxia cause irreversible damage to the myocardium, leading to death (Reed et al., 2017). According to statistics, more than seven million people worldwide are diagnosed with acute myocardial infarction (AMI) each year, and approximately 2.4 million people die of acute myocardial infarction (AMI) each year in the United States alone, resulting in an enormous health and economic burden (Yeh et al., 2010). Prompt reperfusion is the only way to save ischemic myocardium in myocardial infarction. Reperfusion has been shown to limit infarct size, improve long-term myocardial function, change the healing pattern of infarcted areas, and, more importantly, reduce mortality (Hausenloy et al., 2017). Data from France showed that between 1995 and 2015, the use of reperfusion therapy increased from 82% to 49%, whereas the 1-year mortality rate of reperfusion-treated patients decreased from 11.9% to 5.9% (Puymirat et al., 2019). Much experimental and clinical evidence supports the hypothesis that reperfusion causes additional myocardial damage. Neutrophil aggregation, calcium overload or redistribution, impaired mitochondrial energy synthesis, and burst production of oxygen free radicals occur during the reperfusion of coronary blood to ischemic tissues, further inducing myocardial injury and cardiomyocyte death, known as reperfusion injury (Heusch and Gersh, 2017). This has resulted in the current clinical dilemma that the mortality and morbidity associated with heart failure due to AMI remain high despite the increased use of reperfusion and improved methods (Sánchez-Hernández et al., 2020). Therefore, there is an urgent need for an effective therapy that can target myocardial reperfusion injury and reduce the size of the myocardial infarction. Myocardial ischemia/reperfusion (MI/R) injury is a complex pathology involving several mechanisms and molecules that cause damage to the heart. However, there are currently no satisfactory therapeutic strategies for mitigating myocardial ischemia-reperfusion injury, which may be since targeting one mechanism at a time may not be sufficient to produce a robust effect in a clinical situation where many uncontrolled variables commonly coexist (Heusch, 2020). Therefore, a multitargeted agent may be a potential avenue for addressing MI/R.

Danshen, a traditional Chinese medicine, is widely used in the treatment of angina pectoris, gastric pain, arthralgia, and menstrual disorders and is the main ingredient of Compound Danshen Dripping Pills, Danshen injections, and other medicines in the clinic (Li et al., 2018). The pharmacological effects of Salvia miltiorrhiza are mainly based on water-soluble components such as salicylic acid and fat-soluble components such as tanshinone, among which salvianolic acid B(Sal B) is the water-soluble component with the highest content (Wei et al., 2023). In recent years, researchers have focused on this promising small-molecule compound, and more preclinical studies on Sal B have been conducted. These studies suggest that Sal B exerts protective effects on ischemia-reperfusion myocardium through multiple targets, mainly through its anti-inflammatory and antioxidant effects, modulation of vasodilatation and contraction, promotion of neovascularization, and regulation of cell death functions (Ho and Hong, 2011). SalB also exerts anticoagulant, hypolipidemic, and indirect cardioprotective effects. SalB is a robust and active ingredient with an multi-target promising impact; however, no SalB injections are available on the market. A comprehensive assessment and systematic review of preclinical animal studies is essential before SalB enters clinical trials. Systematic reviews and meta-analyses can not only provide important information about the possibility of translating the results of experimental animal studies into clinical practice but also validate the efficacy, safety, and optimal dosage (Ritskes-Hoitinga et al., 2014).

To the best of our knowledge, no previous review has systematically summarized the effects of SalB in MI/R models.

Therefore, we performed a quality assessment and meta-analysis of preclinical studies using SalB in animal models to form a chain of clinical evidence and provide rigorous and systematic scientific support for further clinical studies.

2 Methods

This review was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The protocol was registered in PROSPERO (registration number: CRD42024526832).

2.1 Search strategy

We searched the following six databases: PubMed, EMBASE, Web of Science, China's National Knowledge Infrastructure (CNKI), WanFang, and the VIP database (VIP). The search strategy is based on the search components "Myocardial Ischemia," "Myocardial I/R," and "Salvianolic acid." The full search strategy is provided in the Supplementary Table 1. The search was limited from its inception to March 2024. We also screened the reference lists of the included studies to identify additional eligible studies.

2.2 Study selection

To minimize bias, the inclusion criteria were as follows: ①animal model of MI/R (modeling methods include ligation of LAD, ligation-reperfusion, and injection of ISO); ②The treatment group received only Sal B at any dose and treatment modality; ③The control group received only an equivalent amount of saline or vehicle or no treatment; ④The primary outcome of animal studies was infarct size, cardiac markers (CK, CK-MB, LDH, AST, and cTnI) and echocardiogram indicators (+dp/dt max, -dp/dt max, LVEF, LVFS, and cardiac output). Secondary outcomes were serum or protein levels associated with myocardial injury and biomarkers related to Sal B mechanisms.

The exclusion criteria were as follows: ①Case report, clinical trial, review, meeting abstract; ②The treatment group that received salvianolic acid complex or received Sal B in conjunction with other treatments; ③Animals with other disease comorbidities or No MI/R model; ④*In vitro or ex vivo* studies; ⑤No predetermined outcome index; ⑥No control group.

2.3 Data extraction

Two reviewers independently screened the retrieved studies' titles and/or abstracts using the search technique to identify articles that met the inclusion criteria mentioned above. They then retrieved all the texts of these possibly eligible studies and separately determined their eligibility. If they cannot agree on whether a particular study qualifies, they will be consulted with a third reviewer to resolve the dispute. To evaluate the research quality and the evidence synthesis, two impartial reviewers gathered data from the included studies using standardized pre-pilot forms.

The extracted information will include: ①first author name and year of publication; ②Specific details on the animals in each study, including species, number, sex, and body weight; ③MI/R model and the anesthetic method used to prepare the model; ④Information about Sal B treatment, including dose, method of administration, course of treatment; as well as corresponding information in the control group; ⑥The mean and standard deviation (SD) of the results. If the article presented results from many different time points or multiple doses of SalB, only data from the last time point or the highest dose group were extracted. Because some of the data were supplied only in graphical form, we attempted to contact the authors for further clarification. If we did not receive a response, we used digital ruler software to determine the value of the graph.

2.4 Assessment of the risk of bias

The two reviewers conduct an independent quality assessment using the SYRCLE's RoB tool (Hooijmans et al., 2014a), and any disagreements are resolved through consultation with the third reviewer.

2.5 Statistical analysis

R was used for statistical analysis. Heterogeneity was determined using the Q statistical test ($p < 0.05$, considered statistically significant) and the I^2 statistical test. Owing to the nature and diversity of animal studies, the random effects model may better reflect reality; thus, we used a random effects model for every outcome. If at least 10 independent comparisons were available, formal subgroup analyses were performed for the modeling method, dosage, method of administration, timing of administration, and species, and sensitivity analyses were performed to assess the robustness of the meta-analysis results. All results were continuous variables; therefore, standardized mean differences (SMDs) and 95% confidence intervals (95%CI) were used to express them. Publication bias was assessed using funnel plots and Egger's regression test.

3 Result

3.1 Study selection

A total of 888 articles were retrieved from the online database, 181 of which remained after duplicates were removed. 92 articles were retained after screening titles and abstracts. After full-text screening and assessment, 34 studies met the inclusion criteria. Because complete data were unavailable for two articles, 32 studies were ultimately included in this meta-analysis (Figure 1).

3.2 Study characteristics

Sprague-Dawley rats were used in 22 studies, Wistar rats in seven studies, ICR mice in one study, New Zealand rabbits, and 4-Way Ovoss in one study. In terms of sex, both female and male animals were used in 10 studies; one study used all female animals, one study did not explicitly report the sex of the animals, and all other studies used male animals. Fourteen of the included studies used ligation of the LAD, 13 used ligation-reperfusion, and the remaining five used ISO injection modeling. The three main routes of administration were intravenous (n = 15), intraperitoneal (n = 11), and gavage (n = 6). The dosage ranged from 3 to 120 mg/kg. In addition, the timing of Sal B administration varied, with 15 studies administering the drug prophylactically before modeling, 13 studies administering the drug after modeling or surgery, and the treatment time points of four studies were at other times. The treatment lasted 28 days Table 1 presents the characteristics of the included studies.

3.3 Risk of bias

Overall, 64.69% of the criteria were marked as "unclear" because basic information on the methodology was missing. For six criteria, all studies scored "unclear," namely, Sequence generation (selection bias); Baseline characteristics (selection bias); Allocation concealment (selection bias); Blinding investigators (performance bias); Random outcome assessment (measurement bias); Blinding outcome assessor (measurement bias). Among these studies, 53.12% reported that animals were randomly grouped and housed in rooms with the same controlled temperature and moderation. One study had a high risk of bias in selective reporting because the results were not fully reported. Eight studies did not report complete data and were therefore considered high-risk. Given the high number of

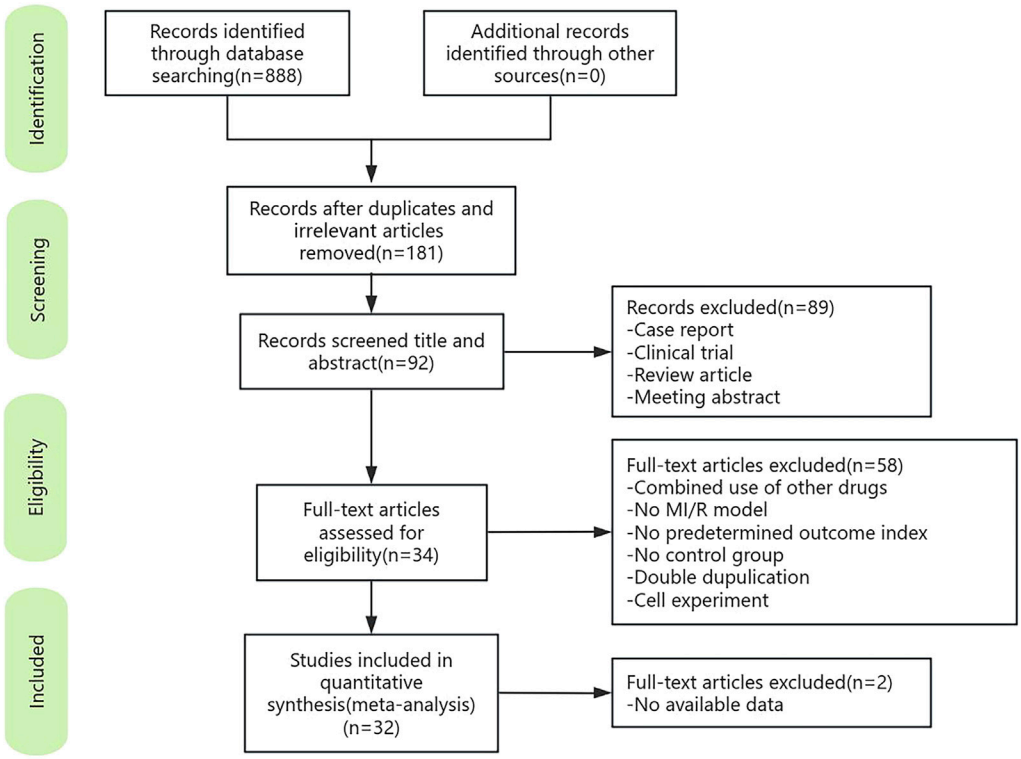


FIGURE 1
Summary of the process for identifying candidate studies.

"unclear" scores, none of the studies were considered to be at low risk of bias. The percentage of inter-evaluator agreement for the risk of bias assessment was 79.6%. The results of the quality assessment of the included studies are shown in Table 2.

3.4 Outcome measures

3.4.1 Infarct size

Nineteen studies reported the infarct size, but data were unavailable for one of these studies. Finally, 18 studies involving 309 animals were included in the meta-analysis. The results showed that Sal B was effective in reducing myocardial infarct size compared to the control group (SMD = −4.23, 95%CI(-5.88, −2.58), $p < 0.01$, $I^2 = 85\%$) (Figure 2). However, there was significant heterogeneity across the studies; therefore, sensitivity and subgroup analyses were conducted to explore the potential sources of heterogeneity. Sensitivity analyses were conducted by omitting individual studies that showed reliable results for infarct size (Supplementary Figure 1). Subsequently, separate subgroup analyses were performed based on modeling, administration method, time, dosage, and species (Table 3). The results showed that only the dosage subgroups were statistically significant. In addition, a substantial reduction in heterogeneity was found when blocking the LAD and Intravenous injection. Lower heterogeneity was likewise found in the dose less than 20 mg/kg dose subgroup, other administration time subgroup, and Wistar rat subgroup, but this was not statistically significant.

3.4.2 Cardiac markers

CK, CK-MB, LDH, AST, and cTnI are common markers of myocardial injury and are often measured in combination to monitor the extent of myocardial injury in clinical practice. This meta-analysis indicated that CK (SMD = −1.88, 95% CI(-2.42, −1.33), $p < 0.01$, $I^2 = 47\%$), CK-MB (SMD = −4.06, 95%CI(-5.35, −2.77), $p < 0.01$, $I^2 = 81\%$), LDH (SMD = −4.13, 95%CI(-5.93, −2.33), $p < 0.01$, $I^2 = 87\%$), and cTnI (SMD = −4.71, 95%CI(-7.14, −2.28), $p < 0.01$, $I^2 = 80\%$) were reduced after the Sal B intervention. The SMD for the treatment effect of Sal B on AST was not statistically significant (SMD = −3.71, 95%CI(-9.16, 1.73), $p = 0.18$, $I^2 = 92\%$) (Figure 3).

Heterogeneity was high for the latter four indicators, but only LDH had more than ten publications; thus, we performed sensitivity and subgroup analyses only for LDH. By progressively eliminating each trial from the meta-analysis, no significant differences were observed between the pre-and post-sensitivity pooled effects of LDH (Supplementary Figure 2). The results of the subgroup analyses showed that the differences between subgroups were not statistically significant (Table 4). Heterogeneity was reduced in the ISO group and the subgroup treated with doses less than 20 mg/kg; however, the difference was not statistically significant.

3.4.3 Cardiac function

Echocardiographic indicators, such as + dp/dt max, -dp/dt max, LVEF, LVFS, and cardiac output, can describe changes in cardiac function and structure in MI/R models. The results of this meta-analysis suggest that Sal B had a significant effect in increasing + dp/

TABLE 1 Characteristics of included studies.

Study ID	Species (sex, n=experimental/ control group)	Weight	Model (method)	Anesthetic	Treatment group(dosage)	Administration route	Control group	Outcomes
Qingju Li 2022 (Li et al., 2022)	Sprague–Dawley rats (male, n = 15/15)	250-300 g	Block LAD	pentobarbital sodium (30 mg/kg)	Sal B (32 mg/kg),iv	1 dose at 30 min before surgery and 1 dose at 12 h after surgery	normal saline	1)Infarct size; 2)LDH; 3)CK-MB; 4)cTnI; 5) Tunel; 6) NLRP3 mRNA and protein; 7) Caspase-1 mRNA and protein; 8)ASC mRNA and protein; 9) SIRT1 mRNA and protein; 10) AMPK α2 mRNA and protein; 11) PGC-1α mRNA and protein
Yang Hu 2019 (Hu et al., 2019)	Sprague–Dawley rats (male, n = 10/10)	220-250 g	Block LAD	3% pentobarbital sodium	Sal B (24 mg/kg),iv	1 injection immediately after surgery	normal saline	1)Infarct size; 2)LDH; 3)cTn; 4)IL-1β
Chao Lin 2016 (Lin et al., 2016)	Sprague–Dawley rats (male, n = 8/8)	200-220 g	Block LAD	chloral hydrate(0.3 g/ kg)	Sal B(24 mg/kg),iv	1 dose at 24 h and 28 h after surgery	normal saline	1)Infarct size; 2)LDH; 3)CK; 4)SOD; 5) MDA; 6)Bcl-2/ Bax; 7)cleaved caspase-9; 8) cleaved PARP; 9)LC3-II/LC3-I; 10)Beclin1; 11)VEGF
Lingling Xu 2011 (Xu et al., 2011)	Wistar rats (male, n = 30/30)	230-250 g	Block LAD	Not Mentioned	Sal B(10 mg/kg),iv	1 injection at 30 min and 24 h after surgery	normal saline	1)MAP; 2)-dp/ dt max; 3) LVSP; 4)+dp/dt max; 5)EDP; 6) Cardiac Output; 7) Tunel; 8)PARP-1; 9)cleaved PARP-1; 10) IKKα; 11)IKKβ; 12)p-IKKa; 13) NF-κB
Xiaoying Wang 2011 (Wang et al., 2011)	Wistar rats (male,n = 15/15)	280–320 g	Block LAD	Not Mentioned	Sal B(120 mg/kg),ig	once a day for 28 consecutive days after surgery	No treatment	1)LVIDd; 2) LVIDs; 3)IVSd ; 4)IVSs; 5) LVPWd; 6) LVPWs ; 7) LVEF; 8)LVFS; 9)Infarct size
Baohong Jiang 2010 (Jiang et al., 2010)	Wistar rats (male, n = 20/20)	230-250 g	Block LAD	Not Mentioned	Sal B(10 mg/kg),iv	once a day for 14 consecutive days after surgery	normal saline	1)LVAWd; 2) LVPWd; 3)+dP/dt max; 4)-dP/dt min; 5)EDP; 6)MAP; 7)LVSP; 8) Cardiac Output; 9) Collagen volume fraction; 10) collagen I/III; 11)MMP-9; 12) MMP-2
Xiaojin Xu 2023 (Xu et al., 2023a)	Sprague–Dawley rats (male, n = 12/12)	200-250 g	Ligation for 45 min, then reperfusion for 2h	5% isoflurane	Sal B(20 mg/kg),ip	1 dose at 1 hours and 25 hour before surgery	normal saline	1)Infarct size; 2)TfR1; 3) FTH1; 4)GPX4; 5)ROS; 6) MDA; 7)LDH; 8)Tunel; 9)

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of included studies.

Study ID	Species (sex, n=experimental/ control group)	Weight	Model (method)	Anesthetic	Treatment group(dosage)	Administration route	Control group	Outcomes
								cleaved Caspase-3; 10) Bax; 11)Bcl-2; 12)p-MAPK; 13)p-JNK
Bo Lu 2022 (Lu et al., 2022)	Sprague–Dawley rats(female,n=10/10)	275-325 g	Ligation for 60min, then reperfusion for 27h	Not Mentioned	Sal B(60 mg/kg),iv	1 dose at 3 hours after surgery	normal saline	1)TUNEL; 2) ROS; 3)SOD; 4)MDA
Hanqing Liu 2020 (Liu et al., 2020a)	Sprague–Dawley rats (male, n = 18/18)	250-300 g	Ligation for 30min, then reperfusion for 24h	10% chloral hydrate (350 mg/kg)	Sal B(60 mg/kg),ip	once a day for 4 consecutive days before surgery	No treatment	1)Infarct size; 2)Cardiac Output; 3) LVEF; 4)LVFS; 5)Stroke Volume; 6) Heart Rate; 7) LDH; 8)CK-MB; 9)TNF-α; 10)IL-18; 11) IL-1β; 12) HMGB1; 13) TUNEL;14) Bax; 15)Bcl-2; 16)p-AKT; 17) T-AKT
Zengyong Qiao 2016 (Qiao and Xu, 2016)	Sprague–Dawley rats(male, n = 10/10)	200-250 g	Ligation for 60min, then reperfusion for 3h	ketamine hydrochloride (90 mg/kg) and xylazine hydrochloride (10 mg/kg)	Sal B(30 mg/kg),ig	once a day for 20 consecutive days before surgery	normal saline	1)LVEDV; 2) LVEDP; 3)+dp/dt max; 4)-dp/dt min; 5) MDA; 6)SOD; 7)CAT; 8)GSH-Px; 9)TNF-α; 10)IL-1β; 11) Infarct size; 12) Caspase-3; 13) Bax; 14)Bcl-2
Ling Xue 2014 (Xue et al., 2014)	Sprague–Dawley rats(male, n = 10/10)	170-190 g	Ligation for 30min, then reperfusion for 1h	20% urethane(1g/kg)	Sal B(60 mg/kg),iv	No detailed	No treatment	1)Infarct size; 2)cTnI; 3)CK-MB; 4)NO; 5) ET; 6)SOD; 7) MDA; 8) TUNEL
Zengyong Qiao 2011 (Qiao et al., 2011)	Wistar rats of (male and female, n = 10/10)	220-280 g	Ligation for 15min, then reperfusion for 2h	pentobarbitone sodium (60 mg/kg)	Sal B(55 mg/kg),ig	once a day for 12 consecutive days before surgery	distilled water	1)Infarct size; 2)AST; 3)LDH; 4)CK-MB; 5) ROS; 6)NOS; 7) MDA; 8)GSH; 9)SOD; 10) CAT; 11)GSH-Px activities
Qi Chen 2023 (Chen et al., 2023)	ICR mice (male, n = 5/5)	20-25 g	ISO	_	Sal B(10 mg/kg),ip	once a day for 7 consecutive days before modelling	No treatment	1)LDH; 2)AST; 3)CK; 4)Ca2+; 5)Bax; 6)Bcl-2; 7)NO; 8)NOS; 9)eNOS; 10) PDGF; 11) VEGF; 12)Atg5; 13)CD31; 14) LC3Ⅰ; 15)LC3Ⅱ; 16)Beclin1; 17)P62
Yang Hu 2020 (Hu et al., 2020)	Sprague–Dawley rats (male, n = 10/10)	180-220 g	ISO	_	Sal B(15 mg/kg),ip	once a day for 7 consecutive days before modelling	normal saline	1)CK-MB; 2) IL-1β; 3)NLRP3 mRNA; 4)ASC mRNA; 5) Caspase-1 mRNA; 6)IL-1β mRNA

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of included studies.

Study ID	Species (sex, n=experimental/control group)	Weight	Model (method)	Anesthetic	Treatment group(dosage)	Administration route	Control group	Outcomes
Jun Liu 2018 (Liu et al., 2018)	Sprague–Dawley rats (male, n = 8/8)	240-260 g	ISO	_	Sal B(20 mg/kg),ip	once a day for 28 consecutive days before modelling	No treatment	1)Heart-to-body weight; 2) MDA; 3)SOD; 4)CAT; 5)GPx; 6)cTnT; 7)CK-MB; 8)LDH; 9) TNF-α; 10)NF-κB; 11)IL-1β; 12)IL-6; 13)MAP
Dan Zhou 2018 (Zhou et al., 2018)	Sprague–Dawley rats (male, n = 10/10)	250-270 g	Block LAD	Not Mentioned	Sal B(60 mg/kg), iv	once a day for 7 consecutive days after surgery	normal saline	1)Infarct size; 2)CK-MB; 3) cTnI; 4)LDH; 5)VEGF; 6) Nrf2; 7)HO-1
Dan Zhou 2013 (Zhou et al., 2013)	Sprague–Dawley rats (male, n = 10/10)	250-270 g	Ligation for 30min, then reperfusion for 3h	3% pentobarbital sodium	Sal B(60 mg/kg),iv	1 injection at the start of reperfusion	normal saline	1)Infarct size; 2)CK-MB; 3) LDH; 4)p-Akt/Akt; 5)p-eNOS/eNOS。
Guifeng Zhao 2004 (Zhao et al., 2004)	Wistar rats (male and female, n = 12/12)	200-300 g	Ligation for 30min, then reperfusion for 2h	3% pentobarbital sodium(30 mg/kg,ip)	Sal B(100 mg/kg),ig	once a day for 4 consecutive days before surgery	normal saline	1)SOD; 2)CK; 3)LDH
Qiang Zhang 2013 (Zhang et al., 2013)	Sprague–Dawley rats (male and female, n = 10/10)	200-300 g	Block LAD	2% pentobarbital sodium(40 mg/kg,ip)	Sal B(120 mg/kg),ip	once a day for 7 consecutive days before surgery	distilled water	1)CK; 2)AST; 3)LDH; 4)IL-1β; 5)IL-6; 6) TNF-α; 7) TUNEL
Fuguo Yang 2008 (Yang et al., 2008)	New Zealand rabbits (male, n = 8/8)	3.25±0.56 kg	Ligation for 30min, then reperfusion for 4h	20% urethane(5 ml/kg,iv)	Sal B(3 mg/kg),iv	1 injection after surgery	normal saline	1)NO; 2)ET
Jiangping Xu 2003 (Xu et al., 2003)	Sprague–Dawley rats (male, n = 10/10)	250-300 g	Ligation for 10min, then reperfusion for 0.5h	pentobarbital sodium(45 mg/kg,ip)	Sal B(15 mg/kg),iv	1 injection after 10 min of ischaemia	normal saline	1)Infarct size; 2)CK
Yang Xia 2018 (Xia et al., 2018)	Sprague–Dawley rats (male and female, n = 20/20)	180-220 g	Ligation for 30min, then reperfusion for 2h	Not Mentioned	Sal B(20 mg/kg), ip	once a day for 7 consecutive days before surgery	normal saline	1)Infarct size; 2)CK; 3)LDH; 4)TNF-α; 5)IL-1β; 6)ICAM-1
Baohe Wang 2004 (Wang et al., 2004)	Wistar rats (male and female, n = 12/12)	200-300 g	Ligation for 30min, then reperfusion for 2h	3% pentobarbital sodium(30 mg/kg,ip)	Sal B (100 mg/kg), ig	once a day for 4 consecutive days before surgery	normal saline	1)SOD; 2)AT-1; 3)ET; 4)TNF-α; 5)PGI2; 6) TXB2
Xinyu Wang 2016 (Wang et al., 2016)	Sprague–Dawley rats (male, n = 10/10)	180-220 g	ISO	—	Sal B(15 mg/kg),ip	once a day for 7 consecutive days before modelling	normal saline	1)CK; 2)GOT; 3)LDH; 4) MDA; 5)SOD; 6)IL-1β; 7) NLRP3; 8) Caspase-1 P20
Yanping Song 2007 (Song et al., 2007)	Sprague–Dawley rats (male and female, n = 8/8)	160-190 g	Block LAD	urethane(ip)	Sal B(10 mg/kg),iv	1 dose at 15 min after surgery	normal saline	1)Infarct size; 2)CK; 3)LDH
Chang Liu 2022 (Liu et al., 2022)	Sprague–Dawley rats (Not mentioned, n = 12/12)	Not mentioned	Block LAD	pentobarbital sodium(40 mg/kg,ip)	Sal B (40 mg/kg),ip	Started 2 days after surgery and administered once a day for 28 consecutive days	normal saline	1)CK-MB; 2) cTnI; 3)LDH; 4)ROS; 5) MDA; 6)GSH
Zhirong Lin 2011 (Lin et al., 2011)	Sprague–Dawley rats (male, n = 10/10)	240-260 g	Ligation for 30min, then reperfusion for 3h	20% urethane(0.6 ml/100g,ip)	Sal B(64 mg/kg), iv	1 injection before surgery	vehicle(5% glucose solution)	Infarct size
Lin Li 2004 (Li et al., 2004)	4-Way Ovoss(male and female, n = 5/5)	9-14 kg	Block LAD	3% pentobarbital sodium(30 mg/kg,ip)	Sal B (10 mg/kg),iv	1 injection after surgery	normal saline	1)Infarct size; 2)LDH

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of included studies.

Study ID	Species (sex, n=experimental/ control group)	Weight	Model (method)	Anesthetic	Treatment group(dosage)	Administration route	Control group	Outcomes
Xuguang Hu 2010 (Hu et al., 2010)	Sprague–Dawley rats (male and female, n = 10/10)	180-220 g	ISO	—	Sal B(10 mg/kg),ip	once a day for 5 consecutive days before modelling	normal saline	1)LDH; 2)CK; 3)SOD; 4)MDA
Yingchang Fan 2004 (Fan et al., 2004)	Wistar rats (male and female, n = 10/10)	200-300 g	Block LAD	3% pentobarbital sodium(30 mg/ kg,ip)	Sal B(100 mg/kg), ig	once a day for 6 consecutive days before surgery	normal saline	Infarct size
Hengxia Chen 2012 (Chen et al., 2012)	Sprague–Dawley rats (male and female, n = 10/10)	180-220 g	Block LAD	3% pentobarbital sodium(30 mg/ kg,ip)	Sal B(6.4 mg/kg), iv	once a day for 14 consecutive days after surgery	normal saline	1)Infarct size; 2)NO; 3)NOS; 4)VEGF
Yuehong Shen 2022 (Shen et al., 2022)	Sprague–Dawley rats (male, n = 8/8)	220-250 g	Block LAD	isoflurane inhalation	Sal B(50 mg/kg), ip	once a day for 14 consecutive days after surgery	No treatment	1)Infarct size; 2)LDH; 3)CK; 4)CK-MB; 5) MDA; 6)GSH; 7)LVEF; 8) LVFS; 9)Nrf2

Note: +dp/dt max, maximal left ventricular pressure rising rate; -dp/dt max, maximal left ventricular pressure decreasing rate; Bcl-2, B-cell lymphoma-2; CAT, catalase; CK, creatine kinase; CK-MB, creatine kinase isoenzymes MB; cTnI, cardiac troponin I; cTnT, cardiac troponin T; eNOS, endothelial nitric oxide synthase; GPx, myocardial glutathione peroxidase; GSH, glutathione; IL, interleukin; ISO, isoproterenol; IVSd, end-diastolic interventricular septum; IVSs, end-systolic interventricular septum; LAD, left anterior descending branch; LC3, microtuble-associated protein light chain 3; LDH, lactic dehydrogenase; LVAWd, left ventricular anterior wall thickness at diastole; LVEDP, left ventricular end dilated pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; LVIDd, left ventricular internal dimension in end diastole; LVIDs, left ventricular internal dimension in end systole; LVPWd, Left ventricular posterior wall end diastole; LVPWs, Left ventricular posterior wall end systole; LVSP, left ventricular systolic pressure; MAP, mean arterial pressure; MDA, malondialdehyde; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa B; NOS, nitric oxide synthase; Nrf2, NF-E2-related factor-2; p-AKT, phosphorylated protein kinase B; PDGF, platelet derived growth factor; ROS, reactive oxygen species; SIRT1, sirtuin1; SOD, superoxide dismutase; TNF, tumor necrosis factor; TUNEL, the terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling; VEGF, vascular endothelial-derived growth factor.

dt max (SMD = 5.75, 95%CI(2.53, 8.96), $p < 0.01$, $I^2 = 90\%$), -dp/dt max (SMD = 4.47, 95%CI(3.77, 5.16), $p < 0.01$, $I^2 = 0\%$), LVFS(SMD = 2.78, 95%CI(0.77, 4.79), $p < 0.01$, $I^2 = 89\%$), and cardiac output (SMD = 5.07, 95%CI(4.36, 5.79), $p < 0.01$, $I^2 = 0\%$) compared to the control group (Figure 4). However, Sal B had no apparent effect on LVEF (SMD = 4.36, 95%CI(-0.19, 8.92), $p = 0.06$, $I^2 = 94\%$).

3.4.4 Oxidative stress

Oxidative stress can be measured using reactive oxygen species (ROS), oxidative products, and antioxidant enzymes. MDA levels indicate the degree of lipid peroxidation. SOD and CAT are antioxidant enzymes that scavenge free radicals and prevent oxidative damage. Summarizing the available reports on the cardioprotective effects of Sal B, it was reported that Sal B intervention reduced ROS (SMD = −7.81, 95%CI(-10.77, −4.84), $p < 0.01$, $I^2 = 71\%$) and MDA (SMD = −4.90 95%CI(-6.54, −3.26), $p < 0.01$, $I^2 = 90\%$) levels and increased SOD (SMD = 4.36, 95% CI(1.87, 6.85), $p < 0.01$, $I^2 = 91\%$), CAT (SMD = 5.51, 95%CI(2.10, 8.91), $p < 0.01$, $I^2 = 87\%$) and GSH (SMD = 5.55, 95%CI (0.22, 10.88), $p = 0.04$, $I^2 = 88\%$) levels as compared to the control group (Figure 5). These results suggest that Sal B is a cardioprotective agent by restoring the oxidative-antioxidant balance.

3.4.5 Inflammatory biomarkers

Overexpression of inflammatory markers is an indication of MI/R. It is associated with myocardial injury in the early stages of ischemia/reperfusion and myocardial repair after injury. The results of this meta-analysis revealed that Sal B alleviated the expression of inflammatory factors including IL-1β(SMD = −3.26, 95%CI(-4.13, −2.39), $p < 0.01$, $I^2 = 70\%$), IL-6(SMD = −1.74, 95%CI(-2.54, −0.95), $p < 0.01$, $I^2 = 0\%$) and TNF-α(SMD = −2.85 95%CI(-4.03, −1.66), $p < 0.01$, $I^2 = 76\%$) (Figure 6).

3.4.6 Neovascularization and vasoregulation

Neovascularization is an important compensatory mechanism after MI, and the vascular endothelial growth factor (VEGF) is a major biological mediator of angiogenesis *in vivo*. Promoting normal vasodilatory and contractile functions is likewise one of the important methods for alleviating MI/R injury. NO and ET are the vasodilatory and vasoconstrictive factors, respectively. Therefore, the VEGF, NO, and ET levels were considered in this meta-analysis. The results showed that SalB treatment significantly increased VEGF (SMD = 15.17, 95%CI(1.58, 28.75), $p = 0.03$, $I^2 = 94\%$) and NO levels (SMD = 4.68, 95%CI(1.36, 8.00), $p < 0.01$, $I^2 = 85\%$). Meta-analyses showed no significant effect on ET (SMD = −10.28, 95%CI(-26.02, 5.47), $p = 0.20$, $I^2 = 93\%$) (Figure 7).

3.4.7 Apoptosis

Bax and Bcl-2 are markers of apoptosis, and the TUNEL assay is commonly used to detect apoptosis ratios. The results revealed that SalB significantly decreased Bax (SMD = −11.08, 95%CI(-19.84, −2.33), $p < 0.01$, $I^2 = 94\%$) and elevated Bcl-2 (SMD = 11.52, 95%CI(0.94, 22.11), $p < 0.01$, $I^2 = 93\%$). The level of apoptosis detected by the TUNEL also declined compared to the control group (SMD = −6.02, 95%CI(-8.23, −3.81), $p < 0.01$, $I^2 = 76\%$) (Figure 8).

3.5 Publication bias

Publication bias is a phenomenon in which the results of an experiment determine the likelihood of publication, usually leading to an overestimation of positive results. Funnel plots and Egger's regression tests were used to analyze the publication bias of infarction size. Visual inspection of the funnel plots revealed a

TABLE 2 Risk of bias for inclusion of studies.

Study ID	A	B	C	D	E	F	G	H	I	J
Qingju Li2022	?	?	?	?	?	?	?	+	-	-
Yang Hu2019	?	?	?	-	?	?	?	+	-	-
Chao Lin2016	?	?	?	-	?	?	?	-	-	-
Lingling Xu2011	?	?	?	?	?	?	?	-	-	-
Xiaoying Wang2011	?	?	?	?	?	?	?	-	-	-
Baohong Jiang2010	?	?	?	?	?	?	?	-	-	-
Xiaojin Xu2023	?	?	?	-	?	?	?	+	-	-
Bo Lu2022	?	?	?	-	?	?	?	-	-	-
Hanqing Liu2020	?	?	?	-	?	?	?	-	-	-
Zengyong Qiao2016	?	?	?	-	?	?	?	-	+	-
Ling Xue2014	?	?	?	?	?	?	?	-	-	-
Zengyong Qiao2011	?	?	?	-	?	?	?	-	-	-
Qi Chen2023	?	?	?	-	?	?	?	+	-	-
Yang Hu2020	?	?	?	-	?	?	?	-	-	-
Jun Liu2018	?	?	?	-	?	?	?	-	-	-
Dan Zhou2018	?	?	?	?	?	?	?	-	-	-
Dan Zhou2013	?	?	?	-	?	?	?	-	-	-
Guifeng Zhao2004	?	?	?	?	?	?	?	-	-	-
Qiang Zhang2013	?	?	?	-	?	?	?	-	-	-
Fuguo Yang2008	?	?	?	?	?	?	?	-	-	-
Jiangping Xu2003	?	?	?	?	?	?	?	-	-	-
Yang Xia2018	?	?	?	?	?	?	?	-	-	-
Baohe Wang2004	?	?	?	?	?	?	?	+	-	-
Xinyu Wang2016	?	?	?	-	?	?	?	+	-	-
Yanping Song2007	?	?	?	?	?	?	?	+	-	-
Chang Liu2022	?	?	?	-	?	?	?	-	-	-
Zhirong Lin2011	?	?	?	?	?	?	?	+	-	-
Lin Li2004	?	?	?	?	?	?	?	-	-	-
Xuguang Hu2010	?	?	?	-	?	?	?	-	-	-
Yingchang Fan2004	?	?	?	-	?	?	?	-	-	-
Hengxia Chen2012	?	?	?	?	?	?	?	-	-	-
Yuehong Shen2022	?	?	?	-	?	?	?	-	-	-

A, Sequence generation (selection bias); B, Baseline characteristics (selection bias); C, Allocation concealment (selection bias); D, Random housing (performance bias); E, Blinding investigators (performance bias); F,Random outcome assessment (measurement bias); G, Blinding outcome assessor (measurement bias); H, Incomplete outcome data (attrition bias); I, Selective outcome reporting (reporting bias); J, other sources of bias.

large amount of asymmetry, suggesting potential publication bias, as confirmed by Egger's test ($p < 0.05$) (Supplementary Figures 3A, B). Trim-and-fill methods were used to correct for potential publication bias (Supplementary Figure 3C). Although trim-and-fill analyses resulted in corrected novel effect sizes (SMD = −2.27, 95%CI(-4.46, −0.09), $p = 0.04$), the association between Sal B and infarct size remained statistically significant.

4 Discussion

4.1 Summary of evidence

To the best of our knowledge, this is the first preclinical systematic review and meta-analysis investigating the effects of SalB on MI/R. Thirty-two studies involving a total of 32 papers

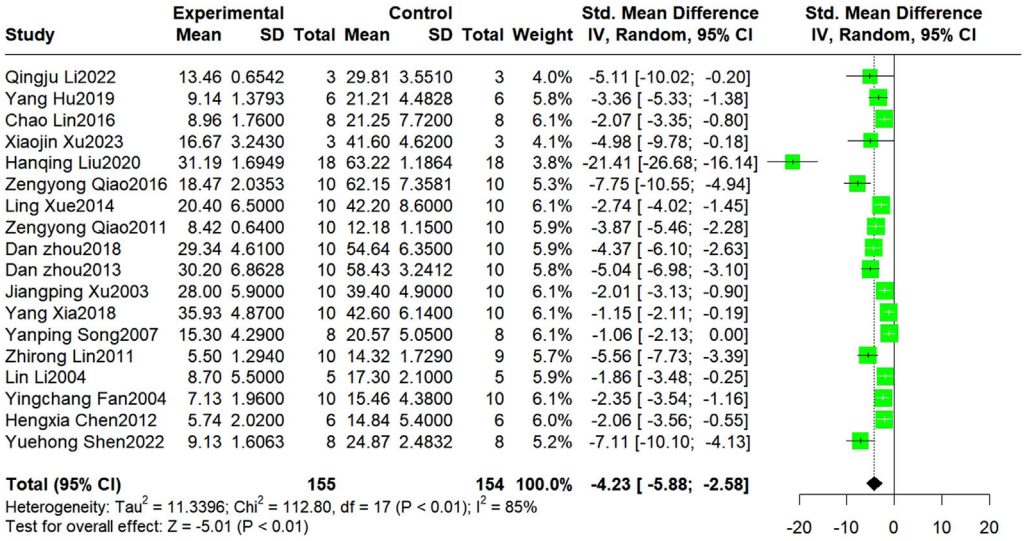


FIGURE 2
The forest plot: effect of Sal B for reducing the infarction size compared with the control group.

TABLE 3 Subgroup analysis of Infarct size.

Subgroup	No.of studies	SMD	95%CI	*p*-Value between subgroups	Heterogeneity within subgroups	
					I^2 (%)	*p*-Value
Model				0.12		
Block LAD	9	−2.79	−3.80, −1.78		66%	<0.01
Ligation and reperfusion	9	−5.72	−9.25, −2.18		91%	<0.01
Dosage				<0.01		
≤20 mg/kg	6	−1.55	−2.08, −1.03		0%	0.46
21–50 mg/kg	5	−4.84	−7.19, −2.49		80%	<0.01
>50 mg/kg	7	−6.12	−10.51, −1.73		89%	<0.01
Administration method				0.29		
Intravenous injection	11	−2.9	−3.76, −2.03		66%	<0.01
gavage	3	−4.43	−7.40, −1.46		84%	<0.01
intraperitoneal injection	4	−8.45	−16.96, 0.05		96%	<0.01
Administration time				0.34		
before modeling	7	−6.42	−11.10, −1.74		93%	<0.01
after modeling	7	−2.83	−4.09, −1.57		73%	<0.01
other times	4	−3.26	−4.79, −1.72		62%	0.05
Species				0.11		
SD rats	15	−4.66	−6.74, −2.58		87%	<0.01
Wistar rats	2	−3.01	−4.49, −1.54		55%	0.13
4-way ovoss	1	−1.86	−3.48, −0.25		-	-

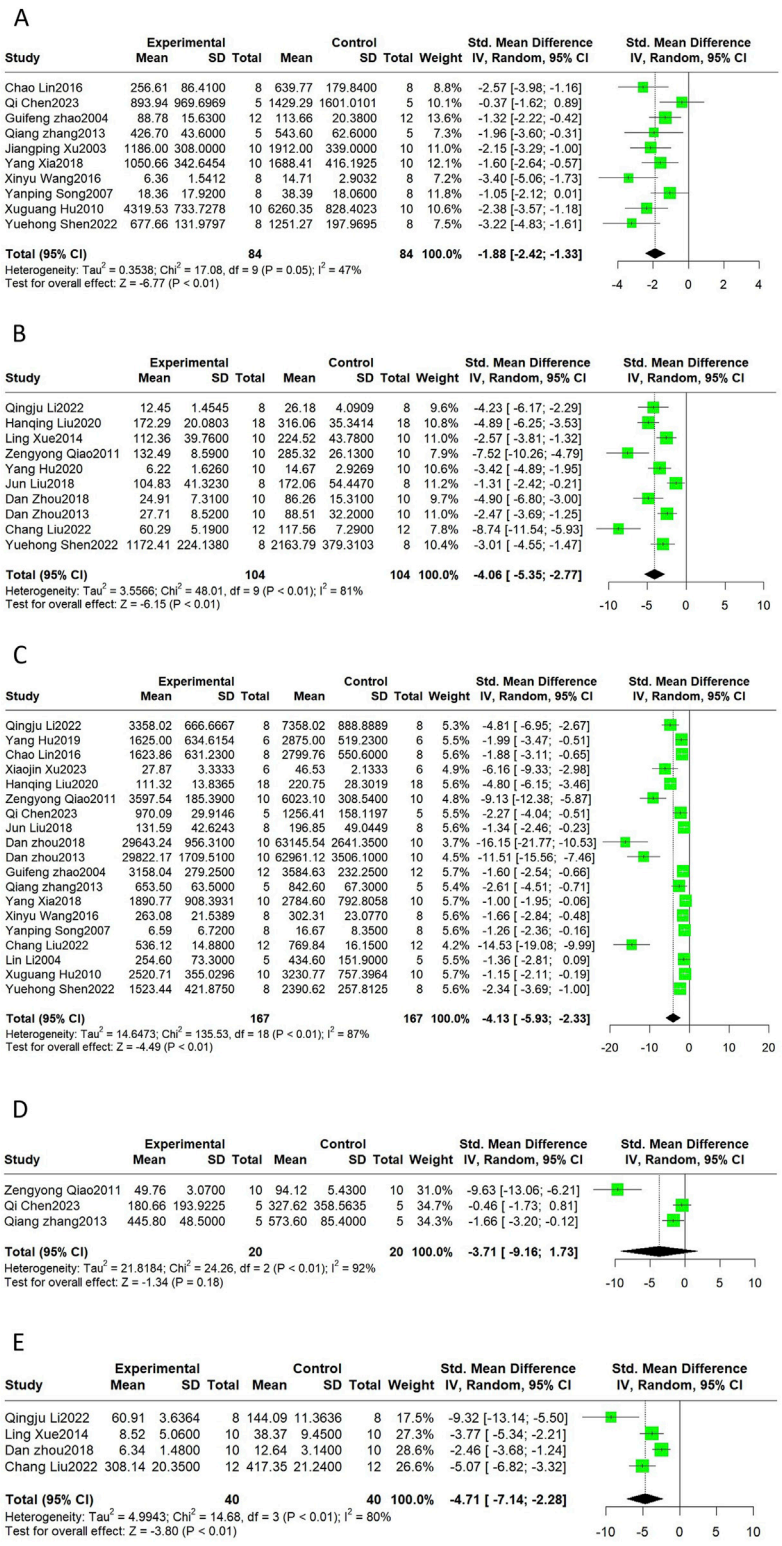


FIGURE 3
The forest plot of cardiac markers: effects of Sal B for decreasing CK **(A)**, CK-MB **(B)**, LDH **(C)**, cTnI **(E)** compared with the control group. No significant effect of Sal B for AST **(D)** compared with the control group.

involving 732 animals were included. The meta-analysis showed that Sal B has a protective effect on the myocardium after ischemia-reperfusion injury and a positive effect on reducing infarct size, improving cardiac function, and reducing myocardial injury. The cardioprotective effects of SalB were mediated by attenuating oxidative stress and inflammation, promoting neovascularization,

TABLE 4 Subgroup analysis of LDH.

Subgroup	No.of studies	SMD	95%CI	*p*-Value between subgroups	Heterogeneity within subgroups	
					I^2 (%)	*p*-Value
Model				0.01		
Block LAD	9	−4.75	−8.13, −1.37		87%	<0.01
Ligation and reperfusion	6	−5.37	−8.59, −2.15		92%	<0.01
ISO	4	−1.45	−2.04, −0.87		0%	0.71
Dosage				0.01		
≤20 mg/kg	8	−1.41	−1.84, −0.98		35%	0.15
21–50 mg/kg	5	−4.76	−9.01, −0.51		88%	<0.01
>50 mg/kg	6	−7.19	−11.48, −2.90		92%	<0.01
Administration method				0.69		
Intravenous injection	7	−5.1	−9.07, −1.13		89%	<0.01
gavage	2	−5.2	−12.56, 2.17		95%	<0.01
intraperitoneal injection	10	−3.38	−5.35, −1.36		86%	<0.01
Administration time				0.22		
before modeling	10	−2.83	−4.22, −1.45		83%	<0.01
after modeling	7	−5.21	−9.78, −0.65		89%	<0.01
other times	2	−7.93	−14.47, −1.39		88%	<0.01
Species				0.06		
SD rats	16	−4.68	−6.84, −2.52		89%	<0.01
ICR mice	1	−2.27	−4.04, −0.51		-	-
Wistar rats	1	−1.60	−2.54, −0.66		-	-
4-way ovoss	1	−1.36	−2.81, 0.09		-	-

modulating vascular function, and attenuating cardiomyocyte apoptosis (Figure 9). A high degree of heterogeneity was observed among the included studies; further subgroup and sensitivity analyses were performed. The results of the subgroup analyses showed that the dose of the drug administered could be a potential source of heterogeneity. In contrast, the differences between subgroups for the time of administration, mode of administration, and modality of modeling were not statistically significant. They did not significantly reduce the heterogeneity across subgroups within the group. There was some publication bias among the included studies. In conclusion, Sal B has a clear protective effect against MI/R; however, the exact magnitude of the cardioprotective effect of Sal B should be interpreted with caution.

4.2 Possible mechanism

MI/R injury involves multiple pathological processes, such as cell death (including apoptosis, autophagy, and ferroptosis), oxidative stress, inflammatory response, vascular endothelial dysfunction, and neovascularization (Ibáñez et al., 2015). There is no satisfactory therapeutic approach in the current clinical practice, and multi-targeted small-molecule drugs may be a solution. Sal B is a promising small-molecule drug for treating MI/R. However, the progression of Sal B from basic research to clinical practice has been hampered by the lack of a comprehensive understanding of its underlying mechanisms. To gain a more comprehensive understanding of the role of Sal B in MI/R, its specific mechanisms and pathways are summarized in this review. In brief, Sal B exerted antioxidant, anti-inflammatory, and modulatory effects on vascular function and regulated cell death (Figure 10).

SalB protects the heart by regulating cardiomyocyte death. Various pathways regulate cardiomyocyte death during MI/R, including apoptosis, ferroptosis, and autophagy, among others (Xiang et al., 2024). Cardiomyocyte apoptosis is a genetically regulated, actively ordered, and self-terminating process involving various enzymes. Caspase-3, Bcl-2, and BAX are important regulators of apoptosis. Caspase-3 is at the crossroads of apoptosis-related signaling pathways. Activating caspase-3 promotes downstream protease cascades that irreversibly amplify apoptotic signaling pathways. Bcl-2 exerts antiapoptotic effects and prevents apoptosis at multiple levels. Bax belongs to a class of pro-apoptotic proteins that promote the subsequent apoptotic cascade

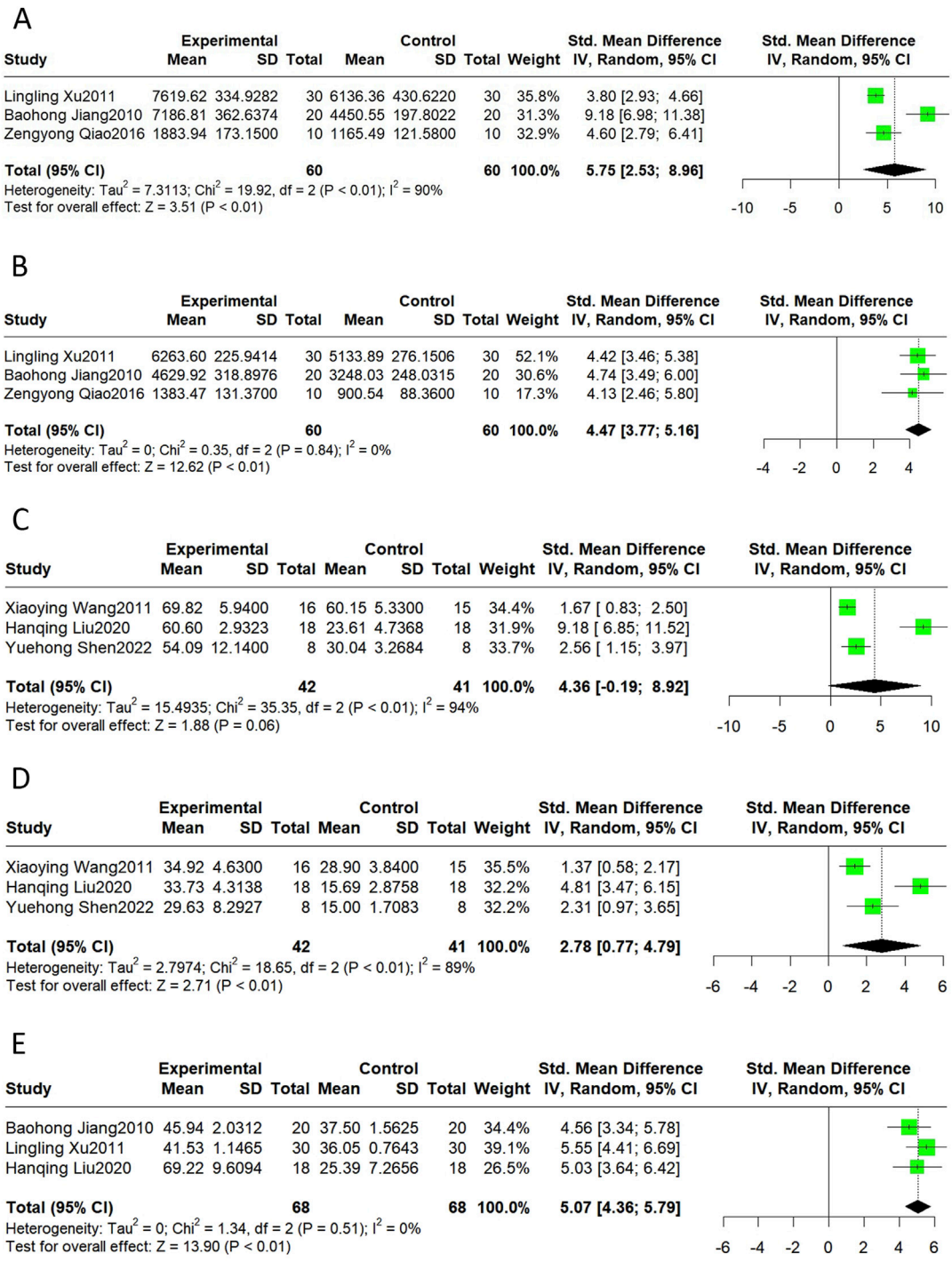


FIGURE 4
The forest plot of cardiac function: effects of Sal B for increasing + dp/dt max **(A)**, -dp/dt max **(B)**, LVFS **(D)**, Cardiac Output **(E)** compared with the control group. No significant effect of Sal B for LVEF **(C)** compared with the control group.

by disrupting the outer mitochondrial membrane (Del et al., 2019). Several studies have shown that Sal B can regulate the expression of Caspase-3, Bcl-2, and Bax and thus exert anti-apoptotic effects on cardiomyocytes. Furthermore, several studies have explored the pathways upstream of these three apoptotic regulators. Sal B inhibited mitochondrial ROS accumulation, which consequently inhibited the downstream JNK/MAPK pro-apoptotic signaling pathway (Xu et al., 2023a). In addition, the PI3K-Akt pathway is also one of the upstream pathways in which Sal B alleviates apoptosis (Liu et al., 2020a).

Ferroptosis is a recently discovered type of regulated cell death (RCD) in recent years (Zhao et al., 2023). The core biochemical features of ferroptosis are iron overload and lipid peroxidation. Iron overload refers to the excessive accumulation of intracellular Fe^{2+}.

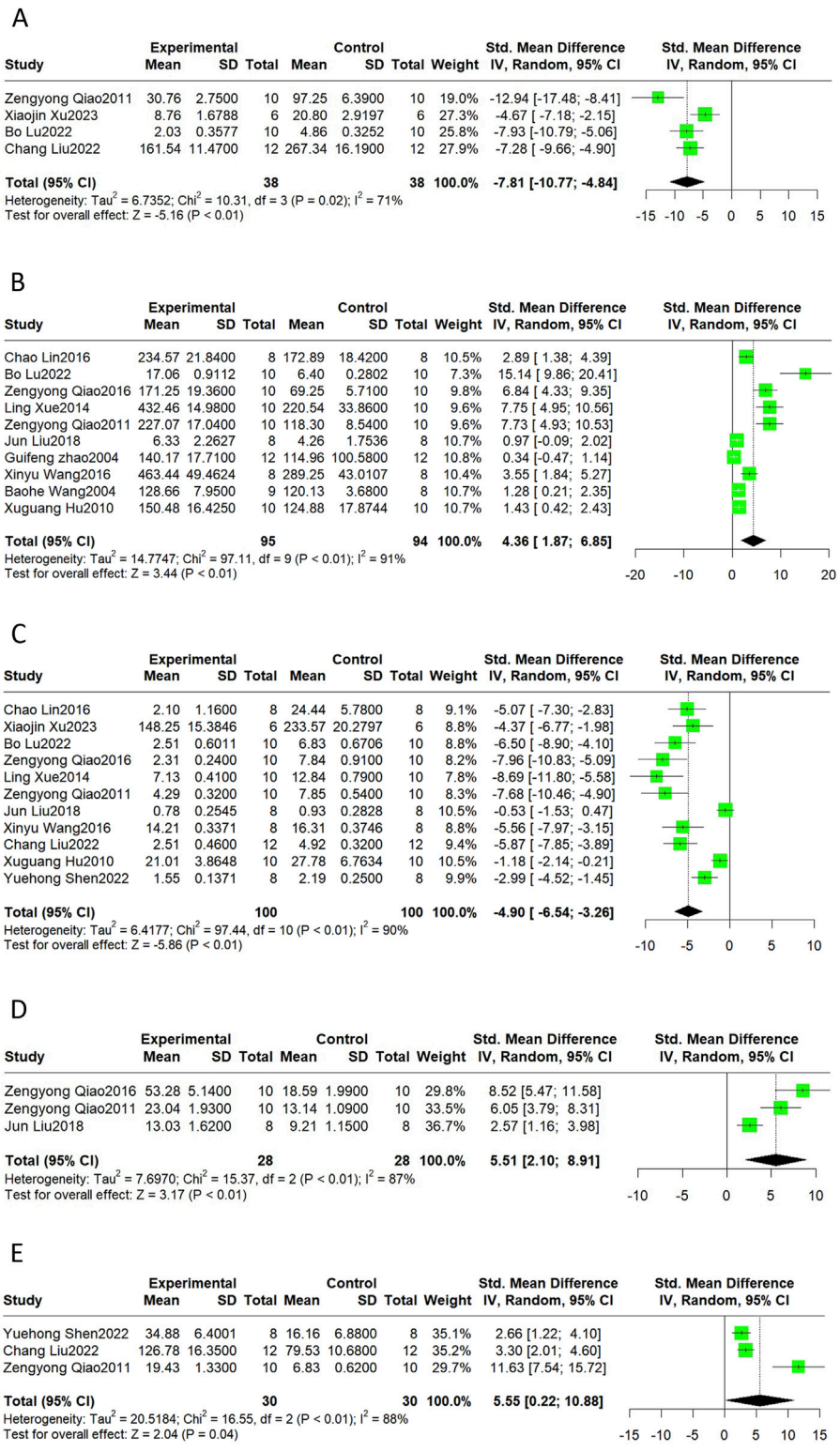


FIGURE 5
The forest plot of oxidative stress indicators: effects of Sal B for decreasing ROS **(A)**, MDA **(C)**, and increasing SOD **(B)**, CAT **(D)**, and GSH **(E)** compared with the control group.

TfR1 and Fpn1 present on the cell membrane are channels for transporting Fe^{3+} and Fe^{2+}. FTH1(ferritin heavy chain-1) is a component of ferritin that catalyzes the storage of Fe^{2+}, thereby reducing free iron levels (Zhang et al., 2024). FTH1 is often used as a biomarker of ferroptosis. The acidic and highly reducing intracellular environment during the early stages of reperfusion

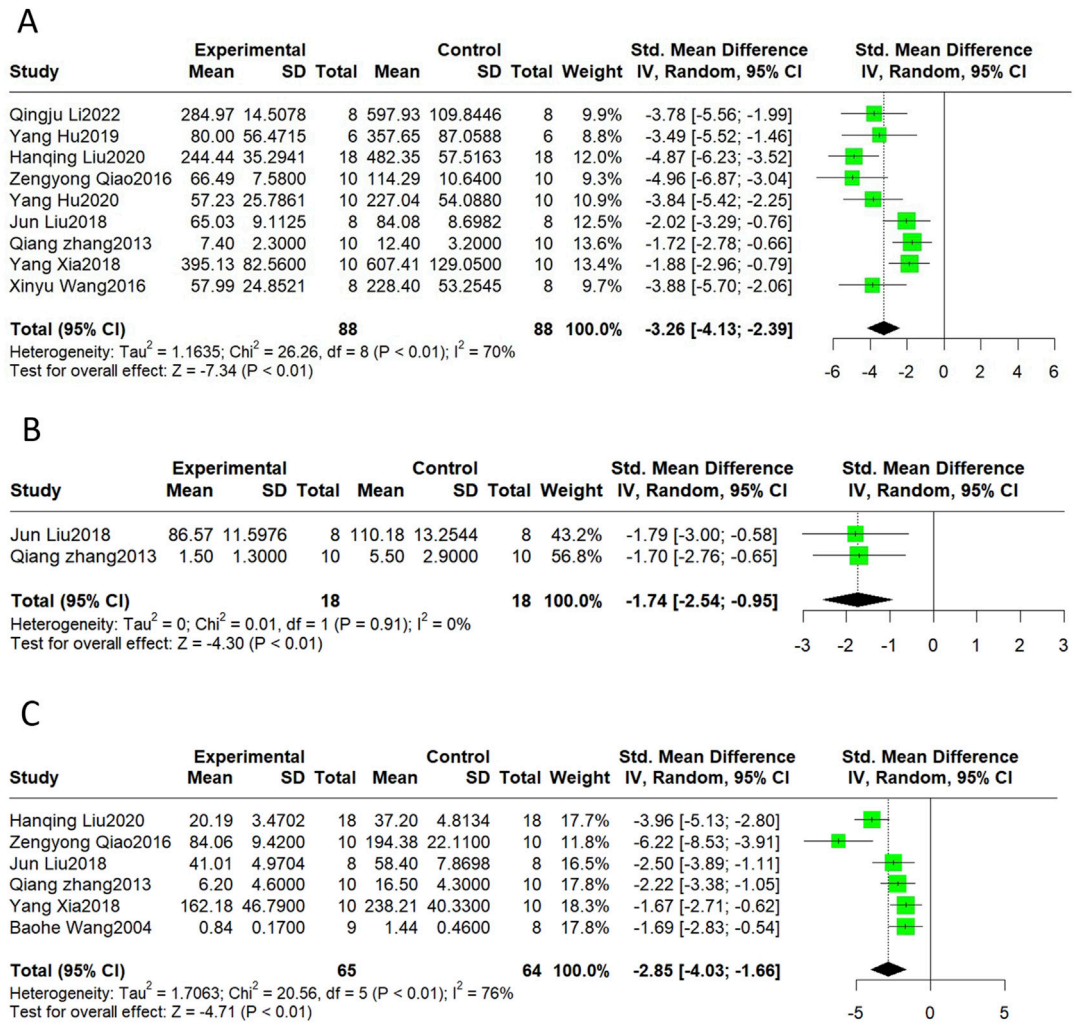


FIGURE 6
The forest plot of inflammation indicators: effects of Sal B for decreasing IL-1β **(A)**, IL-6 **(B)**, TNF-α **(C)** compared with the control group.

promotes the release of iron and iron from ferritin. Iron uptake, utilization, and recirculation balance are disrupted (Xiang et al., 2024). Free iron ions accumulate and catalyze the Fenton reaction, producing increased ROS. Sal B attenuates intracellular free iron accumulation and reduces mitochondrial ROS by decreasing the expression of TfR1 and promoting high expression of FTH1, thereby protecting the myocardium from ferroptosis (Xu et al., 2023a). Lipid peroxidation is another characteristic of ferroptosis. Glutathione peroxidase 4 (GPX4) is the most important intracellular anti-lipid peroxidase and a central regulator of ferroptosis. In the early and middle stages of myocardial infarction, GPX4 expression is markedly reduced, causing the accumulation of lipid peroxides and ultimately leading to ferroptosis (Han et al., 2023). Sal B reduces ubiquitination-proteasome degradation of GPX4 and attenuates MI/R-induced ferroptosis. It was also found that another pathway by which salt B inhibits lipid peroxidation is the inhibition of the Nrf2/HO-1 pathway (Shen et al., 2022).

Autophagy is a lysosome-dependent degradation pathway (Popov et al., 2023). Autophagic lysosomes play a crucial role in autophagy. It degrades damaged cytoplasmic structures and produces amino acids, free fatty acids, and other protein and energy synthesis substances. Autophagy is beneficial during ischemia in MI/R. Autophagy helps cardiomyocytes adapt to environments such as hypoxia and starvation and delays the occurrence of irreversible cell damage (Dong et al., 2019). However, excessive autophagy during reperfusion can induce the progressive consumption of cellular constituents, leading to autophagic cell death. Thus, moderate autophagy activation is cardioprotective and ensures the availability of energy substrates (Bravo-San Pedro et al., 2017). Autophagy is regulated by specific autophagy-related (Atg) genes, among which Atg5 is involved in the formation of phagocytic vesicle expansion on the one hand and promotes the recruitment of LC3II on the other, contributing to the transition from LC3Ⅰ to LC3Ⅱ. LC3II and LC3II/Ⅰ are key indicators of autophagic activity (Sciarretta et al., 2018). In addition, Beclin1 and its complexes are involved in the formation of the isolation membrane as well as the recruitment of Atg proteins to the autophagosomal membrane, and their elevation marks the initiation of autophagy (Shi et al., 2019). Sal B upregulates autophagy

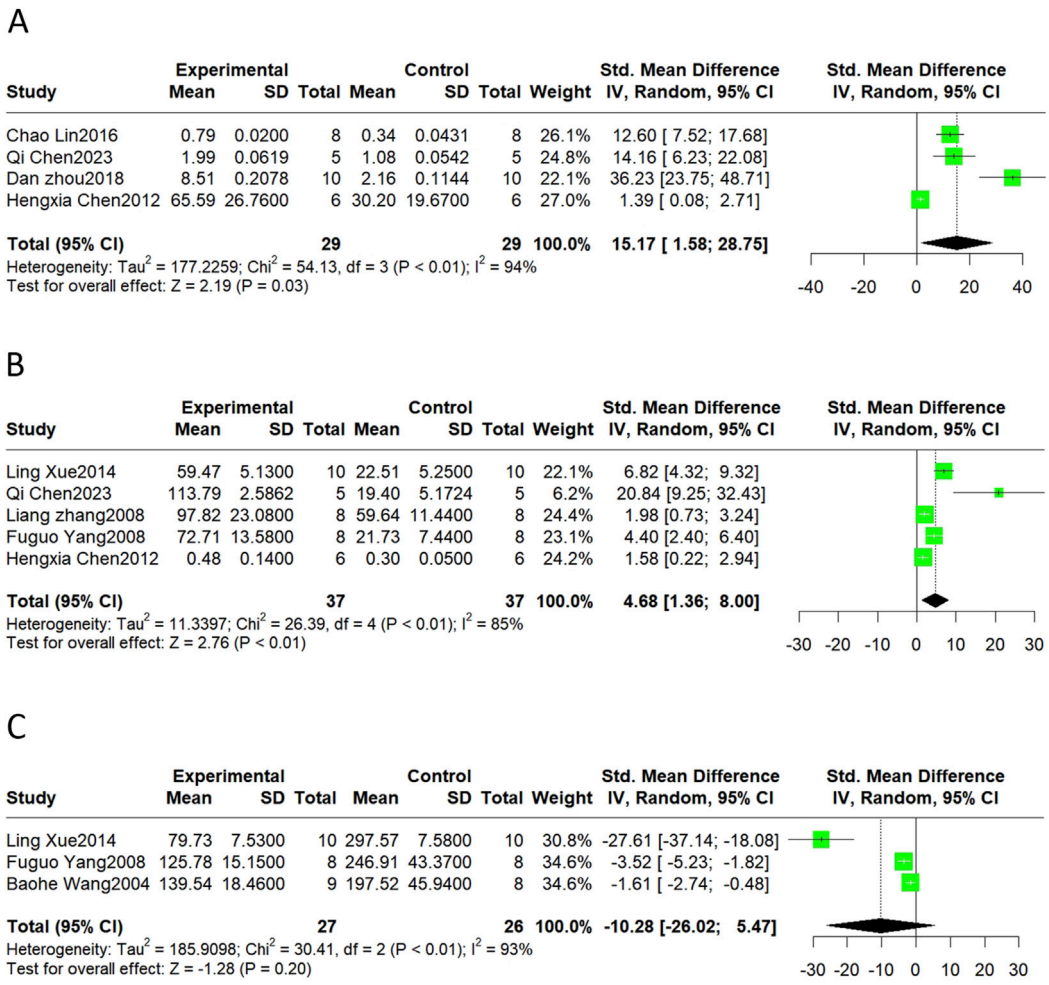


FIGURE 7
The forest plot of neovascularization and vasoregulation: effects of Sal B for increasing VEGF **(A)**, NO **(B)** compared with the control group. No significant effect of Sal B for ET **(C)** compared with the control group.

lysosomes and the expression of LC3II/l and Beclin1 in a myocardial ischemia model in mice induced by ISO. This suggests that Sal B enhances the autophagic activity during myocardial ischemia (Chen et al., 2023). However, whether the effect of Sal B on autophagy during reperfusion is consistent with that during the ischemic process has not yet been investigated.

Oxidative stress is considered one of the major factors that cause myocardial injury in MI/R. During MI/R, particularly during reperfusion, the balance between ROS generation and scavenging is disrupted. A large accumulation of oxygen free radicals damages subcellular membranes and structural systems through several mechanisms (Granger and Kvietys, 2015; Bugger and Pfeil, 2020). Several studies have revealed that Sal B attenuates oxidative stress by reducing ROS production and increasing the expression of the antioxidants SOD, CAT, and GSH(31–34). GPX1 is an important antioxidant enzyme responsible for scavenging ROS accumulated in cells. Ubiquitination and degradation of GPX1 are mediated by TRIM8. Studies have shown that SalB inhibits TRIM8 expression and reduces GPX1 degradation, resulting in accelerated ROS elimination (Lu et al., 2022).

Macrophages regulate the MI/R repair processes. In the early stages of MI/R, M1 macrophages predominate and produce oxidative metabolites and proinflammatory factors. During the following 3–5 days, M2 macrophages gradually replace M1, and M2 macrophages produce anti-inflammatory factors and promote scar formation and angiogenesis (Xu et al., 2023b). Therefore, timely regulation of their transition to the M2 phenotype is essential to ensure cardiac tissue healing and avoid adverse remodeling and systolic dysfunction. Changing the mode of macrophage energy metabolism is one way of changing the polarization direction (Kim et al., 2021). Sal B inhibits the activation of mTORC1 and glycolysis mediated by Rag D, resulting in the inhibition of M1 polarization and an increase in M2 macrophages, ultimately leading to a reduction in myocardial inflammatory factor infiltration and cardioprotective effects (Zhao et al., 2020).

Regulation of vascular endothelial function and promotion of neovascularization are also important for improving MI/R. MI/R injury leads to an imbalance between vasodilatory and vasoconstrictive factors, manifesting as a marked increase in the content of vasoconstrictive factors and a decrease in the release of vasodilatory factors. This imbalance causes vasoconstriction and spasms, leading to worsening of partial ischemia and hypoxia. Sal B can inhibit the release of ET and TXB2 from the vascular

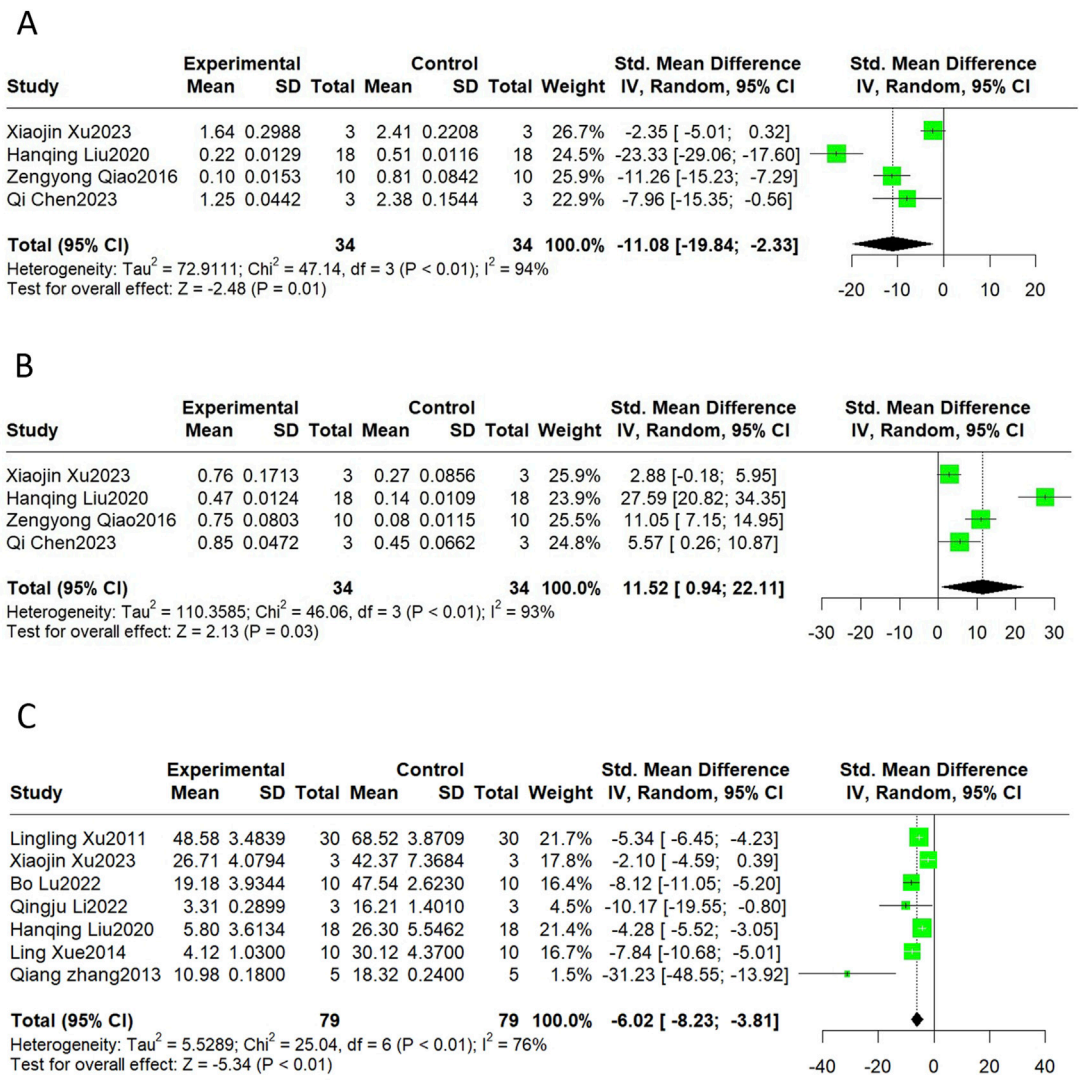


FIGURE 8
The forest plot of apoptosis indicators: effects of Sal B for decreasing Bax **(A)** and TUNEL **(C)** and increasing Bcl-2 **(B)** compared with the control group.

endothelium and increase the content of NO and PGI2, thereby regulating endothelial dysfunction and increasing the myocardial blood supply (Wang et al., 2004; Zhang et al., 2008; Yang et al., 2008; Xue et al., 2014). This suggests that this effect may be achieved through the AMPK/PI3k/Akt pathway (Pan et al., 2011). Neovascularization is another approach to repair MI/R damage. VEGF is one of the most widely studied positive regulators of vascular neovascularisation. It also promotes the proliferation and differentiation of vascular endothelial cells. PKD1 is an upstream protein of VEGF that mediates the proliferation, migration, and lumen formation of endothelial progenitors and stem cells. It was found that Sal B induced VEGF synthesis by regulating the PKD1/HDAC axis and the PKD1/HIF-α axis, which promoted neovascularization of ischemic myocardial tissues and increased microcirculatory blood supply in ischemic myocardium (Liu et al., 2020b; Liu et al., 2020c). Additionally, Sal B activates the Nrf2/HO-1 pathway and induces VEGF synthesis, which is involved in the regulation of neovascularization after ischemic injury (Zhou et al., 2018).

The inflammatory response also plays an important role in the myocardial injury caused by MI/R. During ischaemia, inflammation is activated. During reperfusion, restoration of blood flow and oxygen delivery further activates inflammatory signalling pathways. Inflammatory vesicles are sensors that link injury to inflammation. NLRP3 inflammatory vesicles orchestrate the inflammatory response in the absence of pathogens by inducing downstream caspase-1 cleavage and releasing the inflammatory factors IL-1β and IL-18 (Algoet et al., 2023). Sal B promotes the inactivation of NLRP3 inflammatory vesicles via several pathways. First, Sal B can further induce NLRP3 inactivation by inhibiting intracellular ROS production during myocardial ischemia, increasing the mitochondrial membrane potential, regulating the expression levels of SIRT1, Parkin, and PINK1 proteins, and promoting mitochondrial autophagy (Hu et al., 2020). Secondly, Sal B could activate AMPK and PGC-1α-mediated mitochondrial biogenesis via SIRT1, which in turn blocked NLPR3-mediated inflammatory response (Li et al., 2022). Finally, Sal B blocks

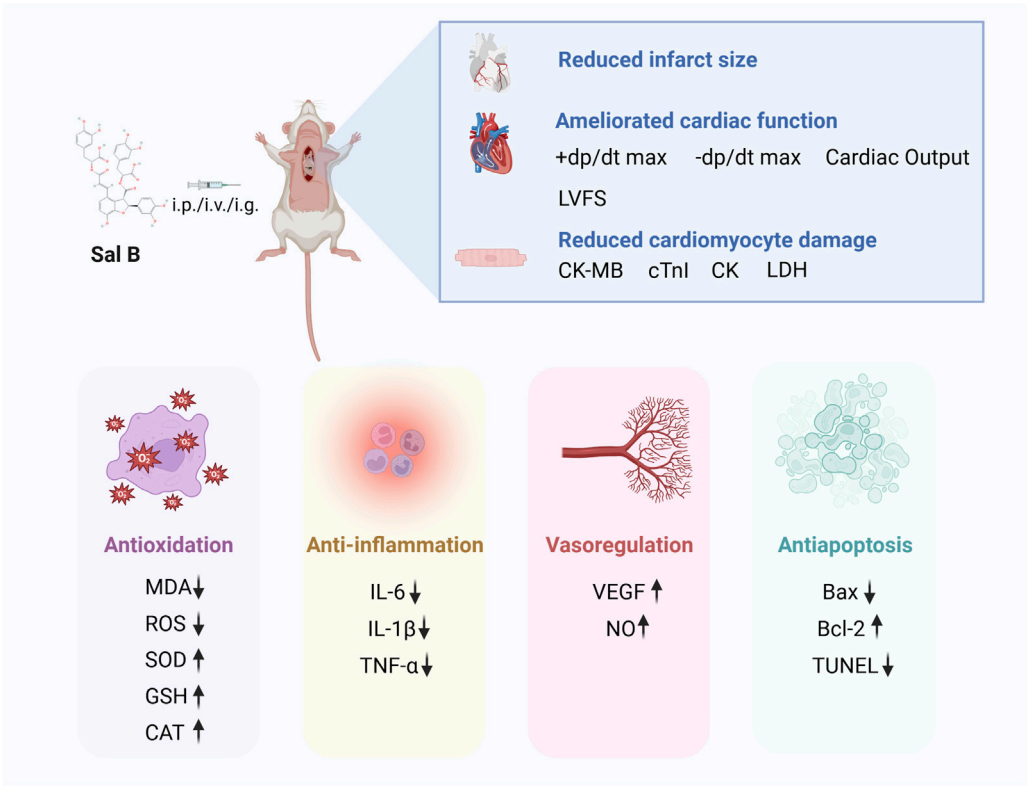


FIGURE 9
Overview of Sal B protection of MI/R injury.

TLR4 dimerization through competitive chimerism with MD-2 and reduces HMGB1 expression, thereby inhibiting the TLR4/NF-κB pathway, reducing the inflammatory cascade, and attenuating MI/R injury (Hu et al., 2019).

4.3 Limitations

This study systematically reviewed the potential efficacy and mechanism of action of SalB in an animal model of MI/R. This systematic review and meta-analysis had several limitations when interpreting the results.

1) The literature search was conducted only on commonly used Chinese and English databases; articles published in other languages may have been ignored. The included studies were conducted in China, hindering our results' generalizability.
2) Pre-specifying the methodological details of the meta-analysis reduces the risk of inappropriate *post hoc* analyses and selective result reporting (reporting only the results of subgroup analyses showing significant effects) (Bannach-Brown et al., 2024). Therefore, subgroups were established in advance for this meta-analysis. The subgroup analyses for infarct size and LDH levels showed statistically significant differences only between the dose subgroups for myocardial infarct size. Differences between the subgroups regarding administration method, administration time, modeling, and species were not statistically significant. However, no statistical differences between these subgroups should never be interpreted as evidence that the covariates are not related to the effect size (Hooijmans et al., 2022). In addition, the fact that substantial heterogeneity within groups remained after subgroup analyses does not mean that subgroups were not a source of heterogeneity, as these results were obtained under different experimental conditions and need to be investigated in further depth (Hooijmans et al., 2014b).
3) Among the included studies, the duration of administration varied considerably, ranging from one dose to 28 consecutive days. However, considering the diversity of dosing durations in different studies and the limitations of the number of studies, this heterogeneity was not explored, although it may be an important source of heterogeneity.
4) Publication bias was found in this study, which is common in preclinical systematic reviews and meta-analyses (Korevaar et al., 2011; Marks-Anglin and Chen, 2020). Subsequently, this study used the trim-and-fill methods to adjust for publication bias. The results indicated that the direction of the identified effect was reliable. In conclusion, the precise overall effect estimates calculated in this review should be interpreted cautiously, and more high-quality studies are needed to clarify the specific effect sizes.

4.4 Implications

In clinical practice, systematic reviews of animal studies can facilitate better scientific research and improve translation, offering

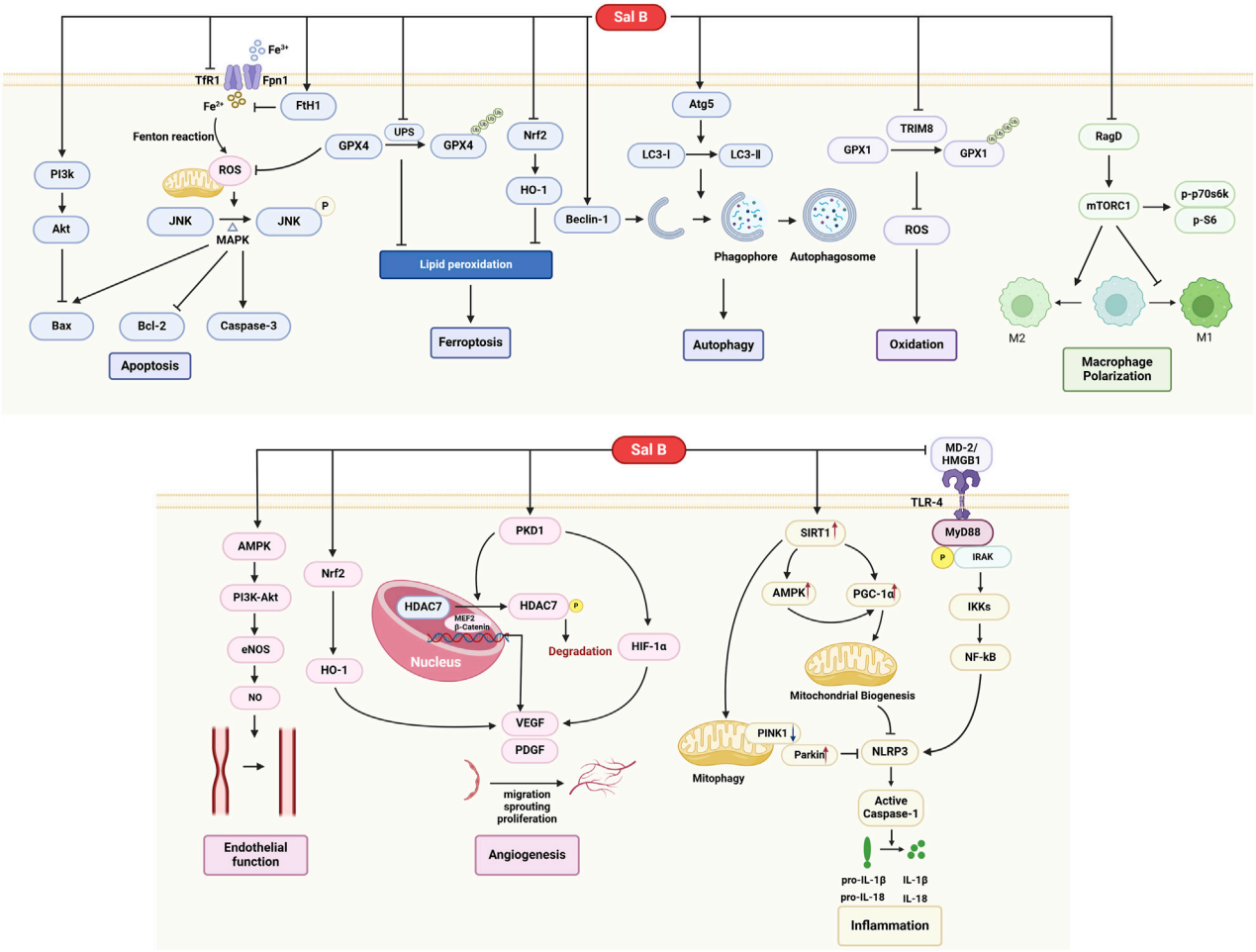


FIGURE 10
A schematic representation of cardioprotective mechanisms of Sal B for MI/R injury.

the possibility of providing evidence for the potential translational value of animal models for humans (Hooijmans et al., 2018). For future preclinical studies, a systematic review of published studies can reduce unnecessary repetition of costly animal experiments. At the same time, a systematic review and synthesis of evidence can expose biases and deficiencies in the methodology of individual studies, thus reducing misinterpretation of evidence.

The present study systematically reviewed 32 included studies and found that only one study was conducted using female animals, ten did not differentiate between animal sexes, and all other studies included males. However, there were differences in the degree of tolerance to MI/R between the sexes. In animal models of MI/R, females have a smaller infarct size, reduced ischemic systolic dysfunction, and limited fibrotic remodeling compared to males (Medzikovic et al., 2023). Reliable sex subgroup analyses were not possible due to the lack of detailed reporting on the sex of the individual metrics originating from the included studies. Few studies on female animals are currently available, highlighting the need for further studies.

Safe and effective dose ranges are essential for future animal experiments and clinical studies. Interestingly, the different studies' dosages ranged from 3 to 480 mg/kg; in almost every study, the maximum dose was more effective, with no reports of adverse effects. However, in clinical practice, there is a safe dose range for any drug. A small-sample clinical trial in a Chinese population explored the safe dose of SalB. Adverse events (SAEs) in the single-ascending-dose (SAD) and multiple-ascending-dose (MAD) studies were observed with an incidence of approximately 50% (Cheng et al., 2023). Therefore, further investigation of the optimal SalB dose range of Sal B is required.

The risk of bias assessment showed that the risk of bias for most of the included studies was rated as "unclear" because essential sources of bias, such as allocation sequence concealment, baseline characteristics, and implementation of blinding, were missing from the report. It is difficult to judge the impact of these sources of bias on the results. The lack of methodological details may distort the interpretation of the study results, and there is a risk of overestimating the effect of the intervention. Future animal studies should refine their methodological reporting as much as possible, adhering to the ARRIVE guidelines for reporting animal studies (Percie du Sert et al., 2020).

5 Conclusion

Overall, the results of this systematic review and meta-analysis suggest that Sal B has a protective effect against MI/R injury, which

may be accomplished through a complex multi-target and multi-pathway mechanism. This study provides an evidence-based assessment and reference evidence for future basic and clinical studies on SalB. Further studies are needed to elucidate the extent to which Sal B exerts its cardioprotective effects and the safety of its use.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

YY: Writing–original draft, Methodology, Investigation, Formal Analysis, Data curation, Conceptualization. ZS: Writing–review and editing, Software, Methodology, Investigation, Data curation. XS: Writing–review and editing, Software, Methodology, Investigation, Data curation. JZ: Writing–review and editing, Validation, Supervision, Methodology, Formal Analysis. TT: Writing–review and editing, Validation, Supervision, Methodology, Formal Analysis. XZ: Writing–review and editing, Validation, Supervision, Methodology, Formal Analysis. KY: Writing–review and editing, Supervision, Funding acquisition, Conceptualization.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The authors declare that this research was supported by Central High Level Traditional Chinese Medicine Hospital Project of eye Hospital China Academy of Chinese medical science (grant numbers GSP2-02).

Acknowledgments

We would like to thank Editage (www.editage.cn) for English language editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1452545/full#supplementary-material

References

Algoet, M., Janssens, S., Himmelreich, U., Gsell, W., Pusovnik, M., Van den Eynde, J., et al. (2023). Myocardial ischemia-reperfusion injury and the influence of inflammation. *Trends Cardiovasc Med.* 33 (6), 357–366. doi:10.1016/j.tcm.2022.02.005

Bannach-Brown, A., Rackoll, T., Kaynak, N., Drude, N., Aquarius, R., Vojvodić, S., et al. (2024). Navigating PROSPERO4animals: 10 top tips for efficient pre-registration of your animal systematic review protocol. *BMC Med. Res. Methodol.* 24 (1), 20. doi:10.1186/s12874-024-02146-0

Bravo-San Pedro, J. M., Kroemer, G., and Galluzzi, L. (2017). Autophagy and mitophagy in cardiovascular disease. *Circ. Res.* 120 (11), 1812–1824. doi:10.1161/CIRCRESAHA.117.311082

Bugger, H., and Pfeil, K. (2020). Mitochondrial ROS in myocardial ischemia reperfusion and remodeling. *Biochim. Biophys. Acta Mol. Basis Dis.* 1866 (7), 165768. doi:10.1016/j.bbadis.2020.165768

Chen, H. X., Xu, L., and Xu, B. H. (2012). Effect of salvianolic acid B on angiogenesis of ischemic myocardium in myocardial ischemia rats. *Chin. J. Exp. Traditional.* 18, 180–183. doi:10.13422/j.cnki.syfjx.2012.20.056

Chen, Q., Xu, Q. Y., Zhu, H., Wang, J., Sun, N., Bian, H., et al. (2023). Salvianolic acid B promotes angiogenesis and inhibits cardiomyocyte apoptosis by regulating autophagy in myocardial ischemia. *Chin. Med.* 18 (1), 155. doi:10.1186/s13020-023-00859-wAvailable at: https://www.embase.com/search/results?subaction=viewrecord&id=L2026873317&from=export.

Cheng, J., Long, J., Zhang, J., Han, L., Hu, Y., Liu, J., et al. (2023). Safety, tolerance, and pharmacokinetics of salvianolic acid B in healthy Chinese volunteers: a randomized, double-blind, placebo-controlled phase 1 clinical trial. *Front. Pharmacol.* 14, 1146309. doi:10.3389/fphar.2023.1146309

Del, Re D. P., Amgalan, D., Linkermann, A., Liu, Q., and Kitsis, R. N. (2019). Fundamental mechanisms of regulated cell death and implications for heart disease. *Physiol. Rev.* 99 (4), 1765–1817. doi:10.1152/physrev.00022.2018

Dong, Y., Chen, H., Gao, J., Liu, Y., Li, J., and Wang, J. (2019). Molecular machinery and interplay of apoptosis and autophagy in coronary heart disease. *J. Mol. Cell Cardiol.* 136, 27–41. doi:10.1016/j.yjmcc.2019.09.001

Fan, Y. C., Zhao, G. F., and Zhang, W. Z. (2004). Influence of Salvianolic acid B on pathomorphology in myocardial infarction rats. *J. Tianjin Univ. Traditional Chin. Med.* 23 (1), 12–14.

Granger, D. N., and Kvietys, P. R. (2015). Reperfusion injury and reactive oxygen species: the evolution of a concept. *Redox Biol.* 6, 524–551. doi:10.1016/j.redox.2015.08.020

Han, X., Zhang, J., Liu, J., Wang, H., Du, F., Zeng, X., et al. (2023). Targeting ferroptosis: a novel insight against myocardial infarction and ischemia-reperfusion injuries. *Apoptosis* 28 (1–2), 108–123. doi:10.1007/s10495-022-01785-2

Hausenloy, D. J., Botker, H. E., Engstrom, T., Erlinge, D., Heusch, G., Ibanez, B., et al. (2017). Targeting reperfusion injury in patients with ST-segment elevation myocardial infarction: trials and tribulations. *Eur. Heart J.* 38 (13), 935–941. doi:10.1093/eurheartj/ehw145

Heusch, G. (2020). Myocardial ischaemia–reperfusion injury and cardioprotection in perspective. *Nat. Rev. Cardiol.* 17 (12), 773–789. doi:10.1038/s41569-020-0403-y

Heusch, G., and Gersh, B. J. (2017). The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. *Eur. Heart J.* 38 (11), 774–784. doi:10.1093/eurheartj/ehw224

Ho, J. H. C., and Hong, C. Y. (2011). Salvianolic acids: small compounds with multiple mechanisms for cardiovascular protection. *J. Biomed. Sci.* 18 (1), 30. doi:10.1186/1423-0127-18-30

Hooijmans, C. R., de Vries, R. B. M., Ritskes-Hoitinga, M., Rovers, M. M., Leeflang, M. M., IntHout, J., et al. (2018). Facilitating healthcare decisions by assessing the certainty in the evidence from preclinical animal studies. *PLoS One* 13 (1), e0187271. doi:10.1371/journal.pone.0187271

Hooijmans, C. R., Donders, R., Magnuson, K., Wever, K. E., Ergün, M., Rooney, A. A., et al. (2022). Assessment of key characteristics, methodology, and effect size measures used in meta-analysis of human-health-related animal studies. *Res. Synth. Methods* 13 (6), 790–806. doi:10.1002/jrsm.1578

Hooijmans, C. R., IntHout, J., Ritskes-Hoitinga, M., and Rovers, M. M. (2014b). Meta-analyses of animal studies: an introduction of a valuable instrument to further improve healthcare. *ILAR J.* 55 (3), 418–426. doi:10.1093/ilar/ilu042

Hooijmans, C. R., Rovers, M. M., de Vries, R. B., Leenaars, M., Ritskes-Hoitinga, M., and Langendam, M. W. (2014a). SYRCLE's risk of bias tool for animal studies. *BMC Med. Res. Methodol.* 14 (1), 43. doi:10.1186/1471-2288-14-43

Hu, X. G., Xiang, X., Yang, C. Y., and Zhou, Y. S. (2010). Protective effect of salvinorin B against acute myocardial ischaemia in experimental rats. *Guangdong Med. J.* 31, 334–336. doi:10.13820/j.cnki.gdx.2010.03.005

Hu, Y., Li, Q., Pan, Y., and Xu, L. (2019). Sal B alleviates myocardial ischemic injury by inhibiting TLR4 and the priming phase of NLRP3 inflammasome. *Molecules* 24 (23), 4416. doi:10.3390/molecules24234416Available at: https://www.embase.com/search/results?subaction=viewrecord&id=L630116289&from=export.

Hu, Y., Wang, X., Li, Q., Pan, Y., and Xu, L. (2020). Salvianolic acid B alleviates myocardial ischemic injury by promoting mitophagy and inhibiting activation of the NLRP3 inflammasome. *Mol. Med. Rep.* 22 (6), 5199–5208. doi:10.3892/mmr.2020.11589

Ibáñez, B., Heusch, G., Ovize, M., and Van de Werf, F. (2015). Evolving therapies for myocardial ischemia/reperfusion injury. *J. Am. Coll. Cardiol.* 65 (14), 1454–1471. doi:10.1016/j.jacc.2015.02.032

Jiang, B., Chen, J., Xu, L., Gao, Z., Deng, Y., Wang, Y., et al. (2010). Salvianolic acid B functioned as a competitive inhibitor of matrix metalloproteinase-9 and efficiently prevented cardiac remodeling. *BMC Pharmacol.* 10. doi:10.1186/1471-2210-10-10

Kim, Y., Nurakhayev, S., Nurkesh, A., Zharkinbekov, Z., and Saparov, A. (2021). Macrophage polarization in cardiac tissue repair following myocardial infarction. *Int. J. Mol. Sci.* 22 (5), 2715. doi:10.3390/ijms22052715

Korevaar, D. A., Hooft, L., and Ter Riet, G. (2011). Systematic reviews and meta-analyses of preclinical studies: publication bias in laboratory animal experiments. *Lab. Anim.* 45 (4), 225–230. doi:10.1258/la.2011.010121

Li, L., Sun, L. S., and Xu, J. P. (2004). Therapeutical effects of salvianolic acid B on myocardial infarction in dogs. *Chin. Tradit. Pat. Med.* 26 (3), 215–218.

Li, Q., Zuo, Z., Pan, Y., Zhang, Q., Xu, L., and Jiang, B. (2022). Salvianolic acid B alleviates myocardial ischemia injury by suppressing NLRP3 inflammasome activation via SIRT1-AMPK-PGC-1α signaling pathway. *Cardiovasc Toxicol.* 22 (9), 842–857. doi:10.1007/s12012-022-09760-8

Li, Z. M., Xu, S. W., and Liu, P. Q. (2018). Salvia miltiorrhizaBurge (Danshen): a golden herbal medicine in cardiovascular therapeutics. *Acta Pharmacol. Sin.* 39 (5), 802–824. doi:10.1038/aps.2017.193

Lin, C., Liu, Z., Lu, Y., Yao, Y., Zhang, Y., Ma, Z., et al. (2016). Cardioprotective effect of Salvianolic acid B on acute myocardial infarction by promoting autophagy and neovascularization and inhibiting apoptosis. *J. Pharm. Pharmacol.* 68, 941–952. doi:10.1111/jphp.12567

Lin, Z. R., Chen, C., Tian, D. K., Gu, Q., Qu, S. F., Ruan, A. H., et al. (2011). Comparative study of salvinorin A and salvinorin B against myocardial ischaemia-reperfusion injury in rats. *Lishizhen Med. Materia Medica Res.* 22, 412–414. doi:10.3969/j.issn.1008-0805.2011.02.068

Liu, C., Chen, X. D., Sun, J. A., Zhang, S. H., and Zhang, Q. (2022). Study of the protective mechanism of salvinorin B in a rat model of myocardial infarction by inhibiting iron death through modulation of Cx43. *Chin. J. Pathophysiol.* 38, 1032–1039. doi:10.3969/j.issn.1000-4718.2022.06.010

Liu, H., Liu, W., Qiu, H., Zou, D., Cai, H., Chen, Q., et al. (2020a). Salvianolic acid B protects against myocardial ischaemia-reperfusion injury in rats via inhibiting high mobility group box 1 protein expression through the PI3K/Akt signalling pathway. *Schmiedeb. Arch. Pharmacol.* 393 (8), 1527–1539. doi:10.1007/s00210-019-01755-7

Liu, J., Chen, L., and Lu, H. (2018). Cardioprotective effect of salvianolic acid B against isoproterenol-induced inflammation and histological changes in a cardiotoxicity rat model. *Trop. J. Pharm. Res.* 17 (11), 2189–2197. doi:10.4314/tjpr.v17i11.12

Liu, N., Yang, L., and Liu, P. (2020c). Protective effects of Salvia divinorum B on ischaemic myocardial tissue in rats studied based on the PKD1/HDAC7 axis. *Chin. Pharmacol. Bull.* 36 (12), 1704–1710. doi:10.3969/j.issn.1001-1978.2020.12.014

Liu, N., Yang, L., and Mao, B. Y. (2020b). Angiogenesis promotion function of salvianolic acid B in rats with myocardial infarction via PKD1 - HIF - 1α - VEGF pathway. *Chin. Pharmacol. Bull.* 36 (7), 984–990. doi:10.3969/j.issn.1001-1978.2020.07.018

Lu, B., Li, J., Gui, M., Yao, L., Fan, M., Zhou, X., et al. (2022). Salvianolic acid B inhibits myocardial I/R-induced ROS generation and cell apoptosis by regulating the TRIM8/GPX1 pathway. *Pharm. Biol.* 60 (1), 1458–1468. doi:10.1080/13880209.2022.2096644

Marks-Anglin, A., and Chen, Y. (2020). A historical review of publication bias. *Res. Synth. Methods* 11 (6), 725–742. doi:10.1002/jrsm.1452

Medzikovic, L., Azem, T., Sun, W., Rejali, P., Esdin, L., Rahman, S., et al. (2023). Sex differences in therapies against myocardial ischemia-reperfusion injury: from basic science to clinical perspectives. *Cells* 12 (16), 2077. doi:10.3390/cells12162077

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 74, 790–799. doi:10.1016/j.rec.2021.07.010Available at: https://www.bmj.com/content/372/bmj.n71.

Pan, C., Lou, L., Huo, Y., Singh, G., Chen, M., Zhang, D., et al. (2011). Salvianolic acid B and Tanshinone IIA attenuate myocardial ischemia injury in mice by no production through multiple pathways. *Ther. Adv. Cardiovasc Dis.* 5 (2), 99–111. doi:10.1177/1753944710396538

Percie du Sert, N., Hurst, V., Ahluwalia, A., Alam, S., Avey, M. T., Baker, M., et al. (2020). The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. *PLoS Biol.* 18 (7), e3000410. doi:10.1371/journal.pbio.3000410

Popov, S. V., Mukhomedzyanov, A. V., Voronkov, N. S., Derkachev, I. A., Boshchenko, A. A., Fu, F., et al. (2023). Regulation of autophagy of the heart in ischemia and reperfusion. *Apoptosis* 28 (1–2), 55–80. doi:10.1007/s10495-022-01786-1

Puymirat, E., Cayla, G., Cottin, Y., Elbaz, M., Henry, P., Gerbaud, E., et al. (2019). Twenty-year trends in profile, management and outcomes of patients with ST-segment elevation myocardial infarction according to use of reperfusion therapy: data from the FAST-MI program 1995-2015. *Am. Heart J.* 214, 97–106. doi:10.1016/j.ahj.2019.05.007

Qiao, Z., Ma, J., and Liu, H. (2011). Evaluation of the antioxidant potential of salvia miltiorrhiza ethanol extract in a rat model of ischemia-reperfusion injury. *Molecules* 16 (12), 10002–10012. doi:10.3390/molecules161210002

Qiao, Z., and Xu, Y. (2016). Salvianolic Acid B alleviating myocardium injury in ischemia reperfusion rats. *Afr. J. Trad. Complement. Altern. Med.* 13 (4), 157–161. doi:10.21010/ajtcam.v13i4.20

Reed, G. W., Rossi, J. E., and Cannon, C. P. (2017). Acute myocardial infarction. *Lancet* 389 (10065), 197–210. doi:10.1016/S0140-6736(16)30677-8

Ritskes-Hoitinga, M., Leenaars, M., Avey, M., Rovers, M., and Scholten, R. (2014). Systematic reviews of preclinical animal studies can make significant contributions to health care and more transparent translational medicine. *Cochrane Database Syst. Rev.* 2014 (3), ED000078. doi:10.1002/14651858.ED000078

Sánchez-Hernández, C. D., Torres-Alarcón, L. A., González-Cortés, A., and Peón, A. N. (2020). Ischemia/reperfusion injury: pathophysiology, current clinical management, and potential preventive approaches. *Mediat. Inflamm.* 2020, 8405370. doi:10.1155/2020/8405370

Sciarretta, S., Maejima, Y., Zablocki, D., and Sadoshima, J. (2018). The role of autophagy in the heart. *Annu. Rev. Physiol.* 80, 1–26. doi:10.1146/annurev-physiol-021317-121427

Shen, Y., Shen, X. Y., Wang, S. L., Zhang, Y. Y., Wang, Y., Ding, Y., et al. (2022). Protective effects of Salvianolic acid B on rat ferroptosis in myocardial infarction through upregulating the Nrf2 signaling pathway. *Int. Immunopharmacol.* 112, 109257. doi:10.1016/j.intimp.2022.109257

Shi, B., Ma, M., Zheng, Y., Pan, Y., and Lin, X. (2019). mTOR and Beclin1: two key autophagy-related molecules and their roles in myocardial ischemia/reperfusion injury. *J. Cell Physiol.* 234 (8), 12562–12568. doi:10.1002/jcp.28125

Song, Y. P., Kong, L. S., Wu, J., Miao, A. R., and Zhao, G. (2007). Comparison of the effect of salvianolic acid A and B on acute myocardial ischemia of rats. *Chin. J. Inf. Traditional Chin. Med.*, 36–38.

Wang, B. H., Fu, W., and Li, Z. T. (2004). Mechanistic study on the myocardial protective effect of salvinorin B on rats with acute myocardial ischaemia/reperfusion injury. *J. Tianjin Univ. Traditional Chin. Med.* 23 (3), 132–133.

Wang, X., Wang, Y., Jiang, M., Zhu, Y., Hu, L., Fan, G., et al. (2011). Differential cardioprotective effects of salvianolic acid and tanshinone on acute myocardial infarction are mediated by unique signaling pathways. *J. Ethnopharmacol.* 135 (3), 662–671. doi:10.1016/j.jep.2011.03.070

Wang, X. Y., Wang, M., Sun, S. J., Chen, H. X., Jiang, B. P., and Xu, L. (2016). Correlation between the protection of ischaemic myocardium by salvinorin B and the expression of inflammatory vesicles NLRP3 in rats. *Chin. Pharmacol. Bull.* 32, 1383–1388. doi:10.3969/j.issn.1001-1978.2016.10.011

Wei, B., Sun, C., Wan, H., Shou, Q., Han, B., Sheng, M., et al. (2023). Bioactive components and molecular mechanisms of Salvia miltiorrhiza Bunge in promoting blood circulation to remove blood stasis. *J. Ethnopharmacol.* 317, 116697. doi:10.1016/j.jep.2023.116697

Xia, Y., Zhang, H. J., and Nie, Y. L. (2018). Salvianolic acid B pretreatment protects myocardial ischemia/reperfusion injury through improvement of energy metabolism. *Drug Eval. Res.* 41, 2210–2213. doi:10.7501/j.issn.1674-6376.2018.12.014

Xiang, Q., Yi, X., Zhu, X. H., Wei, X., and Jiang, D. S. (2024). Regulated cell death in myocardial ischemia-reperfusion injury. *Trends Endocrinol. Metab.* 35 (3), 219–234. doi:10.1016/j.tem.2023.10.010

Xu, J., Yang, X., Sun, L., and Wu, H. (2003). Protective effect of savianolic acid B on myocardial ischemia/reperfusion in rats. *Chin. Pharm. J.*, 35–37.

Xu, L., Deng, Y., Feng, L., Li, D., Chen, X., Ma, C., et al. (2011). Cardio-protection of salvianolic acid b through inhibition of apoptosis network. *PLoS ONE* 6 (9), e24036.

doi:10.1371/journal.pone.0024036Available at: https://www.embase.com/search/results?subaction=viewrecord&id=L362504721&from=export.

Xu, S., Xu, C., Xu, J., Zhang, K., and Zhang, H. (2023b). Macrophage heterogeneity and its impact on myocardial ischemia-reperfusion injury: an integrative review. *J. Inflamm. Res.* 16, 5971–5987. doi:10.2147/JIR.S436560

Xu, X., Mao, C., Zhang, C., Zhang, M., Gong, J., and Wang, X. (2023a). Salvianolic acid B inhibits ferroptosis and apoptosis during myocardial ischemia/reperfusion injury via decreasing the ubiquitin-proteasome degradation of GPX4 and the ROS-JNK/MAPK pathways. *Molecules* 28 (10), 4117. doi:10.3390/molecules28104117Available at: https://www.embase.com/search/results?subaction=viewrecord&id=L641431150&from=export.

Xue, L., Wu, Z., Ji, X. P., Gao, X. Q., and Guo, Y. H. (2014). Effect and mechanism of salvianolic acid B on the myocardial ischemia-reperfusion injury in rats. *Asian Pac J. Trop. Med.* 7 (4), 280–284. doi:10.1016/S1995-7645(14)60038-9

Yang, F. G., Zhang, A. Y., Chen, Z. Y., Lian, Z. X., Liu, G. X., and Dong, G. X. (2008). Effects of salvianolic acid B on cardiovascular endothelial cells and platelet activation in a rabbit model of ischemia-reperfusion. *J. Integr. Med.* 6, 1250–1254. doi:10.3736/jcim20081208

Yeh, R. W., Sidney, S., Chandra, M., Sorel, M., Selby, J. V., and Go, A. S. (2010). Population trends in the incidence and outcomes of acute myocardial infarction. *N. Engl. J. Med.* 362 (23), 2155–2165. doi:10.1056/NEJMoa0908610

Zhang, C. H., Yan, Y. J., and Luo, Q. (2024). The molecular mechanisms and potential drug targets of ferroptosis in myocardial ischemia-reperfusion injury. *Life Sci.* 340, 122439. doi:10.1016/j.lfs.2024.122439

Zhang, L., Yuan, D. P., Xu, L., Jiang, B. P., and Fang, H. T. (2008). Protective mechanism of salvianolic acid B on myocardial ischemia-reperfusion injury of rats. *Traditional Chin. Drug Res. Clin. Pharmacol.*, 467–469. doi:10.19378/j.issn.1003-9783.2008.06.017

Zhang, Q., Yang, L. H., and Li, H. (2013). Protective effect of salvianolic acid B on myocardium of myocardial infarction model rats and its molecular mechanism. *J. Jilin Univ. Ed.* 39, 268–272. doi:10.7694/jldxyxb20130217

Zhao, G. F., Zhang, H. X., and Fan, Y. C. (2004). Protective effect of salvinorin B on myocardial ischaemia-reperfusion injury in rats. *J. Liaoning Univ. Traditional Chin. Med.* 6 (1), 55–56. doi:10.13194/j.jlunivtcm.2004.01.56.zhaogf.037

Zhao, K., Chen, X., Bian, Y., Zhou, Z., Wei, X., and Zhang, J. (2023). Broadening horizons: the role of ferroptosis in myocardial ischemia-reperfusion injury. *Naunyn Schmiedeb. Arch. Pharmacol.* 396 (10), 2269–2286. doi:10.1007/s00210-023-02506-5

Zhao, M., Li, F., Jian, Y., Wang, X., Yang, H., Wang, J., et al. (2020). Salvianolic acid B regulates macrophage polarization in ischemic/reperfused hearts by inhibiting mTORC1-induced glycolysis. *Eur. J. Pharmacol.* 871, 172916. doi:10.1016/j.ejphar.2020.172916

Zhou, D., Quan, W., Guan, Y., Zhu, Y. R., Guo, C., Wang, Y. H., et al. (2013). Protective effect of salvinorin B on myocardial ischaemia/reperfusion injury in rats via Akt-eNOS pathway. *Shaanxi J. Traditional Chin. Med.* 34, 104–107.

Zhou, D., Tian, T., Shu, Q., Zhao, X. Y., Ma, W., Zhang, H. J., et al. (2018). Effect of salvianolic acid B on angiogenesis of myocardial ischemia in rats. *Chin. Traditional Herb. Drugs* 49, 5166–5169. doi:10.7501/j.issn.0253-2670.2018.21.031

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 30 October 2024
DOI 10.3389/fphar.2024.1444388

OPEN ACCESS

EDITED BY
Kuo Gao,
Beijing University of Chinese Medicine, China

REVIEWED BY
Diraviyam Thirumalai,
SASTRA University, India
Yunhui Chen,
Chengdu University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Bojun Chen,
gzcbj@gzucm.edu.cn
Jing Zeng,
15148980978@163.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 05 June 2024
ACCEPTED 21 October 2024
PUBLISHED 30 October 2024

CITATION
Yu L, Wu L, Peng W, Huang P, Chen L, Deng Y, Wang M, Zeng J and Chen B (2024) Efficacy and safety of guanxinshutong capsule combined with western medicine on stable angina pectoris: a systematic review and meta-analysis. *Front. Pharmacol.* 15:1444388. doi: 10.3389/fphar.2024.1444388

Efficacy and safety of guanxinshutong capsule combined with western medicine on stable angina pectoris: a systematic review and meta-analysis

Liyuan Yu[1,2†], Lulu Wu[1,2†], Weihang Peng[1,2†], Peiying Huang[1,2], Li Chen[2,3], Yi Deng[1,2], Meida Wang[1,2], Jing Zeng[2,3*] and Bojun Chen[1,2,3*]

[1]The Second Clinical Medical School of Guangzhou University of Chinese Medicine, Guangzhou, China, [2]Guangdong Provincial Key Laboratory of Research on Emergency in Traditional Chinese Medicine, Clinical Research Team of Prevention and Treatment of Cardiac Emergencies with Traditional Chinese Medicine, Guangzhou, China, [3]Emergency Department of Guangdong Provincial Hospital of Traditional Chinese Medicine, Guangzhou, China

Aims: To systematically evaluate the efficacy and safety of the Guanxinshutong capsule (GXST) combined with Western medicine (WM) in treating stable angina pectoris (SAP).

Methods: Randomized controlled trials (RCTs) evaluating the efficacy of GXST combined with WM for the treatment of patients with SAP were searched across several databases, including the Cochrane Library, PubMed, Embase, the Chinese National Knowledge Infrastructure (CNKI), the Chinese Science and Technology Journal Database (VIP), and Wan Fang, from inception until 30 April 2024. Two independent reviewers rigorously performed study selection, data extraction, and quality assessment. Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was employed to assess the methodological quality of included RCTs. R version 4.2.2 was applied for data synthesis.

Results: Between 2012 and 2024, 31 RCTs involving 4,172 patients were identified, with 2,101 in the experimental group and 2,071 in the control group. GXST and WM combination was significantly more effective than WM alone across several metrics: clinical efficacy rate (odds ratio [OR] = 4.05, 95% confidence interval [CI] = 3.42–4.80), electrocardiogram improvement (OR = 3.39, 95% CI = 2.35–4.87), enhancement in left ventricular ejection fraction (mean difference [MD] = 1.07, 95% CI = 0.69–1.46), reduction in total cholesterol levels (MD = −0.78, 95% CI = −1.20 to −0.35), decrease in tumor necrosis factor-alpha (MD = −1.36, 95% CI = −2.18 to −0.53), and improvement in Chinese medicine evidence score (OR = 3.77, 95% CI = 2.20–6.43). No significant difference was observed in the reduction in C-reactive protein levels (MD = −6.66, 95% CI = −15.91 to 2.59), triglyceride levels (MD = −1.62, 95% CI = −3.39 to 0.15), or in the occurrence of adverse drug reactions (OR = 0.60, 95% CI = 0.23–1.57). Based on meta-regression and subgroup analyses, the observed heterogeneity was attributed to variations in GXST capsule dosage, the duration of treatment, and the baseline characteristics of patients.

Conclusion: GXST and WM combination therapy demonstrates the potential to enhance clinical outcomes for SAP patients. Nevertheless, additional rigorous studies are imperative to substantiate the reliability and safety of this combined treatment modality.

Systematic Review Registration: The protocols for this meta-analysis were registered in the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=543537, Identifier CRD42024543537).

KEYWORDS

stable angina pectoris, guanxinshutong capsule, efficacy, safety, meta-analysis

1 Introduction

Stable angina pectoris (SAP) is a manifestation of coronary heart disease (CHD) (Karabağ et al., 2018). The underlying mechanism involves severe stenosis and obstruction of coronary arteries, resulting in an imbalance between coronary blood flow and myocardial demand (Ford et al., 2018). This imbalance, often due to increased cardiac load, leads to acute ischemia and hypoxia of the myocardium (Gunata and Parlakpinar, 2021). Symptoms present as transient discomfort in the posterior sternum and precordial area, characterized by short-lived compressive pain, heaviness, or suffocation (i.e., angina pectoris (Gunata and Parlakpinar, 2021)). These symptoms can be triggered by factors such as exertion, emotional stress, and overeating (Joshi and de Lemos, 2021). Typically, the symptoms subside within minutes after rest or administration of nitrates (Shao et al., 2020). Additionally, among non-communicable diseases (NCDs), cardiovascular diseases (CVDs) are a major contributor to the disease burden and the leading cause of death worldwide (2020).

The treatment priorities for SAP are to alleviate symptoms, improve quality of life, and prevent myocardial infarction and death (Feng et al., 2023). First-line medications include nitrates, β-blockers, calcium channel blockers, and antiplatelet agents (Liu et al., 2022). These medications belong to a category of chemically synthesized drugs and are not derived from natural plants; therefore, they are commonly referred to as Western medicine (WM). These drugs aim to achieve several therapeutic goals, including reducing myocardial oxygen demand and heart workload, improving blood flow, and preventing thrombus formation. Nitrates can relax vascular smooth muscle and reduce heart preload, thereby decreasing myocardial oxygen demand and alleviating angina symptoms (Patra et al., 2023; Singh et al., 2024). β-Blockers have been shown to reduce heart rate, blood pressure, and contractility, thereby decreasing myocardial oxygen demand and alleviating angina symptoms (Palatini et al., 2024). In low-risk populations, aspirin, used for primary prevention, has been shown to reduce the risk of non-fatal myocardial infarction, non-fatal stroke, and vascular death (Judge et al., 2020). However, these WM therapies have some drawbacks. For example, β-blockers are associated with bradycardia and atrioventricular block (Lu et al., 2016); nitrate drugs may cause hypotension, increased intracranial pressure, dizziness, and headache (Londono-Hoyos et al., 2018; Rivasi et al., 2020); and antiplatelet agents may lead to severe bleeding and gastrointestinal adverse reactions (Benamouzig et al., 2022), with the risk of bleeding potentially outweighing the benefits. For patients with severe CHD who are inadequately controlled with medication, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) may be considered (Xie et al., 2021). While PCI and CABG can effectively improve blood flow and alleviate angina symptoms, they also pose risks of postoperative complications such as thrombus formation, myocardial infarction, and heart failure (Beerkens et al., 2022). Moreover, these surgeries are often characterized by a long recovery period, which significantly reduces the quality of life of patients. Furthermore, continuous medical treatment and monitoring are essential due to the chronic nature of SAP. Therefore, developing new adjunctive medications is crucial to address these limitations, improve the quality of life, and enhance treatment adherence among patients with SAP.

Guanxinshutong capsule (GXST) is a traditional Chinese medicine (TCM) that possesses therapeutic effects such as promoting blood circulation to remove blood stasis, activating meridians and collaterals, and promoting the flow of qi to relieve pain (Li et al., 2019). It is clinically used for the treatment of CHD, acute myocardial infarction, angina pectoris, and other diseases (Wang et al., 2021). This capsule is composed of five distinct traditional Chinese medicines (TCMs), including *Salvia miltiorrhiza* Bunge [Lamiaceae, salviae miltiorrhizae radix et rhizoma], *Choerospondias axillaris* (Roxb.) [Anacardiaceae, Choerospondiatis Fructus], *Syzygium aromaticum* (L.) [Myrtaceae, Caryophylliflos], *Cinnamomum camphora* (L.) Presl [Lauraceae, Borneolum], and *Cephalostachyum chinense* (Rendle) [Poaceae, Bambusae Concretio Silicea]. In the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, http://tcmspw.com/tcmsp.php), the screening criteria were established as Dyslipidemia (DL) ≥0.18, Obesity (OB) ≥40%, Cancer Colon 2 (Caco-2) ≥−0.4, and Hyperlipidemia (HL) ≥4 (Zhang et al., 2020), and the botanical drug ingredients of GXST were queried. The composition is detailed in Supplementary File S1.

Previous clinical studies have shown that the addition of GXST to conventional treatment can help alleviate angina symptoms in patients with SAP and improve their quality of life (Wang et al., 2021). Through its effects of promoting blood circulation to remove blood stasis and activating meridians and collaterals, GXST effectively improves coronary blood circulation, increases coronary blood flow, and reduces the degree of myocardial ischemia and hypoxia (Zhang et al., 2021). It can also provide comprehensive health protection for patients by improving blood

circulation, relieving pain, and preventing further deterioration of the disease (Wang et al., 2020). Two previous meta-analyses (Sui et al., 2016; Jia and Wei, 2017) have shown that GXST and WM combination therapy can improve the treatment efficacy and electrocardiogram (ECG) performance of SAP patients. However, there is currently no comprehensive systematic evaluation and safety analysis of the therapeutic effects of this combination therapy, including the improvement of cardiac function, laboratory indicators, and TCM syndrome scores. Moreover, the two previous meta-analyses were published 5 years ago, and the number of included studies was relatively small, with one meta-analysis including 12 studies (Sui et al., 2016) and the other 7 studies (Jia and Wei, 2017). The present meta-analysis has included more up-to-date studies, thus enhancing the reliability and generalizability of the results. Additionally, we have considered more outcome indicators to comprehensively evaluate the efficacy of GXST and WM combination therapy in treating patients with SAP, providing a reference for clinical practice and future research.

2 Materials and methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension Statement and was registered with the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=543537, registration number CRD42024543537). A PRISMA checklist is detailed in Supplementary File S2.

2.1 Search strategy

A comprehensive search for randomized controlled trials (RCTs) evaluating the efficacy of GXST and WM combination therapy in treating patients with SAP was conducted across seven databases, including PubMed, Embase, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wan Fang Database, Chinese Science and Technology Journal Database (VIP), and Chinese Biomedical Literature Database. The search spanned from the inception of each database until 30 April 2024. Search terms in English encompassed “GuanxinShutong capsule” and “stable angina pectoris”. The search methodology applied is delineated in Supplementary File S3.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows.

(1) Study subjects: Patients with SAP.
(2) Control group treatment: The control group received WM treatments, including nitrates, β-blockers, calcium channel blockers, and antiplatelet agents.
(3) Experimental group treatment: The experimental group received a combination of GXST intervention and the same WM treatments as the control group.
(4) Study Design: RCTs.
(5) Selected study outcomes: Studies were considered if any of the following outcomes occurred.

Primary outcomes.

(1) Effective clinical rate: This was defined as the percentage of patients who showed improvement after treatment. The effective clinical rate was calculated by subtracting the number of ineffective cases from the total number of cases and dividing the result by the total number of cases. The assessment of treatment efficacy was based on angina symptoms. Significant efficacy was defined as substantial alleviation of symptoms and signs after therapy. An effective outcome referred to an improvement in symptoms and signs after treatment, whereas an ineffective outcome denoted no significant change or a deterioration in symptoms and signs after treatment.
(2) Effective ECG rate: This was defined as the percentage of patients who showed improved myocardial ischemia, indicated by changes in their ECGs, such as the normalization of T-wave inversion.

Secondary outcomes.

(1) Changes in left ventricular ejection fraction (LVEF) and C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), total cholesterol (TC), and triglyceride (TG) levels were observed before and after treatment.
(2) Chinese medicine evidence score: The Chinese medicine evidence score was calculated according to the Guidelines for Clinical Research of New Chinese Medicines (GCRNCM). Symptoms of chest tightness, shortness of breath, palpitation, and chest pain were observed in both groups and categorized into 2 (mild), 4 (moderate), and 6 (severe) points according to GCRNCM. Significant efficacy was defined as the disappearance of pre-treatment symptoms and reduction in the total score by >80%; an effective outcome was defined as the relief of pre-treatment symptoms and reduction in the total score by about 40%–79%; and an ineffective outcome was defined as insignificant relief of pre-treatment symptoms and reduction in the total score by <40%.
(3) Adverse drug reactions (ADRs).

The exclusion criteria were as follows.

(1) Incomplete or significantly erroneous outcome data.
(2) Patients with other severe CVDs such as acute myocardial infarction or heart failure.
(3) Studies showing randomization failure or significant baseline differences between groups.
(4) The experimental or control group received other TCMs or herbal treatments.

2.3 Data extraction

A comprehensive approach integrating software and manual methods was employed to identify relevant studies. Initially, all

duplicate studies were rigorously eliminated. Subsequently, two reviewers independently screened titles and abstracts, adhering strictly to predefined inclusion and exclusion criteria, followed by a thorough review of the full text of the selected articles and data extraction. The extracted data encompassed the first author's name, publication year, sample size, age range, specific disease progression metrics, treatment duration, and dosage. Outcome indicators and pertinent quality assessment information were also extracted. The obtained results were cross-verified to ensure precision and accuracy. Any discrepancies were resolved through consensus discussions between the two reviewers, or with a third party, if necessary.

2.4 Analysis of study quality

The risk of bias in the included RCTs was rigorously assessed using version 2 of the Cochrane Collaboration's risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019), as outlined by Sterne et al. (2019). This instrument scrutinized five pivotal domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and the selection of the reported result. Each domain was categorized as having "low-risk," "high-risk," or "some concerns" of bias. A trial was considered to have an overall 'low risk' of bias only if all domains were unanimously classified as having a 'low risk'. Any discrepancies were resolved through consensus discussions between two reviewers, or with a third party, if necessary, to ensure accuracy and consistency.

2.5 Data analysis

All statistical analyses were performed using R statistical software (version 4.2.2) and its Meta package (version 6.5.0). Continuous and categorical variables were evaluated using the mean difference (MD) and odds ratio (OR), respectively, along with a 95% confidence interval (95% CI). The statistical significance was set at $p < 0.05$. Heterogeneity within each study was assessed using the Q statistic and I^2 test. Forest and Labbé plots were employed to visually inspect heterogeneity and identify variation sources. The I^2 test was also applied to evaluate heterogeneity during data integration. When I^2 was less than 50%, indicating low heterogeneity, a fixed-effects model was applied. Conversely, a random-effects model was applied when I^2 exceeded 50%, suggesting high heterogeneity. To address potential heterogeneity and ensure the robustness of the results, meta-regression and sensitivity analyses were performed using the "metareg" and "metainf" commands for all outcome indicators with I^2 values $\geq$ 50%. In addition, subgroup analyses were conducted based on positive covariates identified in the meta-regression. Sensitivity analyses were performed by excluding each literature individually. For outcomes involving more than five studies, potential publication bias was explored using adjusted funnel plots and Egger's and Begg's tests, implemented via the "metabias" command.

3 Results

3.1 Literature retrieval and study characteristics

An initial retrieval yielded 236 studies, of which 31 articles (Li and Li, 2012; Wang et al., 2012; Cao and Yue, 2013; Jiang, 2013; Liang et al., 2013; Liu, 2013; Yu et al., 2013; Qi, 2015; Wang and Wu, 2015; Wu et al., 2015; Zhao et al., 2015; An, 2016; Peng, 2016; Ji, 2017; Ren et al., 2017; Yu, 2017; Zhu and Liu, 2017; Geng et al., 2018; Shi and Abudujilili, 2018; Yang and Zhang, 2018; Li, 2019; Li et al., 2019; Liu et al., 2019; Wan et al., 2019; Luo, 2021; Wang, 2021; You, 2021; Cai, 2022; Pan et al., 2022; Shi, 2022; Jia and Li, 2023) were included in the final analysis. The flowchart of the literature search and screening process is depicted in Figure 1. The characteristics of eligible studies are outlined in Table 1.

3.2 Analysis of study quality

Of the included studies, 14 RCTs (45.16%) (Cao and Yue, 2013; Yu et al., 2013; Wang and Wu, 2015; An, 2016; Ren et al., 2017; Zhu and Liu, 2017; Shi and Abudujilili, 2018; Li, 2019; Luo, 2021; Wang, 2021; You, 2021; Pan et al., 2022; Shi, 2022; Jia and Li, 2023) used the randomized table of numbers method, 2 RCTs (6.45%) (Zhao et al., 2015; Li et al., 2019) used envelope sampling, and 1 RCT (3.23%) (Wu et al., 2015) used random lotteries. The remaining 14 RCTs (45.16%) (Li and Li, 2012; Wang et al., 2012; Jiang, 2013; Liang et al., 2013; Liu, 2013; Qi, 2015; Peng, 2016; Ji, 2017; Yu, 2017; Geng et al., 2018; Yang and Zhang, 2018; Liu et al., 2019; Wan et al., 2019; Cai, 2022) did not state the specific randomization method, which might introduce uncertainties in the study results. None of the studies provided an exhaustive explanation of allocation concealment, raising "some concerns" about the randomization process. Only 2 RCTs (6.45%) (Wang et al., 2012; Li et al., 2019) reported using double-blind methods; none of the other studies mentioned blinding. None of the trials clearly described pre-designed procedures or conducted adequate analyses to assess the effects of intervention allocation. This led to "some concerns" about the "selection of the reported result" and "deviations from intended interventions". Since all outcomes were assessed based on a specific number of patients, the likelihood of bias due to missing outcome data is minimal. However, clinical efficiency and the Chinese medicine evidence score were considered "high risk" for "measurement of the outcome" due to their subjective nature. Therefore, the studies were considered "high risk' for 'overall bias" (Figure 2).

3.3 Meta-analysis results

3.3.1 Primary outcomes

3.3.1.1 Effective clinical rate

The efficacy was evaluated based on the improvement of clinical symptoms. Thirty-one studies (Li and Li, 2012; Wang et al., 2012; Cao and Yue, 2013; Jiang, 2013; Liang et al., 2013; Liu, 2013; Yu et al., 2013; Qi, 2015; Wang and Wu, 2015; Wu et al., 2015; Zhao et al., 2015; An, 2016; Peng, 2016; Ji, 2017; Ren et al., 2017; Yu, 2017; Zhu

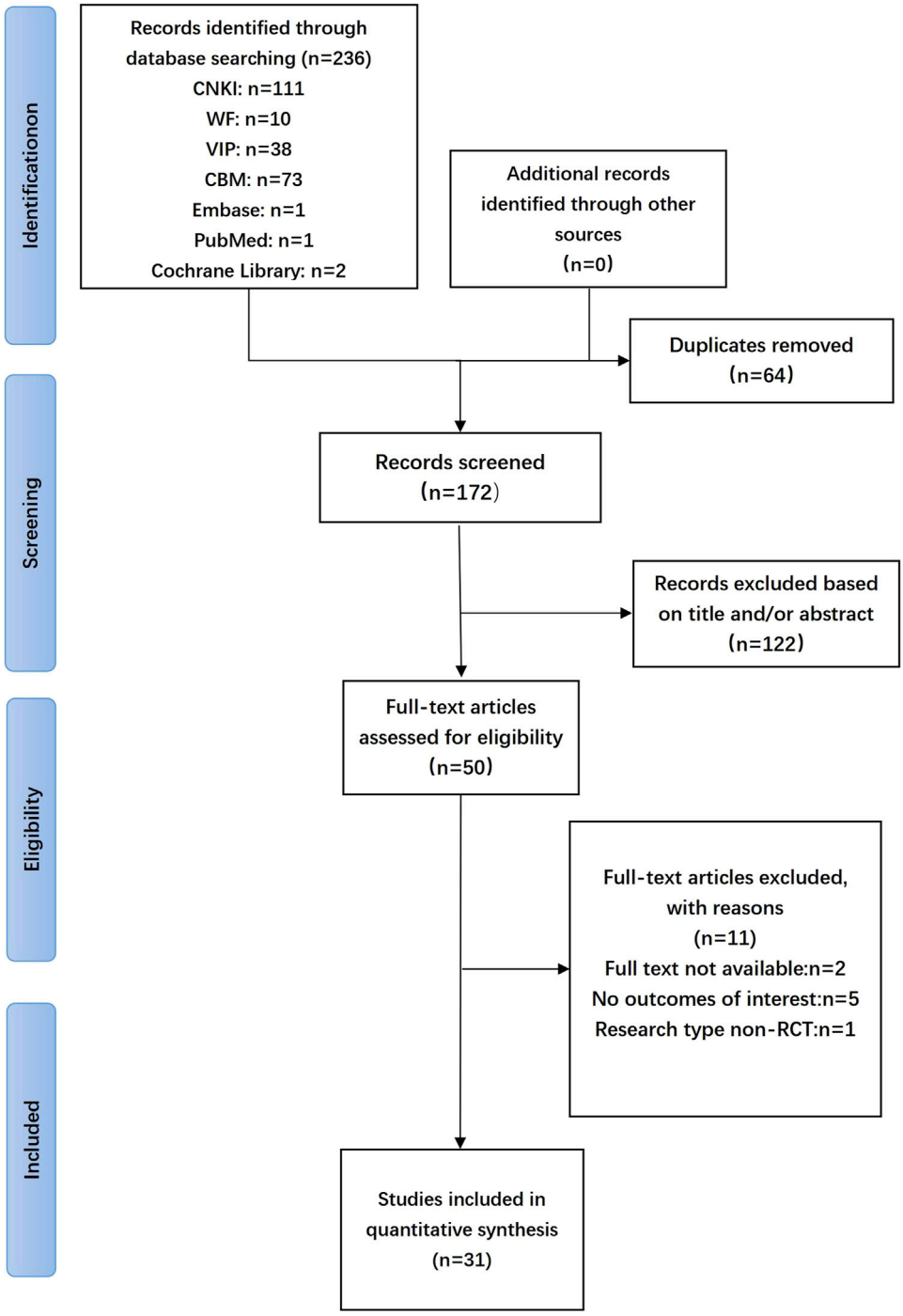


FIGURE 1
Flow diagram of systematic literature search.

and Liu, 2017; Geng et al., 2018; Shi and Abudujilili, 2018; Yang and Zhang, 2018; Li, 2019; Li et al., 2019; Liu et al., 2019; Wan et al., 2019; Luo, 2021; Wang, 2021; You, 2021; Cai, 2022; Pan et al., 2022; Shi, 2022; Jia and Li, 2023) discussed clinical efficacy. Since homogeneity was found between the studies (p = 0.42, I^2 = 3%), the fixed-effects model was utilized, and the results demonstrated that the experimental group exhibited a significant improvement in patients' clinical symptoms (OR = 4.05, 95% CI = 3.42–4.80) (Figure 3).

3.3.1.2 Effective rate in ECG

Thirteen articles (Li and Li, 2012; Wang et al., 2012; Cao and Yue, 2013; Yu et al., 2013; Wang and Wu, 2015; Wu et al., 2015; An, 2016; Peng, 2016; Ren et al., 2017; Geng et al., 2018; Liu et al.,

TABLE 1 Characteristics of the included studies.

Study ID	Sample size (M/F)		Age (years)		Course of disease (years)		Interventions		
	T	C	T	C	T	C	T	C	
Li et al. (2019)	143 (73/70)	144 (82/62)	56.6 ± 8.1	55.3 ± 8.3	NR	NR	GXST + WM	WM	Aspirin Atorvastatin ACEI/ARB β-receptor blocker CCB
Ji (2017)	43 (20/23)	42 (24/18)	45.12 ± 0.61	46.12 ± 0.41	1–5	1–6	GXST + WM	WM	Aspirin 100 mg po, qd Atorvastatin 10 mg po, qd ISDN 10 mg po, qd
Ren et al. (2017)	41 (25/16)	40 (23/17)	66.05 ± 8.48	65.48 ± 8.37	NR	NR	GXST + WM	WM	Aspirin 100 mg po, qd Atorvastatin 10 mg po, qd Metoprolol 90–190 mg po,qd
Wan et al. (2019)	200(NR)	200(NR)	NR	NR	NR	NR	GXST + WM	WM	NR
Liang et al. (2013)	40 (27/13)	40 (29/11)	38–83	40–84	6–24	7–24	GXST + WM	WM	Aspirin Atorvastatin ACEI Metoprolol
Yang and Zhang (2018)	30 (19/11)	30 (18/12)	65.45 ± 1.23	66.45 ± 1.98	4.12 ± 1.34	4.23 ± 1.05	GXST + WM	WM	ISDN 10 mg po, qd Aspirin 100 mg po, qd Atorvastatin 10 mg po, qd
Wang (2021)	40 (24/16)	40 (22/18)	43.42 ± 7.39	43.68 ± 7.45	4.41 ± 1.16	4.58 ± 1.24	GXST + WM	WM	ISDN 20 mg po, tid
You (2021)	30 (16/14)	30 (18/12)	57.43 ± 3.34	56.52 ± 3.51	NR	NR	GXST + WM	WM	ISDN 30 mg po,tid
Jia and Li (2023)	57 (31/26)	57 (34/23)	60.05 ± 5.91	59.42 ± 6.28	0.02–0.06	0.02–0.07	GXST + WM	WM	Fluvastatin 40 mg po, qd
Shi (2022)	48 (26/22)	48 (25/23)	66.18 ± 1.25	62.97 ± 1.20	2.78 ± 1.01	2.90 ± 1.05	GXST + WM	WM	Aspirin Atorvastatin Metoprolol 6.25 mg po,bid
Liu et al. (2019)	66 (37/29)	66 (39/27)	69.5 ± 5.7	69.6 ± 5.2	2.3 ± 0.2	2.1 ± 0.3	GXST + WM	WM	Aspirin Atorvastatin Metoprolol 6.25 mg po,bid
Pan et al. (2022)	54 (31/23)	54 (33/21)	58.69 ± 4.18	57.92 ± 3.96	3.14 ± 0.28	3.19 ± 0.32	GXST + WM	WM	Aspirin β-receptor blocker nicorandil
Luo S (2021)	150 (68/82)	150 (66/84)	58.7 ± 3.9	59.4 ± 3.5	NR	NR	GXST + WM	WM	simvastatin 20 mg po, qn ISDN 20 mg po, qd Clopidogrel 75 mg po,qd
Wu et al. (2015)	181 (114/67)	181 (100/81)	63.0 ± 1.0	62.5 ± 1.0	6.11 ± 1.67	6.01 ± 1.71	GXST + WM	WM	ISDN 20 mg po, bid Aspirin 100 mg po, qd Atorvastatin 10 mg po, qd amlodipine 5 mg po, qd
Yu (2017)	31 (17/14)	31 (15/16)	64–76	65–78	0.5–14	0.6–15	GXST + WM	WM	Trimetazidine Aspirin Atorvastatin ISDN
An (2016)	45 (20/25)	45 (22/23)	58.3 ± 12.3	57.6 ± 10.9	5.7 ± 1.4	6.4 ± 1.8	GXST + WM	WM	bisoprolol 2.5 mg po, qd ISDN 20 mg po, bid Aspirin 100 mg po, qd Atorvastatin 10 mg po, qd
Wang et al. (2012)	150 (89/61)	130 (67/63)	55 ± 10	58 ± 11	5	4.5	GXST + WM	WM	ISDN 5 mg po, tid
Qi (2015)	40 (22/18)	40 (24/16)	45.1 ± 2.9	45.0 ± 3.5	7.2 ± 3.1	6.9 ± 4.0	GXST + WM	WM	ISDN Diltiazem 90 mg po, qd

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (M/F)		Age (years)		Course of disease (years)		Interventions		
	T	C	T	C	T	C	T	C	
Yu et	40 (25/15)	40 (27/13)	63.40 ± 5.24	65.25 ± 5.40	0.17–25	0.25–24	GXST + WM	WM	NR
Li and Li (2012)	96 (42/54)	92 (40/52)	57	55.6	0.5–1.5	0.42–1.5	GXST + WM	WM	NR
Shi and Abudujilili (2018)	41 (21/20)	41 (20/21)	60.4 ± 11.1	59.2 ± 12.4	6.8 ± 3.6	7.1 ± 3.8	GXST + WM	WM	ISDN Aspirin Atorvastatin β-receptor blocker
Liu (2013)	43 (26/17)	40 (27/13)	60.8 ± 5.7	61.1 ± 7.2	NR	NR	GXST + WM	WM	ISDN 10 mg po, qd Aspirin 100 mg po, qd Atorvastatin 10 mg po, qd
Peng (2016)	30(NR)	30(NR)	61.2 ± 3.4	61.2 ± 3.4	7.1 ± 2.5	7.1 ± 2.5	GXST + WM	WM	Aspirin 100 mg po, qd Atorvastatin 10 mg po, qd amlodipine 5 mg po, qd
Wang and Wu (2015)	40 (26/14)	40 (27/13)	59.9 ± 7.4	60.4 ± 7.6	0.25–20	0.5–22	GXST + WM	WM	Aspirin Atorvastatin ISDN
Cao and Yue (2013)	42 (29/13)	42 (31/11)	61.3 ± 5.2	60.1 ± 6.0	7.8 ± 3.7	7.2 ± 4.3	GXST + WM	WM	ISDN Diltiazem 90 mg po, qd
Zhao et al. (2015)	67(NR)	67(NR)	NR	NR	NR	NR	GXST + WM	WM	Aspirin 100 mg po, qd Atorvastatin 20 mg po, qd ISDN 20 mg po, bid
Geng et al. (2018)	60 (31/29)	60 (32/28)	18–68	19–70	2–6	1–5	GXST + WM	WM	NR
Cai (2022)	62 (43/19)	62 (41/21)	62.69 ± 4.80	62.63 ± 4.7	NR	NR	GXST + WM	WM	ISDN+15%GS 20 mg + 500 mL ivgtt, qd amlodipine 10 mg po, qd
Li et al. (2019)	60 (37/23)	60 (40/20)	53.4 ± 2.1	52.6 ± 1.7	4.8 ± 2.2	5.3 ± 1.5	GXST + WM	WM	β-receptor blocker ISDN+15%GS 20 mg + 500 mL ivgtt, qd amlodipine 10 mg po, qd
Zhu ang Liu (2017)	65 (38/27)	65 (40/25)	52.8 ± 2.4	52.4 ± 1.8	4.9 ± 2.1	4.7 ± 1.5	GXST + WM	WM	β-receptor blocker ISDN+15%GS 20 mg + 500 mL ivgtt, qd amlodipine 10 mg po, qd
Jiang (2013)	66 (38/28)	66 (40/26)	40–71	40–71	NR	NR	GXST + WM	WM	β-receptor blocker ISDN+15%GS 20 mg + 500 mL ivgtt, qd amlodipine 10 mg po, qd

Abbreviations: T: treatment group; **C:** control group; **M:** males; F: females; **GXST:** guanxinshutong capsule; **WM:** western medication; NR: not reported.

2019; Wan et al., 2019; Wang, 2021) reported ECG improvement rates. Due to heterogeneity among the trials ($p < 0.01$, $I^2 = 62\%$), a random-effects model was applied. The results showed that the ECG improvement rate was significantly better in the test group than in the control group (OR = 3.39, 95% CI = 2.35–4.87) and the difference was statistically significant (Figure 4A).

3.3.2 Secondary outcome

3.3.2.1 LVEF

Using a random-effects model ($p = 0.1$, $I^2 = 57\%$), three articles (Ren et al., 2017; Pan et al., 2022; Shi, 2022) presented the measurement of LVEF before and after treatment in the two groups. As illustrated in Figure 4B, the GXST and WM combination therapy significantly improved LVEF compared with WM therapy alone (MD = 1.07, 95% CI = 0.69–1.46).

3.3.2.2 CRP

Six studies (Shi and Abudujilili, 2018; Yang and Zhang, 2018; Luo, 2021; Cai, 2022; Pan et al., 2022; Shi, 2022) compared CRP levels between the experimental and control groups. No significant difference was found between the two groups in terms of the reduction of CRP levels ($p < 0.01$, $I^2 = 96\%$, MD = −6.66, 95% CI = −15.91 to 2.59) (Figure 4C).

3.3.2.3 TC

Nine studies (Liu, 2013; Yu et al., 2013; Wu et al., 2015; Geng et al., 2018; Shi and Abudujilili, 2018; Luo, 2021; Cai, 2022; Shi, 2022; Jia and Li, 2023) compared the TC levels between the experimental and control groups. A meta-analysis of the five studies revealed that GXST and WM combination therapy significantly reduced TC levels in SAP patients ($p < 0.01$, $I^2 = 93\%$, MD = −0.78, 95% CI = −1.20 to −0.35) (Figure 5A).

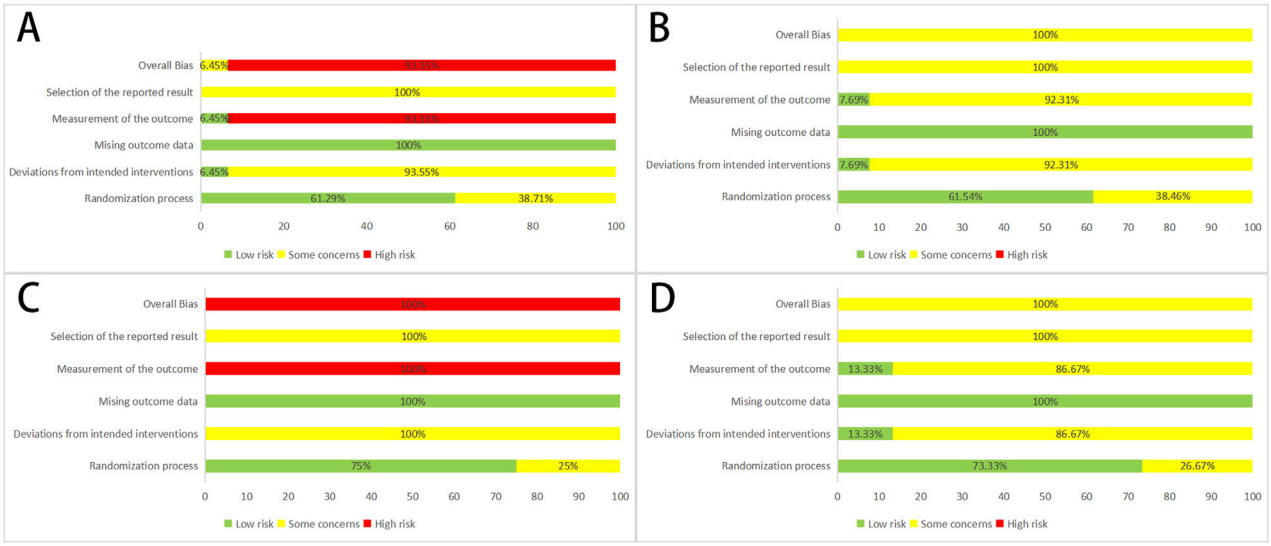


FIGURE 2
Assessment of risk bias **(A)** Effective clinical rate; **(B)** Effective rate in electrocardiogram; **(C)** Chinese medicine evidence score; **(D)** ARDs; ARDs, adverse medicine events.

3.3.2.4 TG

Nine studies (Liu, 2013; Yu et al., 2013; Wu et al., 2015; Geng et al., 2018; Shi and Abudujilili, 2018; Luo, 2021; Cai, 2022; Shi, 2022; Jia and Li, 2023) reported TG levels. A meta-analysis conducted using a random-effects model (p < 0.01, I^2 = 99%) showed no significant difference in the improvement of TG levels between the two groups (MD = −1.62, 95% CI = −3.39 to 0.15) (Figure 5B).

3.3.2.5 Chinese medicine evidence score

Four RCTs (Yu et al., 2013; Zhao et al., 2015; An, 2016; Geng et al., 2018) reported Chinese medicine evidence score. Since homogeneity was found between the four studies (p = 0.84, I^2 = 0), the fixed-effects model was utilized and the results demonstrated a significant improvement in the Chinese medicine evidence score in the experimental compared with the control group (OR = 3.77, 95% CI = 2.20–6.43) (Figure 5C). This score reflects the overall quality and effectiveness of the Chinese medicine treatment. The studies were homogeneous, indicating consistency in the methods and results. This was further confirmed by Labbé plots (Supplementary File S4).

3.3.2.6 TNF-α

A meta-analysis of five studies (Yang and Zhang, 2018; Wang, 2021; Pan et al., 2022; Shi, 2022; Jia and Li, 2023) showed that the GXST and WM combination therapy significantly reduced the TNF-α levels compared to WM therapy alone (p < 0.01, I^2 = 92%, MD = −1.36, 95% CI = −2.18 to −0.53) (Figure 6A).

3.3.3 ADRs

Fifteen studies (Wang et al., 2012; Cao and Yue, 2013; Liang et al., 2013; Liu, 2013; Wu et al., 2015; Zhao et al., 2015; Zhu and Liu, 2017; Geng et al., 2018; Shi and Abudujilili, 2018; Yang and Zhang, 2018; Li, 2019; Li et al., 2019; You, 2021; Cai, 2022; Pan et al., 2022) provided information on ADRs such as dizziness, nausea, and gastrointestinal bleeding. Due to heterogeneity between trials (p < 0.01, I^2 = 77%), a random-effects model was used. The meta-analysis showed no significant difference in the incidence of ADRs between the two groups (OR = 0.60, 95% CI = 0.23–1.57) (Figure 6B).

3.3.4 Analysis of publication bias

For outcomes comprising >10 studies, potential publication bias was explored using Egger's and Begg's tests, implemented through the "metabias" command. Egger's test revealed no significant publication bias, using effective clinical rate as an example (Egger's test: t = 0.23, p = 0.8206). However, the result of Begg's test showed a potential publication bias (Begg's test: z = 2.06, p = 0.0397). This suggests that studies with significant results or large effect sizes were more likely to be published, while those with non-significant results were overlooked. Considering that Egger's test is based on a linear regression approach with more stringent assumptions about the distribution of the data and that the funnel plots show approximate symmetry (Supplementary File S5), it was concluded that there was no publication bias. Nevertheless, Begg's test suggested a potential bias. Therefore, our conclusions should be interpreted with caution.

3.3.5 Heterogeneity, meta-regression, and subgroup analyses

Meta-regression analyses were performed for all outcome indicators with $I^2 \geq 50\%$ and over five studies included. These analyses considered three covariates: treatment duration, medication dosage, and subject age. The choice of these covariates was based on their potential impact on the treatment outcomes. The results showed that subject age and treatment duration were correlated with the decline in TC and TG levels in both the experimental and control groups (Supplementary File S6). However, no significant correlation was observed between the three

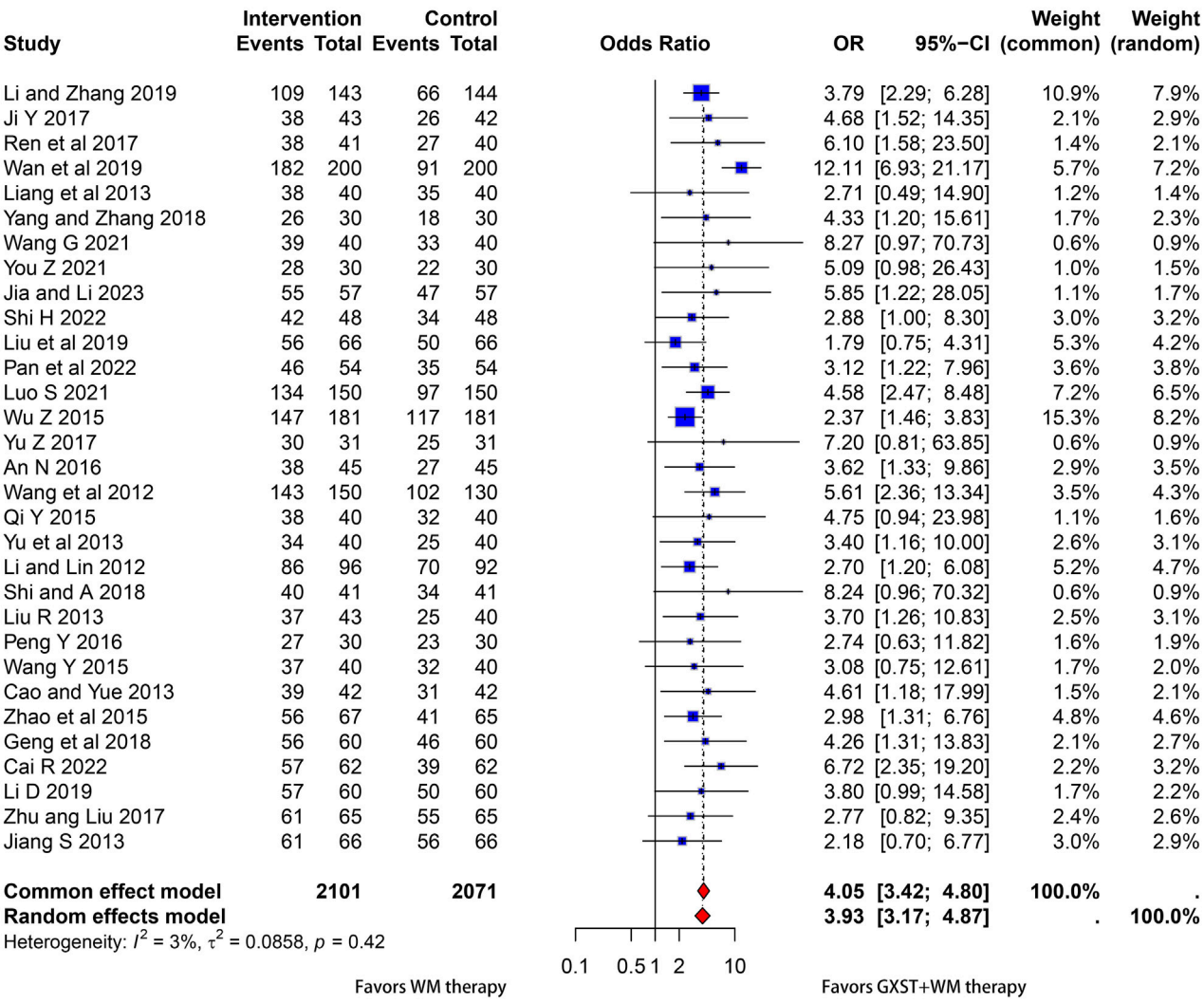


FIGURE 3
Forest plot for the meta-analysis. Effective clinical rate; GXST, Guanxinshutong; WM, Western medicine.

covariates and ECG, ADRs, or CRP levels in both groups. When subgroup analyses were performed for TC levels based on treatment duration, the relative heterogeneity within these subgroups was reduced, indicating that treatment duration was a significant contributor to the observed heterogeneity in the studies. Nevertheless, further investigation is needed to identify potential unmeasured covariates that may explain the remaining heterogeneity.

3.3.6 Sensitivity analysis

For sensitivity analyses, each study was reviewed individually, and the original effective rate was specifically excluded in the ECG study that contained over five publications and demonstrated significant variability. The omission of a study by (Wan et al., 2019) led to a notable decrease in heterogeneity. Furthermore, there was an alteration in the OR and its 95% CI (Supplementary File S7). This evidence implies that the study could be the primary contributor to the detected heterogeneity.

4 Discussions

To the best of our knowledge, this is the first meta-analysis to explore the comprehensive efficacy of GXST and WM combination therapy in patients with SAP. The results indicated that the combination therapy significantly improved clinical efficacy, ECG, and symptoms of angina pectoris. Additionally, the study reveals that compared with the WM monotherapy group, the combined therapy group exhibited a significant increase in LVEF, a key determinant of cardiac function and prognosis in SAP patients. Moreover, the combination therapy significantly reduced TC and TNF-α levels but had no significant difference in the reduction of TG and CRP levels. Furthermore, the combined therapy alleviated symptoms such as chest tightness, palpitations, shortness of breath, and fatigue, thereby improving the scores of Chinese medicine evidence. It is noteworthy that no significant difference was found in the reduction of ADRs between the combined therapy and the WM monotherapy.

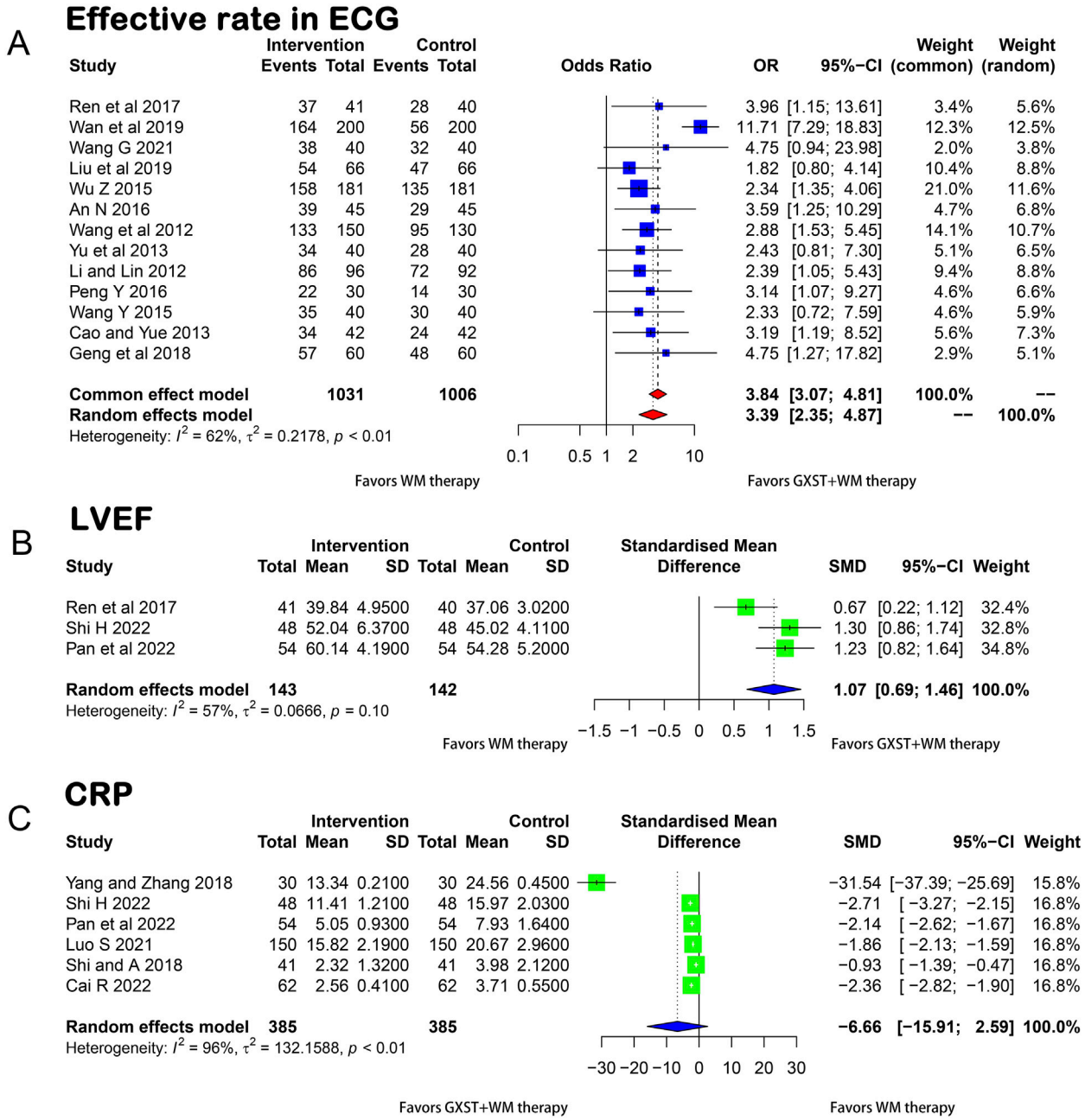


FIGURE 4
Forest plot for the meta-analysis **(A)** Effective rate in ECG; **(B)** LVEF; **(C)** CRP; GXST, Guanxinshutong; WM, Western medicine; ECG, Electrocardiogram; LVEF, Left Ventricular Ejection Fraction; CRP, C-reactive Protein.

Based on its clinical manifestations and pathological characteristics, TCM has categorized stable coronary artery disease into "chest impediment," "heart pain", etc. (Yu et al., 2023) TCM posits that the pathogenesis of angina pectoris is characterized by "stagnation of Qi and blood," where the impaired circulation of Qi and blood leads to localized stagnation of Qi and blood in the heart, forming an "impediment" that causes chest pain (Jin et al., 2021). GXST, with its efficacy in promoting blood circulation, removing blood stasis, and unblocking the channels, is the first new Mongolian medicine approved for clinical treatment of coronary heart disease angina pectoris (Li et al., 2019; Wang et al., 2021). In the formula, *S. miltiorrhiza* and Fructus Choerospondiatis primarily function to enhance Qi and activate blood circulation, while *Caryophyllus aromaticus* (Clove) and Borneol mainly serve to relieve pain. Bambusae Concretio Silicea plays a role in clearing heat and dissolving phlegm, which helps improve cardiac function and alleviate angina pectoris (Wang et al., 2024). Modern pharmacological studies have shown that the active metabolites in GXST can inhibit platelet aggregation and the release of inflammatory mediators, reduce blood viscosity, and improve hemorheology (Lu et al., 2020). This helps to reduce the cardiac burden and improve myocardial oxygen and blood supply

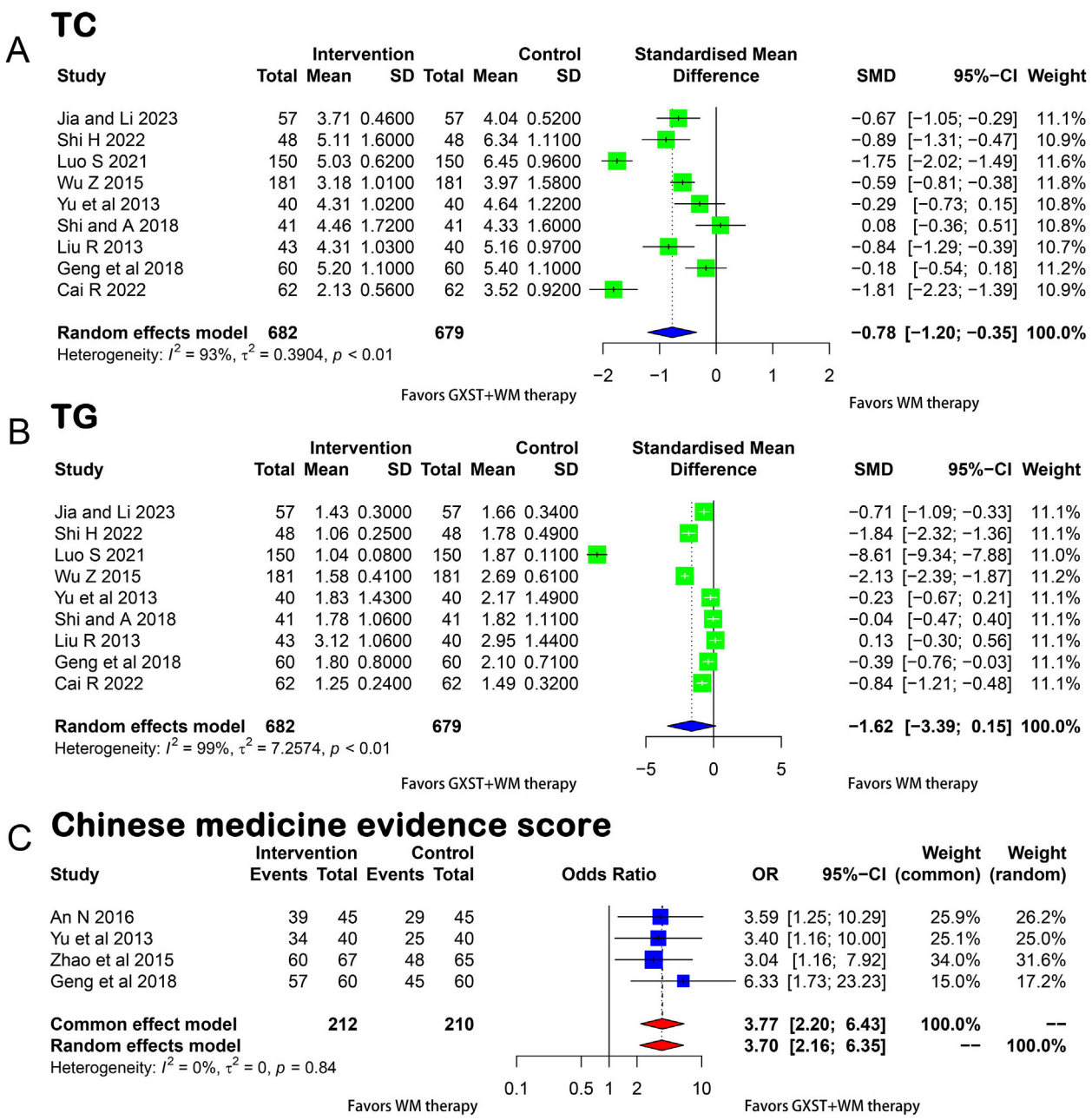


FIGURE 5
Forest plot for the meta-analysis **(A)** TC; **(B)** TG; **(C)** Chinese medicine evidence score; GXST, Guanxinshutong; WM, Western medicine; TC, Total Cholesterol; TG, Triglyceride.

conditions, thereby alleviating symptoms of angina pectoris. GXST can also lower blood lipids and inhibit the formation and development of atherosclerotic plaques, thereby playing a positive role in preventing the occurrence and progression of CVDs (Gao et al., 2021).

Dyslipidemia is an independent risk factor for CHD (Ariyanti and Besral, 2019). Research indicates that tanshinone, the primary active metabolite of *S. miltiorrhiza*, inhibits the activity of cholesterol synthesis enzymes in hepatocytes (such as 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase), thereby reducing endogenous cholesterol production and effectively lowering lipid levels (Wresdiyati et al., 2023). Borneol can reduce lipid deposition in the body by promoting the oxidation and decomposition of fatty acids, thereby indirectly reducing lipid levels (Ran et al., 2021). Other metabolites in GXST, such as Fructus Choerospondiatis, Clove, and Bambusae Concretio Silicea, are also believed to reduce lipid levels by promoting fatty acid metabolism and inhibiting fat synthesis (Wang et al., 2024).

Inflammatory responses play a significant role in the pathophysiological mechanism of angina pectoris (Anzai, 2018). Tanshinone can inhibit the release of inflammatory mediators, such

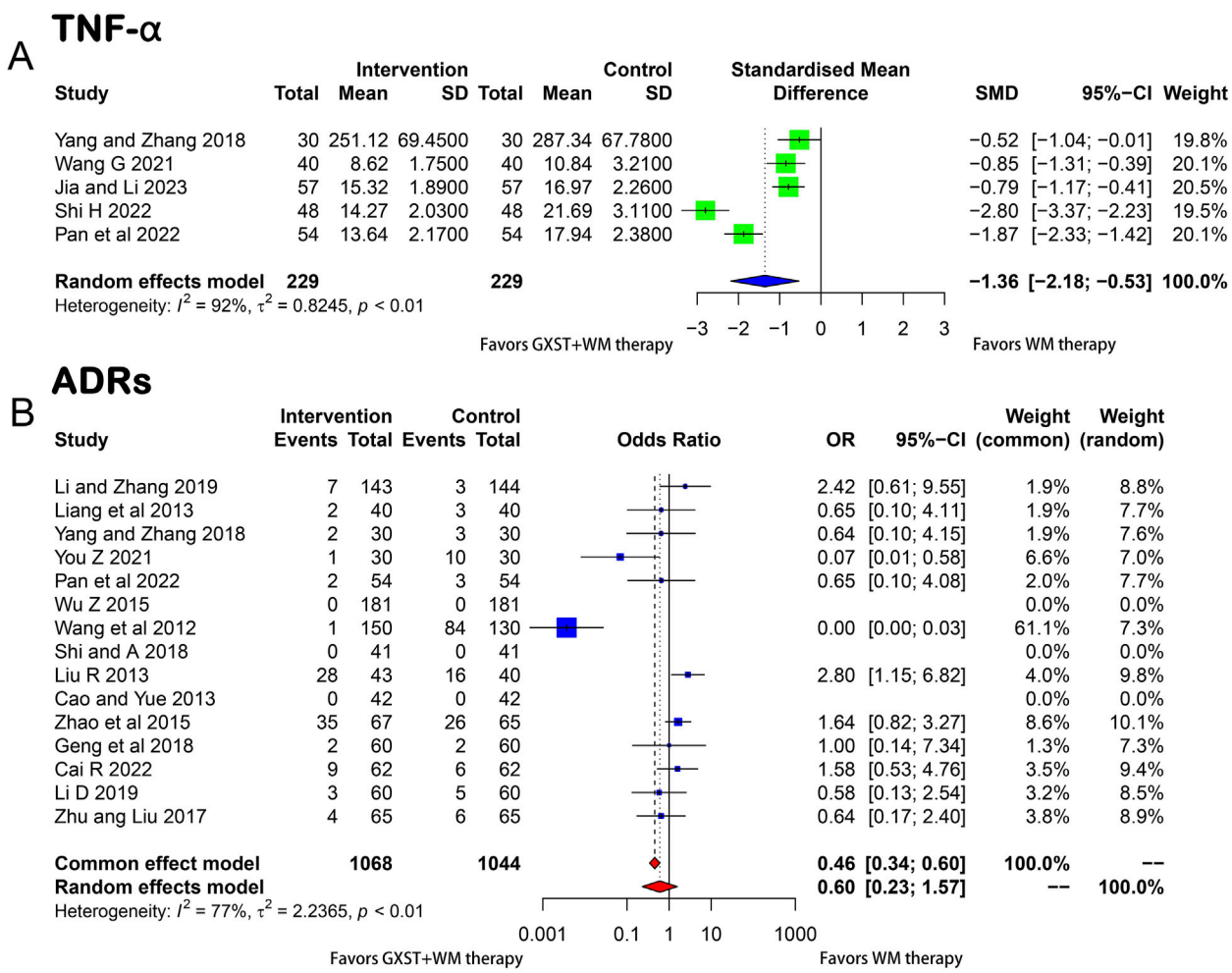


FIGURE 6
Forest plot for the meta-analysis **(A)**TNF-α; **(B)** ARDs; GXST, Guanxinshutong; WM, Western medicine; TNF-α, Tumor Necrosis Factor-alpha; ARDs, adverse medicine events.

as TNF-α and interleukin-1 beta (IL-1β), by inflammatory cells (such as macrophages and neutrophils), alleviating the inflammatory response (Xu et al., 2022). It can also reduce tissue damage caused by inflammatory responses by scavenging free radicals and alleviating oxidative stress (Lu et al., 2022). Protocatechuic acid in Fructus Choerospondiatis can alleviate the inflammatory state during the development of atherosclerosis, protecting vascular endothelial cells (Zhang et al., 2021). Asiatic acid can reduce myocardial cell damage by inhibiting mitochondrial-dependent apoptosis and blocking TNF-α-mediated apoptosis (Zhang et al., 2022). It can also reduce the production of pro-inflammatory cytokines such as IL-1β and TNF-α (Legiawati et al., 2018). Quercetin has strong anti-lipid peroxidation activity and can exert anti-inflammatory effects by reducing the production of nitric oxide, inducible nitric oxide synthase, and IL-6 (Aminnezhad et al., 2023). Ellagic acid, gallic acid, and R-3,4-dihydroxyphenyl lactic acid (danshensu), three metabolites also reported in the literature to have antioxidant and anti-inflammatory biological activities, play a certain role in the treatment of SAP (Gupta et al., 2021). Stigmasterol can block the nuclear factor-kappa B (NF-κB) pathway to inhibit the expression of matrix metalloproteinases (MMPs) and the release of the pro-inflammatory mediator prostaglandin E2 (PGE2), exerting anti-inflammatory effects (Cai et al., 2023). Additionally, tanshinone and other components may reduce myocardial cell damage and protect myocardial function by inhibiting oxidative stress and inflammatory responses. Asiatic acid can reduce myocardial cell damage by inhibiting mitochondrial-dependent apoptosis and blocking TNF-α-mediated apoptosis (Zhang et al., 2022). It can also reduce the production of pro-inflammatory cytokines such as IL-1β and TNF-α (Legiawati et al., 2018). Quercetin has strong anti-lipid peroxidation activity and can exert anti-inflammatory effects by reducing the production of nitric oxide, inducible nitric oxide synthase, and IL-6 (Aminnezhad et al., 2023).

Several meta-analyses (Sui et al., 2016; Jia and Wei, 2017) have evaluated the efficacy of GXST and WM combination therapy for the treatment of angina pectoris and found that this combination therapy can effectively alleviate symptoms of angina pectoris, improve ECGs, and reduce the occurrence of ADRs. However, the scope of these studies is relatively narrow. Moreover, the lack of sensitivity or meta-regression analysis to systematically analyze the sources of heterogeneity reduces the

reliability and validity of the results. Therefore, the current study comprehensively evaluated the efficacy and safety of the GXST and WM combination therapy for the treatment of patients with SAP in terms of clinical efficacy, ECG, LVEF, levels of TC, TG, CRP, TNF-α, Chinese medicine evidence score, and ADRs. Additionally, we conducted meta-regression and sensitivity subgroup analyses to identify and analyze the sources of heterogeneity, ensuring the robustness of the results.

Despite the encouraging results, our study has some limitations. Chiefly, studies' Chinese focus limits generalizability, and methodological issues compromise reliability. Future studies should adopt rigorous designs and cover broader regions. Heterogeneity in outcome measures highlights the need for standardization. Long-term safety, sustainability, and cost-effectiveness remain unaddressed due to short follow-ups. Assessing publication bias and exploring diverse patient populations are crucial to strengthen the evidence base. In conclusion, while our findings are insightful, addressing these limitations through rigorous, long-term, and comprehensive studies is necessary to establish a stronger evidence foundation.

Therefore, the current study results should be interpreted with caution. We believe that future large-scale RCTs using standardized intervention protocols will help obtain more reliable evidence. Moreover, a strict selection of studies to ensure study quality and relevance, ensuring methodological rigor, enhancing the objectivity of interpretations, and improving methodological quality will also boost the quality of future research.

5 Conclusion

In summary, the present study demonstrates that the GXST and WM combination therapy can improve clinical efficacy in SAP patients. However, this conclusion warrants further validation before the combination therapy can be implemented in clinical practice.

Author contributions

LY: Writing–original draft. LW: Writing–original draft. WP: Writing–original draft. PH: Writing–original draft. LC: Writing–original draft. YD: Writing–original draft. MW: Writing–original draft. JZ: Writing–review and editing. BC: Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The National Natural Science Foundation of China sponsored this work (NO. 81303117 and NO. 82074342).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1444388/full#supplementary-material

References

Aminnezhad, S., Zonobian, M. A., Moradi Douki, M., Mohammadi, M. R., and Azarakhsh, Y. (2023). Curcumin and their derivatives with anti-inflammatory, neuroprotective, anticancer, and antimicrobial activities: a review. *Micro Nano Bio Asp.* 2 (4), 25–34. doi:10.22034/mnba.2023.417415.1047

An, N. (2016). Clinical efficacy guanxin shutong capsule combined with western patients with stable angina pectoris with anxiety and depression. *J. Liaoning Univ. Tradit. Chin. Med.* 18 (02), 154–156. doi:10.13194/j.issn.1673-842x.2016.02.052

Anzai, T. (2018). Inflammatory mechanisms of cardiovascular remodeling. *Circ. J.* 82 (3), 629–635. doi:10.1253/circj.CJ-18-0063

Ariyanti, R., and Besral, B. (2019). Dyslipidemia associated with hypertension increases the risks for coronary heart disease: a case-control study in harapan kita hospital, national cardiovascular center, jakarta. *J. Lipids* 2019, 2517013. doi:10.1155/2019/2517013

Beerkens, F. J., Claessen, B. E., Mahan, M., Gaudino, M. F. L., Tam, D. Y., Henriques, J. P. S., et al. (2022). Contemporary coronary artery bypass graft surgery and subsequent percutaneous revascularization. *Nat. Rev. Cardiol.* 19 (3), 195–208. doi:10.1038/s41569-021-00612-6

Benamouzig, R., Guenoun, M., Deutsch, D., and Fauchier, L. (2022). Review article: gastrointestinal bleeding risk with direct oral anticoagulants. *Cardiovasc. Drugs Ther.* 36 (5), 973–989. doi:10.1007/s10557-021-07211-0

Cai, R. Y. (2022). Treatment effects, safety and effective rates of guanxin shutong capsule in angina pectoris with hypertension. *Liaoning J. Tradit. Chin. Med.* 49 (06), 127–130. doi:10.13192/j.issn.1000-1719.2022.06.035

Cai, T., Ye, H., Jiang, H., Lin, C., Lou, C., Wang, W., et al. (2023). Stevioside targets the NF-κB and MAPK pathways for inhibiting inflammation and apoptosis of chondrocytes and ameliorates osteoarthritis *in vivo*. *Int. Immunopharmacol.* 115, 109683. doi:10.1016/j.intimp.2023.109683

Cao, X. Y., and Yue, Y. Y. (2013). Clinical effect of Guanxinshutong capsule on angina pectoris of coronary heart disease. *Guide China Med.* 11 (26), 249–250. doi:10.15912/j.cnki.gocm.2013.26.030

Feng, R., Lin, Q., Wei, D., Li, Y., Zhang, R., Jiang, K., et al. (2023). Tongxinluo capsule in combination with conventional therapies for stable angina pectoris: a meta-analysis and systematic review. *Med. Baltim.* 102 (41), e35405. doi:10.1097/md.0000000000035405

Ford, T. J., Corcoran, D., and Berry, C. (2018). Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need. *Heart* 104 (4), 284–292. doi:10.1136/heartjnl-2017-311446

Gao, X., Zhang, Y., Mu, J. Q., Chen, K. X., Zhang, H. F., and Bi, K. S. (2021). A metabonomics study of guan-xin-shu-tong capsule against diet-induced hyperlipidemia in rats. *Russ. J. Bioorg. Chem.* 47 (2), 420–431. doi:10.1134/S1068162021020138

Geng, Q., Niu, T. F., Qi, H. X., Qu, R. B., Yang, L. L., Wang, J. P., et al. (2018). Observation on curative effect of Guanxinshutong Capsule on stable angina pectoris combined with hyperlipidemia of phlegm-stasis interjunction coronary heart disease. *Shanxi Med. J.* 47 (13), 1575–1577. doi:10.16040/j.cnki.cn15-1101.2017.05.055

Gunata, M., and Parlakpinar, H. (2021). A review of myocardial ischaemia/reperfusion injury: pathophysiology, experimental models, biomarkers, genetics and pharmacological treatment. *Cell Biochem. Funct.* 39 (2), 190–217. doi:10.1002/cbf.3587

Gupta, A., Kumar, R., Ganguly, R., Singh, A. K., Rana, H. K., and Pandey, A. K. (2021). Antioxidant, anti-inflammatory and hepatoprotective activities of Terminalia bellirica and its bioactive component ellagic acid against diclofenac induced oxidative stress and hepatotoxicity. *Toxicol. Rep.* 8, 44–52. doi:10.1016/j.toxrep.2020.12.010

Ji, Y. Y. (2017). Curative effect of Guanxinshutong capsule on stable angina pectoris of coronary heart disease. *Cardiovasc Dis. Electron J. Integr. Tradit. Chin. West Med.* 5 (1), 169–172. doi:10.3969/j.issn.2095-6681.2017.01.132

Jia, Q. F., and Li, X. W. (2023). Clinical observation of Guanxinshutong capsule combined with fluvastatin in the treatment of angina pectoris of coronary heart disease. *J. Practi Tradit. Chin. Med.* 39 (8).

Jia, W. X., and Wei, F. X. (2017). Meta analysis of clinical effects and the safety of GuanXin ShuTong capsules in treating stable angina pectoris. *West J. Tradit. Chin. Med.* 30 (08), 67–70. doi:10.3969/j.issn.1004-6852.2017.08.021

Jiang, S. M. (2013). Clinical effect of Guanxinshutong capsule on patients with angina pectoris complicated with hypertension. *China Pract. Med.* 8 (08), 137–138. doi:10.14163/j.cnki.11-5547/r.2013.08.009

Jin, Y., Yin, X., Li, Z., and Xu, J. (2021). Mechanism of Baihe Decoction in the treatment of coronary heart disease based on network pharmacology and molecular docking. *Ann. Palliat. Med.* 10 (3), 3205–3218. doi:10.21037/apm-21-543

Joshi, P. H., and de Lemos, J. A. (2021). Diagnosis and management of stable angina: a review. *Jama* 325 (17), 1765–1778. doi:10.1001/jama.2021.1527

Judge, C., Ruttledge, S., Murphy, R., Loughlin, E., Gorey, S., Costello, M., et al. (2020). Aspirin for primary prevention of stroke in individuals without cardiovascular disease-A meta-analysis. *Int. J. Stroke* 15 (1), 9–17. doi:10.1177/1747493019858780

Karabağ, Y., Çağdaş, M., Rencuzogullari, I., Karakoyun, S., Artaç, İ., İliş, D., et al. (2018). Relationship between C-reactive protein/albumin ratio and coronary artery disease severity in patients with stable angina pectoris. *J. Clin. Lab. Anal.* 32 (7), e22457. doi:10.1002/jcla.22457

Legiawati, L., Fadilah, F., Bramono, K., and Indriatmi, W. (2018). *In silico* study of centella asiatica active compounds as anti-inflammatory agent by decreasing IL-1 and IL-6 activity, promoting IL-4 activity. *J. Pharm. Sci. Res.* 10, 2142–2147.

Li, D. L. (2019). Clinical effi cacy of guanxin shutong capsules in the treatment of angina pectoris combined with hypertension and its effect on prognosis. *Chin. J. Ration. Drug Use* (7). doi:10.3969/j.issn.2096-3327.2019.7.06

Li, G. L., and Li, X. L. (2012). Efficacy of guanxin shutong capsules for treatment of chronic seable angina *chin J integr med cardio-cerebrovasc dis* 10(11), 1401–1402.

Li, Y., Zhang, L., Lv, S., Wang, X., Zhang, J., Tian, X., et al. (2019). Efficacy and safety of oral Guanxinshutong capsules in patients with stable angina pectoris in China: a prospective, multicenter, double-blind, placebo-controlled, randomized clinical trial. *BMC Complement. Altern. Med.* 19 (1), 363. doi:10.1186/s12906-019-2778-z

Liang, J. Y., Chen, X. H., Wang, J., Su, B. Y., and Li, S. X. (2013). Clinical observation of Guanxinshutong capsule to improve symptoms of angina pectoris. *Chin. J. Clin. Ration. Drug Use* 6 (31), 40. doi:10.15887/j.cnki.13-1389/r.2013.31.010

Liu, D., Zeng, Y., Liang, P., Jiang, Y., An, S., and Ren, P. (2022). Efficacy and safety of Xuefu Zhuoyue Granules combined with western medicine in the treatment of angina pectoris of coronary heart disease: a study protocol of a randomized, double-blind, placebo-controlled clinical trial. *Med. Baltim.* 101 (43), e31235. doi:10.1097/md.0000000000031235

Liu, R. Q. (2013). Observation of curative effect of Guanxinshutong capsule on stable angina pectoris of coronary heart disease. *China Pharm.* 16 (05), 731–732. doi:10.3969/j.issn.1008-049X.2013.05.038

Liu, S. S., Li, J., Shi, Y. X., Huang, Z. Z., and Li, Z. G. (2019). Effect of Guanxinshutong capsule combined with metoprolol on angina pectoris and plasma homocysteine level in elderly patients with coronary heart disease. *Mod. J. Integr. Tradit. Chin. West Med.* 28 (17), 1892–1895. doi:10.3969/j.issn.1008-8849.2019.17.017

Londono-Hoyos, F., Zamani, P., Beraun, M., Vasim, I., Segers, P., and Chirinos, J. A. (2018). Effect of organic and inorganic nitrates on cerebrovascular pulsatile power transmission in patients with heart failure and preserved ejection fraction. *Physiol. Meas.* 39 (4), 044001. doi:10.1088/1361-6579/aab2ef

Lu, H. T., Kam, J., Nordin, R. B., Khelae, S. K., Wang, J. M., Choy, C. N., et al. (2016). Beta-blocker use and risk of symptomatic bradyarrhythmias: a hospital-based case-control study. *J. Geriatr. Cardiol.* 13 (9), 749–759. doi:10.11909/j.issn.1671-5411.2016.09.009

Lu, T. C., Wu, Y. H., Chen, W. Y., and Hung, Y. C. (2022). Targeting oxidative stress and endothelial dysfunction using tanshinone IIA for the treatment of tissue inflammation and fibrosis. *Oxid. Med. Cell Longev.* 2022, 2811789. doi:10.1155/2022/2811789

Lu, Y., Sun, Y., Jiang, Z., Zhang, D., Lin, H., Qu, Y., et al. (2020). Guanxinshutong alleviates atherosclerosis by suppressing oxidative stress and proinflammation in ApoE(-/-) mice. *Evid. Based Complement. Altern. Med.* 2020, 1219371. doi:10.1155/2020/1219371

Luo, S. F. (2021). The clinical efficacy of coronary heart sultan capsule combined with western medicine to treat coronary heart disease stable angina and its effect on blood lipids and hs-CRP. *Smart Healthc.* 7 (08), 173–175. doi:10.19335/j.cnki.2096-1219.2021.08.056

Palatini, P., Faria-Neto, J. R., and Santos, R. D. (2024). The clinical value of β-blockers in patients with stable angina. *Curr. Med. Res. Opin.* 40 (Suppl. 1), 33–41. doi:10.1080/03007995.2024.2317443

Pan, L., Li, P., Ouyang, S. K., Song, H., and Li, J. X. (2022). Effects of Guanxinshutong capsule combined with nicorandil on cardiac function, hemorheology and inflammatory factors in patients with stable angina pectoris and heart blood stasis type. *Prog. Mod. Biomed.* 22 (21). doi:10.13241/j.cnki.pmb.2022.21.022

Patra, S., Gupta, P., Kumari, R., Jana, S., Haldar, P. K., Bhowmik, R., et al. (2023). "Chapter 14 - insights into the mode of action of antianginal and vasodilating agents," in *How synthetic drugs work*. Editors I. Kazmi, S. Karmakar, M. A. Shaharyar, M. Afzal, and F. A. Al-Abbasi (Academic Press), 329–348.

Peng, Y. J. (2016). Clinical observation of Guanxinshutong capsule in treating stable angina pectoris of coronary heart disease. *J. Front. Med.* 6 (11).

Qi, Y. (2015). Clinical analysis of Guanxinshutong capsule in treating coronary heart disease complicated with angina pectoris. *Med. Health Care* (2), 68–69.

Ran, D., Hong, W., Yan, W., and Mengdie, W. (2021). Properties and molecular mechanisms underlying geniposide-mediated therapeutic effects in chronic inflammatory diseases. *J. Ethnopharmacol.* 273, 113958. doi:10.1016/j.jep.2021.113958

Ren, S. H., Zhang, R. J., Ke, S. X., Liu, J. B., Shi, Y. F., Guo, Y., et al. (2017). Effects of Guanxinshutong Capsule on cardiac function and hemorheology indexes in patients with coronary heart disease. *J. Pract. Tradit. Chin. Med.* 33 (05), 492–493. doi:10.3969/j.issn.1004-2814.2017.05.022

Rivasi, G., Rafanelli, M., Mossello, E., Brignole, M., and Ungar, A. (2020). Drug-related orthostatic hypotension: beyond anti-hypertensive medications. *Drugs Aging* 37 (10), 725–738. doi:10.1007/s40266-020-00796-5

Shao, C., Wang, J., Tian, J., and Tang, Y. D. (2020). Coronary artery disease: from mechanism to clinical practice. *Adv. Exp. Med. Biol.* 1177, 1–36. doi:10.1007/978-981-15-2517-9_1

Shi, H. (2022). Effect of guanxin shutong capsule combined with metoprolol in treatment of stable angina pectoris of coronary heart disease and its influence on blood lipids and hs-CRP. *Liaoning J. Tradit. Chin. Med.* 49 (9). doi:10.13192/j.issn.1000-1719.2022.09.039

Shi, J., and Abudujilili (2018). Clinical study of Guanxinshutong capsule in treating stable angina pectoris of coronary heart disease. *Chin. J. Integr. Med. Cardio-Cerebrovasc Dis.* 16 (02), 199–201. doi:10.3969/j.issn.1672-1349.2018.02.020

Singh, S., Zahoor, I., Dhiman, P., Sharma, N., Grewal, S., Behl, T., et al. (2024). "9 - expatiating the role of angiogenesis, inflammation, and oxidative stress in angina pectoris: a state-of-the-art on the drug delivery approaches," in *Targeting angiogenesis, inflammation, and oxidative stress in chronic diseases*. Editors T. Behl, S. Singh, and N. Sharma (Academic Press), 191–214.

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj* 366, l4898. doi:10.1136/bmj.l4898

Sui, J. Y., Xu, H., Qin, L., and Xu, G. L. (2016). A meta-analysis of guanxin shutong capsule on patients with unstable angina. *J. Emerg. Tradit. Chin. Med.* 25 (10), 1863–1865+1893. doi:10.3969/j.issn.1004-745X.2016.10.009

Wan, L. H., Zhang, J. H., and Peng, X. M. (2019). Clinical study on long-term curative effect of Guanxinshutong on chronic stable coronary heart disease in the elderly. *Chin. Community Dr.* 35 (11), 98. doi:10.3969/j.issn.1007-614x.2019.11.068

Wang, A., Song, Q., Li, Y., Fang, H., Ma, X., Li, Y., et al. (2024). Effect of traditional Chinese medicine on metabolism disturbance in ischemic heart diseases. *J. Ethnopharmacol.* 329, 118143. doi:10.1016/j.jep.2024.118143

Wang, D., Shi, C., Ge, Z. H., Wei, Y. X., Liu, T. T., Wang, Y., et al. (2021). Study of the mechanism of action of guanxin shutong capsules in the treatment of coronary heart disease based on metabolomics. *Front. Pharmacol.* 12, 650438. doi:10.3389/fphar.2021.650438

Wang, G. (2021). Clinical effect of Guanxinshutong capsule combined with isosorbide mononitrate tablet on patients with angina pectoris of coronary heart disease. *Med. Forum* 25 (05), 648–650. doi:10.19435/j.1672-1721.2021.05.028

Wang, L. N., Zhao, Y., and Yang, D. (2012). Observation on curative effect of Guanxinshutong capsule combined with isosorbide nitrate tablet in the treatment of angina pectoris. *Pract. J. Card. Cereb. Pneumal Vasc. Dis.* 20 (09), 1512–1513. doi:10.3969/j.issn.1008-5971.2012.09.052

Wang, Y., and Wu, J. S. (2015). Observe the clinical effect of Guanxin Shutong capsule treatment of Coronary heart disease with cariac blood stasis syndrome. *Clin. J. Tradit. Chin. Med.* 27 (05), 666–668. doi:10.16448/j.cjtcm.2015.0253

Wang, Y., Xu, J., Yang, J., Zhang, L., Pan, Y., Dou, L., et al. (2020). Effects of Guanxinshutong capsules as complementary treatment in patients with chronic heart failure: study protocol for a randomized controlled trial. *Front. Pharmacol.* 11, 571106. doi:10.3389/fphar.2020.571106

Wresdiyati, T., Rizaldi, D. A., and Purnawan, T. (2023). Hypercholesterolemia and its management using various bioactive compounds: a literature review. *J. Veteriner* 24, 406–421. doi:10.19087/jveteriner.2023.24.3.406

Wu, Z. J., Huang, X. X., and Chen, J. (2015). Clinical observation of Guanxinshutong capsule combined with Western medicine in treating angina pectoris of coronary heart disease. *New J. Tradit. Chin. Med.* 47 (01), 43–44. doi:10.13457/j.cnki.jncm.2015.01.019

Xie, Q., Huang, J., Zhu, K., and Chen, Q. (2021). Percutaneous coronary intervention versus coronary artery bypass grafting in patients with coronary heart disease and type 2 diabetes mellitus: cumulative meta-analysis. *Clin. Cardiol.* 44 (7), 899–906. doi:10.1002/clc.23613

Xu, L., Liu, X., Zhang, Y., Jia, T., Li, L., Du, Y., et al. (2022). Tanshinone IIA improves acute gouty arthritis in rats through regulating neutrophil activation and the NLRP3 inflammasome. *Dis. Markers* 2022, 5851412. doi:10.1155/2022/5851412

Yang, N., and Zhang, J. J. (2018). Clinical effect of Guanxin Shutong capsule combined with conventional western medicine on angina pectoris and its effect on inflammatory factors. *Clin. Res. Pract.* 3 (28), 42–43. doi:10.19347/j.cnki.2096-1413.201828018

You, Z. C. (2021). Clinical efficacy and safety analysis of patients with coronary heart disease in patients with coronary heart disease in patients with coronary heart disease. *Syst. Med.* 6 (19).

Yu, H. Z. (2017). Observation on the curative effect of Guanxinshutong capsule combined with Western medicine in the treatment of diabetes complicated with angina pectoris. *Inn. Mong. J. Tradit. Chin. Med.* 36 (05), 58. doi:10.16040/j.cnki.cn15-1101.2017.05.055

Yu, Q., Xu, X., Wang, S., Fan, Y., Zhang, J., Leng, Y., et al. (2023). Effect of proprietary Chinese medicine on coronary microvascular dysfunction in patients with microvascular angina: a systematic review and meta-analysis. *Evid. Based Complement. Altern. Med.* 2023, 9242752. doi:10.1155/2023/9242752

Yu, Z., Jiang, H. Y., Wang, G. Q., and Zhang, Y. T. (2013). Clinical study of Guanxinshutong capsule treating patients with coronary heart disease complicated with abnormal lipoprotein emia. *China Pract. Med.* 8 (35), 140–141. doi:10.14163/j.cnki.11-5547/r.2013.35.034

Zhang, J., Zhao, J., Ma, Y., Wang, W., Huang, S., Guo, C., et al. (2021). Investigation of the multi-target mechanism of guanxin-shutong capsule in cerebrovascular diseases: a Systems pharmacology and experimental assessment. *Front. Pharmacol.* 12, 650770. doi:10.3389/fphar.2021.650770

Zhang, Q., Peng, Y., Liu, J., Yang, Y., Hu, Z., Zhou, Y., et al. (2022). 7-Hydroxyflavone alleviates myocardial ischemia/reperfusion injury in rats by regulating inflammation. *Molecules* 27 (17), 5371. doi:10.3390/molecules27175371

Zhang, W., Chen, Y., Jiang, H., Yang, J., Wang, Q., Du, Y., et al. (2020). Integrated strategy for accurately screening biomarkers based on metabolomics coupled with network pharmacology. *Talanta* 211, 120710. doi:10.1016/j.talanta.2020.120710

Zhao, K., Meng, K., Ge, C. J., and Lv, S. Z. (2015). Curative effect of Guanxin Shutong Capsules on psychocardiacology in patients with chronic stable angina pectoris (syndrome of heart blood stasis). *Chin. J. Evidence-Based Cardiovasc Med.* 7 (02), 184–187. doi:10.3969/j.1674-4055.2015.02.10

Zhu, X. J., and Liu, J. (2017). Observation of curative effect of Guanxinshutong capsule on patients with angina pectoris complicated with hypertension. *Hebei Med. J.* 39 (02), 269–271. doi:10.3969/j.issn.1002-7386.2017.02.033

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 13 November 2024
DOI 10.3389/fphar.2024.1445950

OPEN ACCESS

EDITED BY
Kuo Gao,
Beijing University of Chinese Medicine, China

REVIEWED BY
Youhua Wang,
Shanghai University of Traditional Chinese Medicine, China
Ahmad Khusairi Azemi,
Universiti Malaysia Terengganu, Malaysia

*CORRESPONDENCE
Chunyan Wang,
sdu_tcm803@163.com
Guiju Zhang,
13685316929@163.com
60170068@sdutcm.edu.cn

RECEIVED 08 June 2024
ACCEPTED 01 November 2024
PUBLISHED 13 November 2024

CITATION
Tian X, Liu P, Wang R, Hou Y, Zhou Y, Wang C and Zhang G (2024) A review on the treatment of hyperlipidemia with Erchen Decoction. *Front. Pharmacol.* 15:1445950. doi: 10.3389/fphar.2024.1445950

A review on the treatment of hyperlipidemia with Erchen Decoction

Xinyang Tian[1], Peiyu Liu[2], Ruolin Wang[3], Yawei Hou[1], Ying Zhou[1], Chunyan Wang[1]* and Guiju Zhang[3]*

[1]Institute of Traditional Chinese Medicine Literature and Culture, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China, [2]The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China, [3]First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, Shandong, China

Hyperlipidemia, commonly referred to as dyslipidemia, is characterized by elevated serum cholesterol and/or triglyceride levels. This condition contributes significantly to the high mortality rates associated with cardiovascular diseases, posing a serious threat to global health. Although statins remain the predominant pharmacological treatment for hyperlipidemia, their associated side effects have led to a growing interest in alternative therapeutic approaches. Traditional Chinese Medicine (TCM) is exploring these alternatives, with the Erchen Decoction (ECD) emerging as a promising candidate. This review aims to summarize current clinical research, elucidate the mechanisms of action, and assess the compatibility of ECD in the management of hyperlipidemia. By doing so, we hope to provide valuable insights and references for clinical practice and future research.

KEYWORDS

Traditional Chinese Medicine, Erchen Decoction, hyperlipidemia, atherosclerotic cardiovascular diseases, cardiovascular disease

1 Introduction

Hyperlipidemia usually refers to elevated levels of total cholesterol (TC), triglycerides (TG), and/or low-density lipoprotein cholesterol (LDL-C) in the serum (Li et al., 2023a), along with a decrease in high-density lipoprotein cholesterol (HDL-C) (Luo et al., 2020). An abnormality in any of these indicators can be diagnosed as hyperlipidemia, also known as dyslipidemia. The prevalence of dyslipidemia in China is showing a year-on-year increase. According to research conducted in 2023, involving approximately 1.3 million Chinese participants, the prevalence of dyslipidemia was found to be 42.1% (Xia et al., 2023). This figure shows a significant rising trend compared to the total prevalence of dyslipidemia

Abbreviations: ECD, Erchen Decoction; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular diseases; CVD, Cardiovascular diseases; NAFLD, non-alcoholic fatty liver disease; Pinellia ternate, P. ternate; Poria cocos, P. cocos; Glycyrrhiza uralensis, G. uralensis; Zingiber officinale, Z. officinale; Fructus mume, F. mume; TNF-α, Tumor Necrosis Factor-α; CRP, C-reactive protein; TNF, tumor necrosis factor; IL-6, Interleukin-6; HFD, high-fat diet; IL-8, Interleukin-8; hs-CRP, high-sensitivity C-reactive protein; PCP, Poria cocos Polysaccharides; GIBP, Glycyrrhiza inflata Batalin polysaccharide; GPSL, Glycyrrhiza polysaccharide liposome; GA, glycyrrhetinic acid; OA, oleanolic acid; HNF1b, Hepatocyte nuclear factor 1b; UA, Ursolic acid.

TABLE 1 Composition of botanical drugs in ECD.

Scientific name	Family	Common name (traditional name)	Part(s) of drug used
Pinellia ternata (Thunb.) Breit	Araceae	Pinellia ternata	"Dried tuber
Citrus reticulata Blanco	Rutaceae	Tangerine Peel (chenpi)	Dried fruit peel
Poria cocos (Schw.) Wolf	Polyporaceae	Poria cocos	Dried sclerotium
Glycyrrhiza uralensis Fisch	Fabaceae	Glycyrrhiza uralensis	Dried root
Zingiber officinale (Willd.) Rosc	Zingiberaceae	Zingiber officinale	Dried rhizome
Prunus mume (Sieb.) Sieb. et zucc	Rosecea	Fructus mume	Dried fruit

among Chinese adults in 2018 (35.6%) (Li et al., 2023a). Hyperlipidemia is closely associated with atherosclerotic cardiovascular diseases (ASCVD), and evidence from genetic, epidemiological, and clinical studies indicates that elevated LDL-C is a major factor in the pathogenesis and mortality of ASCVD (Ference et al., 2017). LDL-C deposits in arterial walls, where it binds with intimal proteoglycans, leading to gradual pathological changes and accumulation at sites prone to plaque formation (Ference et al., 2017; Libby et al., 2019). LDL-C plays a critical role in the development of atherosclerotic plaques and subsequent cardiovascular events (Mach et al., 2020). Cardiovascular diseases (CVDs), primarily resulting from ASCVD, are the leading cause of death among urban and rural populations in China, accounting for over 40% of all mortalities (Li et al., 2023b). Although the mortality rate due to cardiovascular diseases (CVD) has declined in Europe, it remains the most common cause of death among the population (Timmis et al., 2024). Other risk factors associated with hyperlipidemia, such as diabetes mellitus, hypertension (Su and Yu, 2009), and non-alcoholic fatty liver disease (NAFLD) (Deng et al., 2023), also pose significant health threats. Statins are commonly used to treat hyperlipidemia, effectively inhibit the condition, and reduce LDL-C levels (Karalis, 2021). However, long-term excessive use of statins can lead to adverse effects, such as myopathy, liver injury, severe renal impairment, and cytotoxicity in both humans and animals *in vitro* (Liu et al., 2019). Therefore, there is an urgent need to identify medications that are both highly effective and have fewer side effects.

ECD is a classic prescription in TCM, originating from the "Prescriptions of the Bureau of Taiping People's Welfare Pharmacy." This formulation is effective for drying dampness, eliminating phlegm, regulating Qi, and harmonizing the middle, making it suitable for treating the phlegm-dampness syndrome. The formulation consisted of *Pinellia ternata* [Araceae], *Tangerine peel* [Rutaceae], *Poria cocos* [Polyporaceae], *Glycyrrhiza uralensis* [Fabaceae], *Zingiber officinale* [Zingiberaceae], and *Fructus mume* [Rosaceae] (Table 1; Figure 1). Pinellia ternate (P. ternata) and Tangerine peel (T.peel) work to dry dampness and eliminate phlegm, Whereas Poria cocos (P.cocos) dries dampness and regulates Qi. Glycyrrhiza uralensis (G.uralensis) harmonizes various metabolites, strengthens the spleen, and enhances the middle Jiao. ECD and its modified versions are widely used to treat the lung system, heart system, and metabolic disorders (Xiang, 2023). Hyperlipidemia, a common metabolic disease, is frequently treated with ECD. Current research has primarily focused on four aspects: clinical studies, molecular mechanisms, pharmacological effects, and chemical metabolites. This article systematically reviews the research on the treatment of hyperlipidemia with ECD, aiming to provide a comprehensive overview of the forefront of research on this prescription and offer effective references for establishing further research directions for ECD.

2 Clinical application of Erchen Decoction in treating hyperlipidemia

2.1 Case analysis of Erchen Decoction in the treatment of hyperlipidemia

ECD has demonstrated significant efficacy in the treatment of hyperlipidemia, often involving modifications, adaptations, or combinations based on its formulation. Wang et al. suggested that the accumulation of phlegm-dampness in the body slows the circulation and dispersion of body fluids, leading to the stagnation of subtle substances and resulting in hyperlipidemia. Given the close relationship between hyperlipidemia and phlegm generated by the spleen and kidney, treatments should focus on addressing phlegm-dampness. Their study utilized ECD alongside Modified Shenling Baizhu Powder, incorporating lotus leaf and gynostemma, which resulted in significant symptom relief after four treatment courses (Zhu and Wang, 2022). Kuang Bin emphasized the importance of eliminating phlegm and dampness in hyperlipidemia treatment. In their study involving 88 patients, modifications to ECD included the addition of botanical drugs effective in relieving water and expelling dampness, such as Coix seed, Rhizoma Alismatis, and Polyporus umbellatus. This protocol achieved an overall effectiveness rate of 87.5% and successfully controlled lipid levels in patients (Kuang and Huang, 2017). Wang et al. reported an increased prevalence of phlegm-turbidity obstructive hyperlipidemia among patients. They employed a treatment regimen combining Modified ECD with Jiaosanxian, effectively addressing both the underlying causes and symptoms. Following a 12-week treatment period, the results demonstrated a significant improvement, surpassing the efficacy of pravastatin and leading to notable reductions in serum levels of TC and LDL-C in the patients. (Wang, 2022). Luo et al. proposed that the pathogenesis of hyperlipidemia primarily involves organ deficiency, particularly the spleen, with phlegm-turbidity and blood stasis as secondary manifestations. Thus, their treatment focused on invigorating the liver and strengthening the spleen in conjunction with dampness removed. ECD and Modified Astragali Radix Jianzhong Decoction were prescribed, which resulted in the

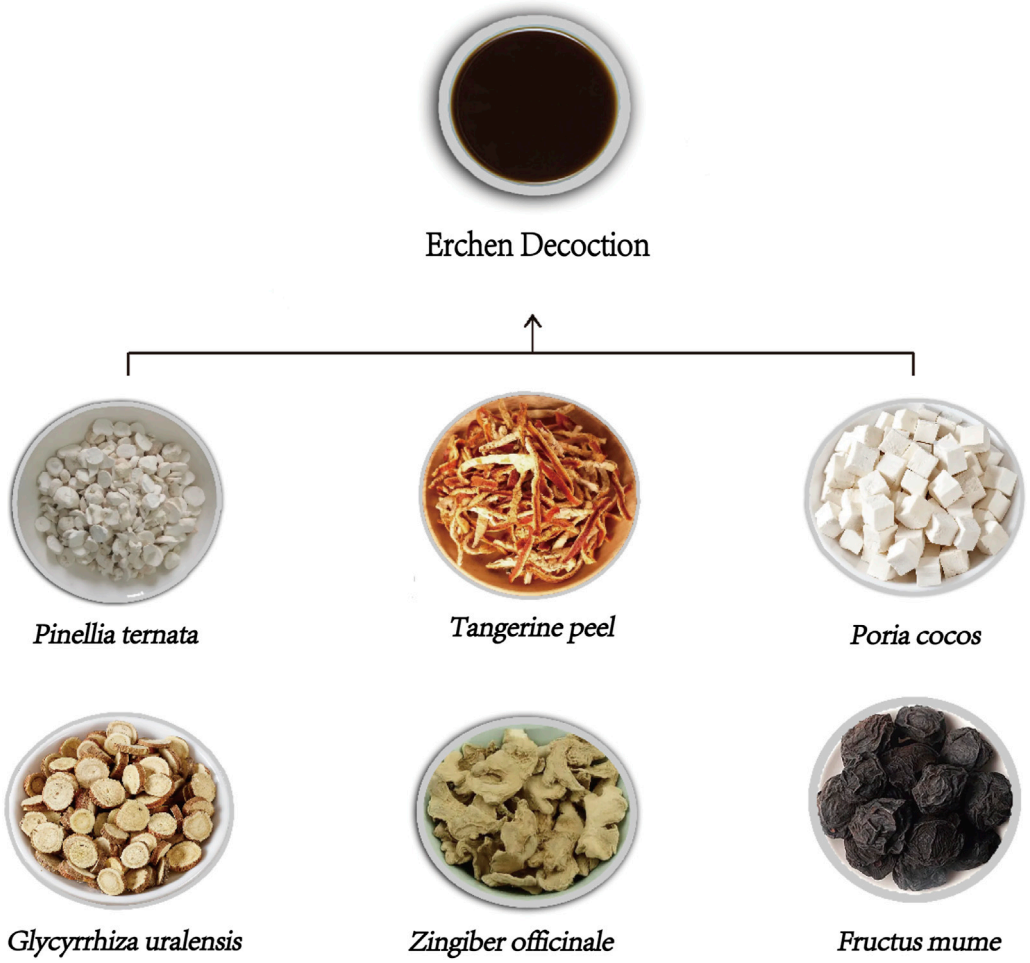


FIGURE 1
Composition of erchen decoction.

disappearance of symptoms after 14 doses (Luo, 2014). Li et al. highlighted the crucial roles of the spleen and stomach in metabolism. Weakness in these organs often leads to phlegm turbidity and blood stasis, which persistently contribute to hyperlipidemia. To address this, treatment commenced by targeting spleen qi deficiency syndrome, recognizing spleen qi deficiency as the root cause and blood stasis as the manifestation. Modifications to ECD, Sijunzi Decoction, and Semen Persicae Siwu Decoction based on symptoms resulted in high patient satisfaction (Li and Liu, 2017).

2.2 Clinical observation study on the treatment of hyperlipidemia with Erchen Decoction

Clinical research indicates that integrating additional medicinal botanical drugs into ECD, or using ECD in combination with other formulas, can enhance the precision of treatment for specific hyperlipidemia patterns (Table 2). Luo et al. conducted a study involving 115 patients with hyperlipidemia, and randomly assigned them to either a treatment or control group. The treatment group received Modified ECD, with patients classified into syndrome types of qi stagnation and blood stasis, liver yang hyperactivity, and liver and kidney yin deficiency, and received tailored botanical drug treatments accordingly. After three treatment courses, a continuous observation period of 3 weeks revealed that the treatment group exhibited higher TC levels than the control group, although lower than their pre-treatment levels. The TG levels in the treatment group were lower than those in the control group. The lipid-lowering effects were statistically significant in both groups, indicating that different modifications of ECD can effectively address hyperlipidemia (Luo, 2012).

Ding conducted a clinical controlled trial of 94 patients with hyperlipidemia. The control group received rosuvastatin and acipimox capsules, while the treatment group was administered doctor-formulated Crataegus pinnatifida ECD. Post-treatment, the efficacy rate was 85.1% in the treatment group compared to 83.0% in the control group, with no significant differences between the two, suggesting that Crataegus pinnatifida ECD has clinical efficacy comparable to that of conventional lipid-lowering medications (Ding, 2013). The study conducted by Chen et al. randomly assigned 80 patients with hyperlipidemia into two groups, the control group receiving atorvastatin, and the observation group receiving additional modified ECD combined with

TABLE 2 Clinical application of Erchen Decoction in the treatment of hyperlipidemia.

	Group	Medication (dosage of drug)	Number of patients	Age (average age)	Treatment effect	The medication time	Inclusion time	Site	References
1	Observation group	On the basis of the control group, Tangerine Peel, Pinellia ternata, poria cocos, burnt Crataegus pinnatifida (10g, 10g, 20g, 20g), Zingiber officinale (3 slices) were added	58	55.6 ± 5.5 (N)	The marked effectiveness rate was 41.4%, and the overall effectiveness rate was 89.7%	3 times a day, 1 dose in the morning, 1 dose at noon and 1 dose in the evening, 30 days was one course, and treatment last 3 consecutive courses	May 2008-September 2011	Guizhou Bijie College Hospital	Luo (2012)
	Control group	Gefilozil Ccapsules	57	54.1 ± 5.7 (N)	The marked effectiveness rate was 43.9%, and the overall effectiveness rate was 91.2%	Twice a day, 30 days was one course, and treatment last 3 consecutive courses	May 2008-September 2011	Guizhou Bijie College Hospital	Luo (2012)
2	Observation group	burnt Crataegus pinnatifida, tangerine peel, Pinellia ternata, radix bupleuri, Largehead Atractylodes Rhizome, Astragalus mongholicus, poria cocos, Rhizoma Alismatis, safflower, salvia miltiorrhiza, l Glycyrrhiza uralensis (30g, 12g, 9g, 9g, 9g, 9g, 9g, 12g, 9g, 10g, 10g, 3g)	47	48.3 ± 12.4	The marked effectiveness rate was 69.1%, and the efficacy rate was 85.1%	Once a day, the treatment time was 12 weeks	February 2007-October 2012	Anhui Huaibei Hospital of Traditional Chinese Medicine	Ding (2013)
	Control group	Rosuvastain	47	50.6 ± 11.2	The marked effectiveness rate was 63.9%, and the efficacy rate was 83.0%	1 dose in the morning and 1 dose in the evening, the treatment time was 12 weeks	February 2007-October 2012	Anhui Huaibei Hospital of Traditional Chinese Medicine	Ding (2013)
3	Observation group	Poria cocos, Medicated Leaven, Hawthorn, Codonopsis pilosula, Pinellia ternata, Tangerine peel, Atractylodes Salvia miltiorrhiza, baked Glycyrrhiza uralensis (15g, 15g, 15g, 15g, 10g, 10g, 10g, 10g, 6g)	40	50.45 ± 6.37	The adverse reaction rate was 7.5%	Twice a day, the treatment time was 2 weeks	January 2019-December 2020	Jiangxi Provincial Hospital of Traditional Chinese Medicine	Chen et al. (2021)
	Control group	Atorvastatin	40	50.27 ± 6.44	The adverse reaction rate was 5.0%	Once a day, the treatment time was 2 weeks	January 2019-December 2020 January 2020-June 2021	Jiangxi Provincial Hospital of Traditional Chinese Medicine	Chen et al. (2021)
4	Observation group	Pinellia ternata, tangerine peel, poria cocos, polygonum	39	58.82 ± 9.87	The efficacy rate was 97.43%	Once a day, the treatment time was 12 weeks	January 2020-June 2021	Yueyang Hospital of Integrated Traditional	Yin and Fu (2022a)

(Continued on following page)

TABLE 2 (*Continued*) Clinical application of Erchen Decoction in the treatment of hyperlipidemia.

	Group	Medication (dosage of drug)	Number of patients	Age (average age)	Treatment effect	The medication time	Inclusion time	Site	References
		cuspidatum, Rhizoma Alismatis, lotus leaf, raw hawthorn, stir-fried cassia seed, Salvia miltiorrhiza, baked Glycyrrhiza uralensis (15g, 9g, 15g, 15g, 9g, 15g, 15g, 12g, 15g, 6g)						Chinese and Western Medicine	
	Control group	Atorvastatin	39	58.90 ± 9.92	The efficacy rate was 82.62%	2 bags per person per day, the treatment time was 12 weeks	January 2020-June 2021	Yueyang Hospital of Integrated Traditional Chinese and Western Medicine	Yin and Fu (2022a)

TABLE 3 Research on the mechanism of Erchen Decoction.

Prescription composition (dosage of drug)	Effective concentrations	Real modules (animal/cell/patients)	Possible mechanisms	References	Apply styles
Pinellia ternata, tangerine peel, Poria cocos, l Glycyrrhiza uralensis (90g, 90g, 81g, 27g)	10 mL/kg/d	HFD-fed rats	Regulating the expression of Cav-1, LDLR, and ABCA1 mRNA in the liver	Ding et al. (2018)	*in vitro*
Pinellia ternata, tangerine peel, Poria cocos, glycyrrhiza uralensis (180g, 180g, 108g, 54g)	8.7 g/(kg· d) of ECD, simvastatin 2 mg/(kg·d)	C57BL/6 mice	Activating and affecting PPARγ expression	Zhang et al. (2020a)	*in vitro*
Pinellia ternata, tangerine peel, Poria cocos, Glycyrrhiza uralensis, Peach kernel, Safflower, Angelica, Chuanxiong, Red peony, Rehmannia (15g, 15g, 12g, 6g, 12g, 9g, 12g, 9g, 9g, 12g)	0.72, 1.44, 2.89 g/mL	SPF ApoE−/−mice,C57BL/6J mice	Inhibiting the Nox4/NF-κB/HIF-1α signaling pathway to improve dyslipidemia and inflammatory responses	Wang et al. (2019)	*in vitro*
Pinellia ternata, tangerine peel, Poria cocos, licoric, Codonopsis pilosula, Rhizoma Alismatis, radix bupleuri, hawthorn, Angelica sinensis, peach kernel, Safflower, Salvia miltiorrhiza, Radix Paeoniae Rubra, Ligusticum chuanxiong, Achyranthes bidentata (10g, 10g, 15g, 6g, 15g, 20g, 15g, 10g, 10g, 6g, 6g, 20g, 20g, 10g, 10g)		Elderly patients with coronary heart disease and hyperlipidemia	Regulating the levels of TC, TG, LDL-C, IL-18, TNF-α, and hs-CRP in elderly patients with coronary heart disease and hyperlipidemia	Luo (2014)	*in vivo*
prepared rehmannia root, Radix Paeoniae Rubra, Angelica sinensis ,chuanxiong rhizome, peach seed, Flos Carthami, tangerine peel, Pinellia ternata, Poria cocos, Glycyrrhiza uralensis (12g, 9g, 12g, 9g,12g, 9g, 15g, 15g, 12g, 6g)	0.72 g/mL, 1.44 g/mL, 2.89 g/mL	C57BL/6Jwild mouse, C57BL/6J background ApoE−/−mice	Regulating the p53/SLC7A11 signaling pathway to effectively inhibit oxidative damage and ferroptosis in EA.hy926 cells induced by ox-LDL.	He (2022)	*in vivo*
Pinellia ternata, tangerine peel, Poria cocos, Fructus mume, Zingiber, officinale, Glycyrrhiza uralensis (15g, 10g, 15g, 3g, 10g, 6g)	4.45g/(kg·d),8.90g/(kg·d),17.80g/(kg·d)	ApoE knockout mice, C57BL/6J mice	Downregulating the p38MAPK signaling pathway improves dyslipidemia and phlegm-turbidity obstruction syndrome by reducing the transcription levels of ICAM and E-Selectin genes and decreasing oxidative stress	Zhang et al. (2024)	*in vivo*

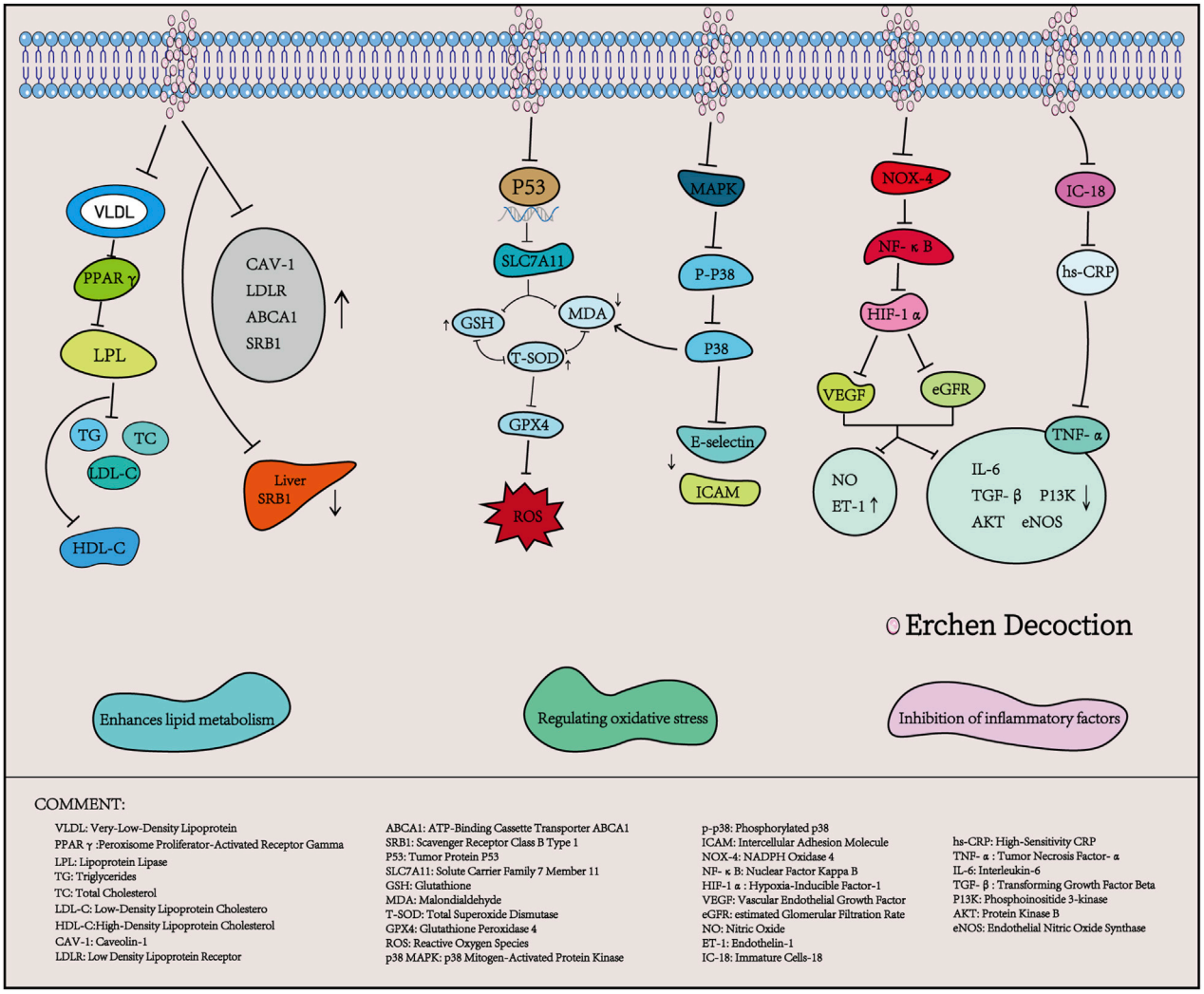


FIGURE 2
Mechanism of action of erchen decoction in treating hyperlipidemia.

spleen-strengthening turbidity-clearing moxibustion (Chen et al., 2021). Both groups were treated continuously for 14 days, showing improvements in TC, TG, HDL-C, and LDL-C levels compared to pre-treatment values, with the observation group demonstrating superior outcomes. Yin and Fu employed modified ECD alongside atorvastatin to treat phlegm-damp obstructive hyperlipidemia, effectively regulating lipid metabolism and stabilizing abnormal lipid levels in patients (Yin and Fu, 2022a).

2.3 Erchen Decoction in the treatment of cardiovascular diseases caused by hyperlipidemia

As previously mentioned, when blood cholesterol levels exceed the body's requirements, LDL-C accumulates on arterial walls and bind with intimal proteoglycans to form aggregates that infiltrate the smooth muscle cells. Pathological changes occur when both smooth muscle and macrophages become laden with lipids (Ference et al., 2017), potentially leading to CVD if not addressed promptly. Dong et al. conducted a randomized controlled trial of 96 patients with coronary heart disease complicated by hyperlipidemia. The observation group received standard statin therapy in conjunction with ECD. The results indicated that the levels of TC, TG, and LDL-C decreased in both groups compared to pre-treatment levels, with the observation group exhibiting significantly lower levels than the control group. Additionally, HDL-C levels increased compared to pre-treatment values, with higher levels observed in the observation group. These findings suggest that combining ECD with statin therapy can effectively regulate lipid levels and inhibit inflammatory responses, significantly enhancing the treatment efficacy for coronary heart disease associated with hyperlipidemia (Dong et al., 2021).

Yin and Fu applied a Modified ECD combined with atorvastatin to treat phlegm-damp obstructive hyperlipidemia and assessed its effects on inflammatory markers, carotid artery plaques, and uric acid levels in patients. The results demonstrated significant reductions in serum interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) levels in both groups after treatment, along with notable decreases in uric acid levels. Furthermore, the observation group exhibited significantly

TABLE 4 Active metabolites and their functions in Erchen Decoction.

Chemical metabolites	Source plant	Main functions	Molecular formula	Molecular weight	CAS number	Related research
β-sitosterol	*Pinellia ternata*	Lowering blood lipids, anti-obesity	C29H50O	414.72 g/mol	83-46-5	Xin et al. (2023), Zhang et al. (2024)
Nobiletin	*Tangerine Peel*	Anti-inflammatory, antioxidant, improving lipid abnormalities	C21H22O8	402.4 g/mol	478-01-3	Mulvihill et al. (2016), Kim et al. (2017)
β-Glucan	*Poria cocos*	Anti-inflammatory, antioxidant, lowering blood lipids	C18H32O16	504.4 g/mol	9041-22-9	Li et al. (2021), Wei et al. (2023)
Glycyrrhiza polysaccharide	*Licorice*	Regulating lipid metabolism, improving hyperlipidemia	-	-	9000-45-7	Wang et al. (2023), Wu et al. (2020)
Gingerenone A	*Ginger*	Anti-obesity, improving lipid metabolism	C21H24O5	356.4 g/mol	128,700-97-0	Suk et al. (2017)
Gingerol	*Ginger*	Anti-lipogenesis,improving metabolism	C17H26O4	294.4 g/mol	23,513-14-6	Gembe-Olivarez et al. (2023)
Oleanolic acid	*Dark Plum*	Lowering blood lipids,anti-inflammatory, improving metabolism	C30H48O3	456.7 g/mol	508-02-1	Luo et al. (2018), Shang and Bai (2022)
Ursolic acid	*Dark Plum*	Anti-inflammatory,antioxidant, lowering blood lipids	C30H48O3	456.71 g/mol	77-52-1	Ruan et al. (2019), Ma et al. (2014)

lower levels of inflammatory factors and uric acid than did the control group. After treatment, carotid plaque Smax in the observation group was significantly reduced compared to that in the control group, indicating that Modified ECD combined with atorvastatin could effectively lower inflammatory factors, carotid plaque area, and uric acid levels in patients with phlegm-damp obstructive hyperlipidemia (Yin and Fu, 2022b). Li et al. suggested that carotid artery stenosis (CAS) results from intermingling and stagnation of phlegm turbidity and blood stasis in neck vessels. They successfully employed a Modified ECD combined with Siwu Decoction to lower blood lipids and prevent, reduce, and eliminate carotid artery plaques. After 8 weeks of treatment, symptoms improved in the treatment group, and TC, TG, LDL-C, and HDL-C levels in serum all showed significant enhancement (Li J. et al., 2019). Another study by Bai and Huang addressed coronary atherosclerotic heart disease (CAD) by applying the Erchen Decoction in combination with Xuefu Zhuyu Decoction. The total effective rate for symptoms such as chest pain, chest tightness, palpitations, fatigue, and shortness of breath was significantly higher in the observation group than in the control group, effectively alleviating lipid levels in patients with coronary heart disease and angina pectoris (Bai and Huang, 2019).

3 The mechanism of Erchen Decoction in the treatment of hyperlipidemia

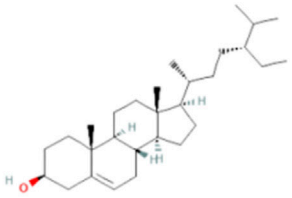
3.1 Erchen Decoction enhances lipid metabolism

Hyperlipidemia is characterized by lipid metabolism disorders, which primarily result from abnormal lipid transportation, wherein lipid transporters and their receptors play a critical role (Milhem et al., 2024). ECD has been widely reported (Luo et al., 2020; Ding et al., 2022) to improve lipid metabolism disorders. A study by Ding et al. indicated that, without intervening in the energy intake of high-fat diet (HFD) rats, the use of Erchen Decoction could increase HDL-C levels while decreasing TC, TG, and LDL-C levels in HFD rats. Furthermore, ECD improved lipid metabolism and reduced blood glucose and insulin resistance by regulating the expression of Cav-1, LDLR, and ABCA1 mRNA in HFD rats, as well as the level of SRB1 in visceral adipose tissue (Ding et al., 2018). Zhang et al. showed that after intervention with ECD, the body weight, Lee's index, and abdominal circumference of mice significantly decreased, and the levels of TG and TC in serum also significantly declined. At the same time, PPARγ mRNA expression in visceral fat was significantly higher than that in the control group (Zhang M. et al., 2020). PPARγ is a key transcription factor in fat metabolism; activating PPARγ can reduce fatty acids transported to the liver and muscles, decrease fat synthesis, and inhibit lipid metabolism. This suggests that ECD can reduce body weight, abdominal circumference, and levels of TG and TC in HFD mice by activating and regulating the expression of PPARγ (Montaigne et al., 2021).

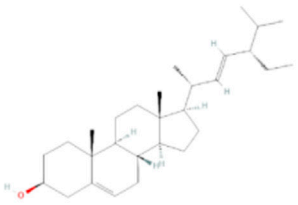
Therefore, ECD represents an effective combination of lipid-lowering metabolites that regulate apolipoproteins, apolipoprotein receptors, and lipid transport mechanisms.

3.2 Erchen Decoction modulates oxidative stress response

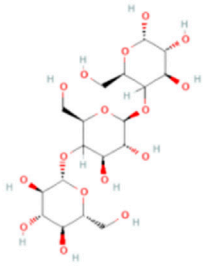
Oxidative stress arises from the excessive accumulation of reactive oxygen species generated during aerobic metabolism (Zhang S. et al., 2020). Increasing evidence suggests that oxidative stress can lead to cellular damage and death, contributing to conditions such as atherosclerosis, hyperlipidemia, stroke, and other cardiovascular diseases (Balan et al., 2024). It is also an important pathological factor for the development of atherosclerotic lesions. Studies have demonstrated that the combination of ECD and Taohong Siwu Decoction can enhance the expression of antioxidant factors, such as total superoxide dismutase



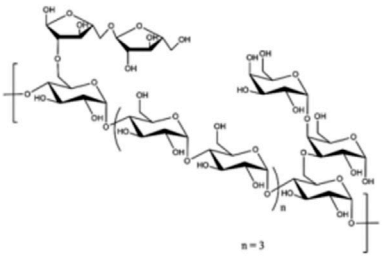
Beta-Sitosterol



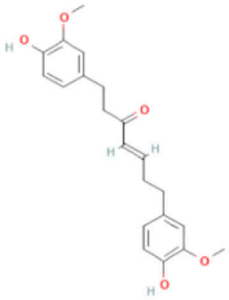
Stigmasterol



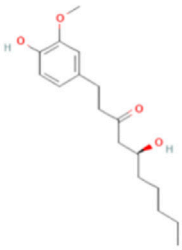
Beta-Glucan



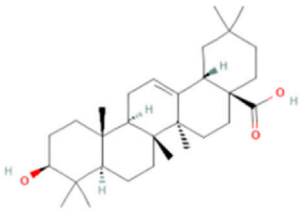
Glycyrrhiza polysaccharide



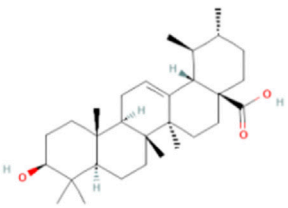
Gingerenone A



Gingerol



Oleanolic acid



Ursolic acid

FIGURE 3
Effective chemical components of erchen decoction in the treatment of hyperlipidemia.

(T-SOD) and glutathione (GSH), by regulating the p53/SLC7A11 signaling pathway. This combination reduces malondialdehyde (MDA) levels and alleviates oxidative stress in mice, showing significant effects on atheroma (He, 2022). Similarly, Zhang et al. reported that after treating mice with hyperlipidemic phlegm-turbidity obstructive syndrome with ECD, the transcription levels of intercellular adhesion molecule (ICAM) and E-selectin genes in the aortic endothelium of all treatment groups decreased, along with significant

reductions in serum MDA concentrations. Following transcription, ICAM and E-selectin genes promote leukocyte adhesion to endothelial cells, facilitate the transformation of monocytes into macrophages, and contribute to the formation of lipid plaques, aggravating oxidative stress and leading to endothelial damage (Zhang et al., 2024). Therefore, ECD can reduce serum oxidative stress and decrease the transcription of aortic endothelial adhesion molecules, thereby playing a protective role in the vascular endothelium. It is speculated that this mechanism may be related to the downregulation of p38/MAPK signaling pathway activation.

3.3 Erchen Decoction inhibits the expression of inflammatory factors

Hyperlipidemia is closely associated with inflammatory responses that promote fat accumulation in the liver, thereby exacerbating inflammation and ultimately leading to elevated blood lipid levels, thereby creating a vicious cycle. Studies have shown that inflammatory factors are highly expressed in patients with hyperlipidemia and are positively correlated with TC, TG, and LDL-C (Shen, 2017). In a study conducted by Wang et al., it was observed that after treatment of ApoE−/−AS mice with ECD combined with Taohong Siwu Decoction, the expression levels of serum inflammatory factors TNF-α and IL-6 decreased, while the levels of nitric oxide (NO) and endothelin-1 (ET-1) increased significantly. Concurrently, the mRNA levels of transforming growth factor beta (TGF-β) and phosphoinositide 3-kinase (PI3K), as well as the protein phosphorylation levels of protein kinase B (AKT) and endothelial nitric oxide synthase (eNOS), were significantly reduced. It is speculated that ECD combined with Taohong Siwu Decoction may improve dyslipidemia and inflammatory responses by inhibiting the Nox4/NF-κB/HIF-1α signaling pathway, thus positively impacting the treatment of atherosclerosis (Wang et al., 2019). CRP is an acute-phase reactive protein produced by the liver cells that accelerates the inflammatory response *in vivo*. It is induced by tumor necrosis factor (TNF), IL-8, IL-6, and other inflammatory factors in mononuclear macrophages. Research has demonstrated that increased CRP levels can disrupt lipid metabolism and accelerate atherosclerosis (López-Mejías et al., 2016). Dong et al. reported that the application of ECD combined with statins significantly reduced the serum levels of IL-18, TNF-α, and high-sensitivity CRP (hs-CRP) in elderly patients with coronary heart disease and hyperlipidemia, suggesting a role in regulating dyslipidemia and suppressing inflammatory responses (Dong et al., 2021).

In summary, ECD plays a significant role in the treatment of hyperlipidemia by regulating apolipoprotein processes, reducing oxidative stress responses, and inhibiting the expression of inflammatory factors (Table 3; Figure 2). Further research is needed to explore additional mechanisms of action.

4 Pharmacological research on the six active metabolites in Erchen Decoction

4.1 Pinellia ternata

Pinellia ternata, a dried tuber from the Araceae family (Thunb), is characterized by its pungent and (Abo-Zaid et al., 2023)warm properties, along with its toxicity. It primarily targets the meridians of the spleen, stomach, and lung. Its therapeutic functions include drying dampness and transformation of phlegm. Clinically, it is commonly used to treat cough, asthma, nausea, vomiting, and scrofula. Modern pharmacological studies have shown that P. ternata possesses anti-inflammatory, antibacterial, and lipid-lowering effects (Zou et al., 2023). In TCM, it is recognized for its efficacy in alleviating vomiting and reducing lumps and distension (Geng et al., 2023). *Pinellia ternata* contains a variety of metabolites, including alkaloids, organic acids, amino acids, phenylpropanoids, and volatile oils (Wang and Wang, 2020). The Alkaloids include various components such as ephedrine, indole alkaloids, isoquinoline alkaloids, and purine alkaloids (Dey et al., 2020), Which Organic acids can be classified into fatty acids, saturated or unsaturated acids, and acids with different numbers of carboxyl groups (Shi et al., 2022).

As the monarch drug in the metabolite formula, P. ternata can directly reduce the expression of TG, LDL-C, IL-6, TNF-α, and other inflammatory markers by mediating the PI3K/Akt pathway, resulting in improved blood lipid levels (Lu et al., 2020). Processed P. ternata has been shown to effectively lower TG and LDL-C levels, improve whole blood viscosity, and inhibit red blood cell aggregation (Yin and Fu, 2022b).

Phytosterols, which are structurally similar to cholesterol, compete with cholesterol for incorporation into micelles, thereby inhibiting their absorption and affecting the synthesis of endogenous cholesterol. This mechanism helps regulate fat formation and reduce circulating triglyceride levels (Lu et al., 2019). *Pinellia ternata* is rich in phytosterols, including stigmasterol and β-sitosterol, both of which exhibit anti-obesity and lipid-lowering effects. Xin et al. found that stigmasterol significantly reduced liver cholesterol levels in mice fed a high-fat, high-cholesterol diet, inhibited the expression of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome and IL-18 genes ($p < 0.05$), lowered TG and TC levels in the liver, and enhanced the α-alternative pathway of the intestinal microbiota (Xin et al., 2023). Zhang et al. also discovered that β-sitosterol can reverse the intestinal microbiome imbalance in mice fed an HFD, modulate bile acid metabolism through the intestinal microbiome and CYP7A1 pathway, effectively alleviating metabolic disorders in mice and exhibit therapeutic effects on obesity and hyperlipidemia induced by HFD (Zhang et al., 2022).

Furthermore, studies have shown that β-sitosterol can decrease serum LDL-C levels in mice, alter lipid profiles, and achieve effects comparable to conventional lipid-lowering medications (Zhang et al., 2024). A study by Abo-Zaid et al. demonstrated that β-sitosterol treatment significantly improved hyperglycemia, transaminase levels (ALT and AST), and lipid levels in HFD rats, suggesting that β-sitosterol directly treats NAFLD by regulating lipid metabolism and alleviating endoplasmic reticulum stress, oxidative stress, and inflammatory responses (Abo-Zaid et al., 2023). Research by Gumede et al. indicated that β-sitosterol effectively prevented NAFLD and large vacuolar fatty change in rats fed a high-fructose diet (Gumede et al., 2020). In conclusion, both stigmasterol and β-sitosterol can improve triglyceride and cholesterol levels, reduce intestinal bile acid levels, and enhance the expression of genes involved in lipid metabolism, thereby ameliorating hyperlipidemia (Feng et al., 2018).

4.2 Tangerine peel

Tangerine peel is characterized by bitter, spicy, and warm properties, targeting the spleen and lung meridians. Its therapeutic effects include regulation of qi, strengthening of the spleen, drying dampness, and elimination of phlegm. The main metabolites of tangerine peel can be categorized into volatile and non-volatile substances. The volatile metabolites comprise over 300 metabolites, including ketones, alcohols, terpenes, acids, phenols, and ethers, whereas the non-volatile metabolites include more than a hundred types, such as flavonoids, alkaloids, and triterpenes. Flavonoids are the most significant metabolites in tangerine peel (Guan et al., 2024). Studies have shown that Citrus flavonoids can significantly inhibit dyslipidemia in conditions such as hepatic steatosis and obesity by reducing inflammatory responses associated with tissue metabolism in the liver, adipose tissue, and kidneys (Mulvihill et al., 2016). In animal experiments, Burke's research team was able to reverse the size and quantity of existing fat, reduce plasma cholesterol, and improve hyperlipidemia by enhancing fatty acid oxidation in the liver and increasing the overall energy expenditure (Burke et al., 2018).

Nobiletin, a polymethoxylated flavonoid derived from citrus peels, exhibits potent anti-inflammatory and antioxidant properties. It primarily prevents hepatic steatosis by enhancing fatty acid oxidation and inhibiting hepatic fatty acid synthesis, thereby playing a crucial role in reducing lipid abnormalities and alleviating atherosclerosis (Mulvihill et al., 2016). Research conducted by Prapassorn et al. found that upregulating the Nrf-2/HO-1 signaling pathway and inhibiting matrix metalloproteinases (MMPs) can alleviate vascular remodeling and functional disorders in L-NAME-induced HFD rats (Potue et al., 2019). In another study, Bunbupha et al. demonstrated that nobiletin could moderate the effects of HFD on the expression of liver adiponectin receptor 1 (AdipoR1) and $gp91^{phox}$, thereby regulating adiponectin levels, reducing oxidative stress, and alleviating metabolic disorders in rats after high-fat intake (Bunbupha et al., 2021). Additionally, Kim et al. found that continuous supplementation of HFD rats with low doses of nobiletin over 16 weeks resulted in reduced plasma total cholesterol, apolipoprotein B (ApoB), and non-high-density lipoprotein levels, ultimately improving dyslipidemia (Kim et al., 2017).

Pinellia ternata and tangerine peel form a high-frequency drug pair for hyperlipidemia treatment. Together, they effectively address arterial endothelial thickening and can enhance the levels of reactive oxygen species in cells through the PI3K-Akt pathway, controlling cell apoptosis and delaying aging (Sun et al., 2018). Zhang et al. investigated the mechanisms of hyperlipidemia via multi-pathway and multi-target interactions of the active metabolites in tangerine peel and P. ternata using network pharmacology, and discovered that this combination significantly improved blood lipid profiles in hyperlipidemic mice (Zhang, 2022).

4.3 Poria cocos (fu ling)

Poria cocos, which is characterized by its sweet, light, and mild properties, targets the heart, lungs, spleen, and kidney meridians. Its therapeutic effects include promoting diuresis, relieving dampness, strengthening the spleen, and tranquilizing the mind and spirit. *Poria cocos* primarily contains various metabolites, including polysaccharides, sterols, triterpenes, proteins, amino acids, organic acids, esters, flavonoids, and trace elements, with polysaccharides being the most abundant (Lü et al., 2024).

Poria cocos polysaccharides (PCP) are among the main active and characteristic metabolites of P. cocos, comprising approximately 80% of the bioactive metabolites in its sclerotium. PCP exhibits anti-inflammatory and antioxidant properties (Ll, 2016; Cheng et al., 2020). β-Glucans are the predominant metabolites of PCP and are characterized by β-(1→3) glucan backbones and β-(1→6) glucan side chains (Li X. et al., 2019). Li et al. showed that PCP can inhibit inflammatory response factors induced by HFD in $ApoE^{-/-}$ mice by controlling the elevation of TNF-α, IL-6, and nitric oxide, inhibiting the activation of the aortic TLR4/NF-κB pathway, and reducing lipid accumulation (Li et al., 2021). Wei et al. administered low, medium, and high doses of PCP to nutritionally obese rats, found that medium and high doses significantly decreased the serum levels of TC, TG, and LDL-C, indicating that PCP can effectively reduce serum lipid levels and regulate lipid abnormalities, demonstrating its lipid-lowering effects (Wei et al., 2023).

Poria cocos oligosaccharides are derived from PCP through processes such as enzymatic hydrolysis and purification, resulting in improved water solubility compared to that of the original polysaccharides. These oligosaccharides can inhibit metabolic disorders in mice fed an HFD, reduce inflammatory responses, and decrease the accumulation of lipid abnormalities (Zhu et al., 2022a). Furthermore, Zhu et al. used P. cocos oligosaccharides to reshape the gut microbiota structure in mice, inhibit intestinal barrier damage, repair insulin resistance and glucose tolerance, and improve the dysregulation of glucose and lipid metabolism (Zhu et al., 2022b).

4.4 Glycyrrhiza uralensis

Glycyrrhiza uralensis, commonly known as licorice, is sweet and mild in properties, and targets the heart, lung, spleen, and stomach meridians. Its therapeutic effects include tonifying the spleen and supplementing qi, clearing heat detoxifying, expelling phlegm, relieving cough, alleviating acute pain, and harmonizing various drugs. The chemical metabolites of G. uralensis mainly consist of triterpenoids such as glycyrrhizin, glycyrrhetinic acid, and glycyrrhizic acid; flavonoid metabolites including liquiritin, isoliquiritin, glycyrrhizin, and isoliquiritigenin; as well as licorice polysaccharides, coumarins, alkaloids, amino acids, and a small amount of volatile metabolites (Xiao et al., 2023).

Pan et al. extracted polysaccharides from medicinal G. uralensis and conducted a series of analyses, leading to the development of a new type of Glycyrrhiza inflata batalin polysaccharide (GIBP). Its antioxidant and anti-α-glucosidase properties effectively alleviate hyperglycemia (Pan et al., 2020). Wu et al. employed the reverse evaporation method to prepare Glycyrrhiza polysaccharide liposomes (GPSL) and optimized them. The results indicated that both GPSL and Glycyrrhiza polysaccharide (GPS) had immunomodulatory effects on chBM-DCs, with GPSL showing a more significant effect than GPS (Wu et al., 2017). Wu et al. found that after administering Glycyrrhiza polysaccharides to mice via

gavage, pro-inflammatory cytokines such as IL-6, interleukin-7, interleukin-10, and TNF-α, were reduced, and the antioxidant capacity was significantly enhanced (Wu et al., 2020). Cao et al. extracted glycyrrhetinic acid (GA) from licorice and discover its anti-inflammatory properties and ability to mediate the NF-κB pathway, inhibiting the expression of downstream inflammatory factors TNF-α, IL-1β, IL-6, and IL-8, thus reducing cytotoxicity (Cao et al., 2017). Wang et al. confirmed that after administering high and low doses of GPS to mice via gavage, the high-dose group showed significant reductions in TC, TG, and LDL-C levels, while HDL-C levels were elevated, in contrast to the low-dose group. This suggests that GPS participates in lipid metabolism in type 1 diabetes mellitus (T1DM) mice, regulating lipid metabolism and improving dyslipidemia (Wang et al., 2023).

Additionally, other metabolites of G. uralensis have therapeutic or alleviating effects on hyperlipidemia. Carbenoxolone, an active metabolite in licorice, has demonstrated potential in treating obesity and hyperlipidemia by activating the JAK2/STAT3 signaling pathway and reducing the expression of sterol regulatory element-binding protein 1c (SREBP-1c) and fatty acid synthase (FAS), thus protecting the liver from lipid metabolic damage induced by a HFD (Chen et al., 2019). GA, another flavonoid metabolite from G. uralensis, was used by Weng et al. in experiments with a hyperlipidemic mouse model, which it alleviated lipid metabolism disorders and enhanced the lipid-lowering effects of dioscin stem cells (Weng et al., 2021).

4.5 Zingiber officinale

Zingiber officinale (Z. officinale), commonly known as ginger, is characterized by its spicy and slightly warm properties, targeting the lung, spleen, and stomach meridians. It exerts effects such as dispersing the exterior cold, warming the middle to stop vomiting, eliminating phlegm, relieving cough, and detoxifying fish and crab toxins. *Zingiber officinale* contains over 200 metabolites, predominantly volatile oils and amino acids. Volatile oils comprise metabolites such as α-zingiberene, β-sesquiphellandrene, shogaol-3, shogaol-4, gingerol, and zingerone, including aspartic acid, glutamic acid, and serine, among others (Wu et al., 2019).

Cheng et al. induced hyperlipidemia in mice using a HFD and discovered that 6-shogaol inhibited hypertrophy and hyperplasia of white adipose tissue (WAT) in mice, down-regulating the TLR3/IL-6/JAK1/STAT3 and PCNA signaling axes, thereby improving liver metabolic disorders and insulin resistance (Cheng et al., 2022). Supplementation with steamed ginger ethanolic extract (SGE) reduces SREBP1c (Srebf1), a factor that promotes lipogenesis, leading to weight loss and decreased body fat in mice. Furthermore, SGE inhibited fat formation and accumulation by lowering key regulators of adipogenesis such as Pparg and Cebpa. Dietary control combined with moderate exercise and supplementation with SGE further supports weight and fat reduction (Park et al., 2020). Suk et al. treated HFD mice with gingerenone A (GA) and found that GA inhibited adipocyte hyperplasia and macrophage infiltration, alleviated symptoms associated with adipose tissue, reduced adipose tissue inflammation (ATI), and the occurrence of obesity (Suk et al., 2017). Gingerol, which is present in the rhizomes of Z. officinale, was studied by Olivarez et al., who found that a mixture of 6-gingerol, 8-gingerol, and 10-gingerol exhibited anti-lipogenic and lipolytic effects on the 3T3-L1 cell line, confirming the anti-obesity effects (Gembe-Olivarez et al., 2023).

4.6 Fructus mume

Fructus mume (F. mume), commonly known as Mume Fructus or dark plum, is characterized by its sour, astringent, and mild properties with channel tropism, including the liver, spleen, lung, and large intestine meridians. It exerts effects such as astringing the lungs, binding the intestines, generating fluids, and calming roundworms (Zhu Y. et al., 2022). The main metabolites of F. mume include terpenoids, organic acids, polysaccharides, amino acids, volatile components, nucleotides, and inorganic elements (Ou et al., 2020). The triterpene metabolites in F. mume primarily include oleanolic acid (OA) and ursolic acid (UA) (Bailly, 2020).

OA, a pentacyclic triterpene metabolite, has been shown to lower blood lipids, demonstrates anticancer and anti-inflammatory properties, and prevents cardiovascular and cerebrovascular diseases (Shang and Bai, 2022). Research indicates that OA can improve glucose tolerance and visceral fat in mice, thereby regulating fat and carbohydrate metabolism and intervening in hyperlipidemia (de Melo et al., 2010). Hepatocyte nuclear factor 1b (HNF1b) is a crucial regulator of lipid and glucose metabolism, and is capable of regulating obesity and redox homeostasis (Wang et al., 2017). OA can regulate and inhibit oxidative damage and glucose/lipid metabolic dysfunction induced by polychlorinated biphenyl mixtures via HNF1b-mediated redox homeostasis and PPARγ signal transduction (Su et al., 2018). Luo et al. administered OA to patients with hyperlipidemia for 4 weeks, which resulted in significant decreases in serum TC and TG levels, and an increase in HDL-C. DNA microarray results also indicated significant changes in mRNA expression; expression increased in 17 patients and decreased in four patients post-treatment, providing evidence for the effectiveness of OA in improving hyperlipidemia (Luo et al., 2018).

UA is a natural triterpenoid carboxylic acid metabolite. Previous studies have demonstrated that UA has anti-inflammatory, antioxidant (Zhao et al., 2023), and lipid-lowering effects (Ruan et al., 2019). Ma et al. found that UA could regulate MAPK and NF-κB pathways by inhibiting the expression of TNF-α, IL-1, and COX-2 proteins, thereby reducing liver oxidative stress and inflammation induced by carbon tetrachloride (CCl4) in mice (Ma et al., 2014). Ruan et al. fed rats different concentrations of UA and found that it effectively reduced lipid synthesis, leading to decreased levels of TG, TC, and LDL (Ruan et al., 2019). Li et al. reported that by feeding atherosclerosis mice UA and rosuvastatin, there was a significant reduction in the necrotic core area in blood vessels, a decrease in atherosclerotic plaque area, and inhibition of NF-κB-mediated LOX-1 expression *in vivo* and *in vitro* through ROS production, which improved outcomes related to atherosclerosis (Li et al., 2018).

In summary, the effective chemical metabolites of the ECD in treating hyperlipidemia primarily include β-sitosterol, nobiletin, PCP, PCP, licorice polysaccharides, GA, gingerol, OA, UA. These metabolites exhibit therapeutic effects on hyperlipidemia through

different pathways and mechanisms (Table 4; Figure 3). However, the specific chemical metabolites of ECD contributing to its effects on hyperlipidemia remain to be clearly defined and warrant further investigation by future researchers.

5 Discussion

Hyperlipidemia is closely related to factors such as age, diet, exercise, and genetics (Opoku et al., 2021; Trinder et al., 2022). In its early stages, hyperlipidemia often presents no obvious symptoms, making it easy to overlook. It is typically discovered during routine check-ups or when other diseases arise, which can lead to serious consequences (Libby et al., 2019). Statins are notably effective in treating hyperlipidemia and significantly reduce mortality rates (Cai et al., 2021). However, owing to their long-term use and potential side effects, TCM has been actively seeking alternative treatments.

ECD, which is known for its ability to dispel phlegm and dampness, has long been effective in treating pulmonary diseases (Deng et al., 2020; Ye et al., 2023). Recently, its application in the treatment of hyperlipidemia has increased, indicating a broader scope for research (Chen et al., 2023). Through a literature review, it has been found that current studies on ECD for hyperlipidemia primarily focus on clinical observations, the mechanisms of metabolite action, the molecular mechanisms of individual botanical drugs, pharmacological effects, and the study of chemical metabolites. Although existing research has sufficiently demonstrated the efficacy of ECD, there are still notable shortcomings. First, there are significant discrepancies in the timing and length of clinical and experimental studies, and there is a lack of international literature outside of China. Second, as this paper is a review, patient-level data cannot be obtained, which limits the in-depth analysis of clinical effects. Lastly, current research on effective metabolites mainly concentrates on individual botanical drugs, while the effective metabolites of ECD in treating hyperlipidemia remain underexplored. The interactions among individual botanical drugs during the decoction process may influence the overall efficacy, and further research is needed to evaluate the efficacy and toxicity, as well as the principles of botanical drug combinations.

Therefore, future research should primarily focus on the effective metabolites of ECD, particularly the active metabolites of the metabolite and their interactions, to elucidate the mechanisms by which it treats hyperlipidemia. Additionally, subsequent studies should comprehensively assess the efficacy and safety of ECD through *in vivo*, *in vitro*, and cellular experiments to ensure its effectiveness and minimal side effects in clinical applications. Attention should also be paid to drug toxicity and the principles of botanical drug combinations to optimize treatment plans and provide theoretical guidance.

A total of 39 articles were sourced from China. While it is challenging to obtain international qualifications, all formulas and traditional Chinese medicines have a rich historical background and comply with the standards set by the Chinese Pharmacopoeia (2015). Therefore, we standardized the relevant Chinese literature using an international taxonomy website in conjunction with the Chinese Pharmacopoeia (2015) (Supplementary Appendix S1). Based on the standards established by the ConPhyMP Declaration (Heinrich et al., 2022), we conducted a detailed assessment of chemical metabolites in the articles (Supplementary Appendix 2A).

In summary, ECD demonstrates significant efficacy in clinical applications for the treatment of hyperlipidemia. In animal experiments, it has been shown to act on hyperlipidemia by enhancing lipid metabolism, regulating oxidative stress responses, and inhibiting the expression of inflammatory factors. Research on the individual effective metabolites in treating hyperlipidemia is clear, and future studies should continue to refine research methodologies that integrate basic practice with experimental approaches, providing more references for the prevention and treatment of hyperlipidemia.

Author contributions

XT: Investigation, Writing–original draft, Conceptualization, Methodology, Visualization, Writing–review and editing. PL: Conceptualization, Methodology, Writing–original draft. RW: Formal Analysis, Writing–original draft. YH: Writing–original draft. YZ: Writing–original draft. CW: Conceptualization, Formal Analysis, Methodology, Writing–review and editing. GZ: Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was supported by the 2021 Traditional Chinese Medicine Ancient Literature and Characteristic Technology Inheritance Special Project (No. GZY-KJS-2021-025), Shandong Province Traditional Chinese Medicine Science and Technology Project (No. 2021M142), and State Key Laboratory of Biobased Material and Green Papermaking, Qilu University of Technology (Shandong Academy of Sciences) (No. GZKF202112).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1445950/full#supplementary-material

References

Abo-Zaid, O. A., Moawed, F. S., Ismail, E. S., and Farrag, M. A. (2023). β-sitosterol attenuates high-fat diet-induced hepatic steatosis in rats by modulating lipid metabolism, inflammation and ER stress pathway. *BMC Pharmacol. Toxicol.* 24 (1), 31. doi:10.1186/s40360-023-00671-0

Bai, Y., and Huang, L. (2019). Clinical effectiveness of Er Chen Decoction combined with Xuefu Zhuyu Decoction in treating coronary artery atherosclerotic heart disease with angina caused by phlegm and stasis intermingling. *China Med.* 14 (05), 659–663.

Bailly, C. (2020). Anticancer properties of Prunus mume extracts (Chinese plum, Japanese apricot). *J. Ethnopharmacol.* 246, 112215. doi:10.1016/j.jep.2019.112215

Balan, A. I., Halațiu, V. B., and Scridon, A. (2024). Oxidative stress, inflammation, and mitochondrial dysfunction: a link between obesity and atrial fibrillation. *Antioxidants (Basel)* 13 (1), 117. doi:10.3390/antiox13010117

Bunbupha, S., Pakdeechote, P., Maneesai, P., and Prasarttong, P. (2021). Nobiletin alleviates high-fat diet-induced nonalcoholic fatty liver disease by modulating AdipoR1 and gp91(phox) expression in rats. *J. Nutr. Biochem.* 87, 108526. doi:10.1016/j.jnutbio.2020.108526

Burke, A. C., Sutherland, B. G., Telford, D. E., Morrow, M. R., Sawyez, C. G., Edwards, J. Y., et al. (2018). Intervention with citrus flavonoids reverses obesity and improves metabolic syndrome and atherosclerosis in obese Ldlr(-/-) mice. *J. Lipid Res.* 59 (9), 1714–1728. doi:10.1194/jlr.M087387

Cai, T., Abel, L., Langford, O., Monaghan, G., Aronson, J. K., Stevens, R. J., et al. (2021). Associations between statins and adverse events in primary prevention of cardiovascular disease: systematic review with pairwise, network, and dose-response meta-analyses. *Bmj* 374, n1537. doi:10.1136/bmj.n1537

Cao, L., Ding, W., Jia, R., Du, J., Wang, T., Zhang, C., et al. (2017). Anti-inflammatory and hepatoprotective effects of glycyrrhetinic acid on CCl(4)-induced damage in precision-cut liver slices from Jian carp (*Cyprinus carpio* var. jian) through inhibition of the nf-kB pathway. *Fish. Shellfish Immunol.* 64, 234–242. doi:10.1016/j.fsi.2017.03.007

Chen, J., Ye, C., Yang, Z., Zhang, C., Li, P., Xu, B., et al. (2023). Erchen decoction to reduce oxidative stress in dyslipidemia phlegm-dampness retention syndrome mice: *in vivo* mechanism revealed by metabolomics (liquid chromatography-mass spectrometry). *Phytomedicine* 115, 154808. doi:10.1016/j.phymed.2023.154808

Chen, W., Fu, C., and Gao, S. (2021). Clinical observation of Er Chen Decoction combined with spleen-strengthening and turbidity-lowering moxibustion therapy for hyperlipidemia (spleen deficiency and phlegm dampness syndrome). *Guangming Tradit. Chin. Med.* 36 (22), 3808–3810.

Chen, Y., Lu, W., Jin, Z., Yu, J., and Shi, B. (2019). Carbenoxolone ameliorates hepatic lipid metabolism and inflammation in obese mice induced by high fat diet via regulating the JAK2/STAT3 signaling pathway. *Int. Immunopharmacol.* 74, 105498. doi:10.1016/j.intimp.2019.03.011

Cheng, Y., Ding, Z., and Zhang, Y. (2020). Protective effects of different Poria cocos extracts on acute liver injury in mice. *J. Anhui Univ. Chin. Med.* 39 (04), 73–77.

Cheng, Z., Xiong, X., Zhou, Y., Wu, F., Shao, Q., Dong, R., et al. (2022). 6-gingerol ameliorates metabolic disorders by inhibiting hypertrophy and hyperplasia of adipocytes in high-fat-diet induced obese mice. *Biomed. Pharmacother.* 146, 112491. doi:10.1016/j.biopha.2021.112491

de Melo, C. L., Queiroz, M. G., Fonseca, S. G., Bizerra, A. M., Lemos, T. L., Melo, T. S., et al. (2010). Oleanolic acid, a natural triterpenoid improves blood glucose tolerance in normal mice and ameliorates visceral obesity in mice fed a high-fat diet. *Chem. Biol. Interact.* 185 (1), 59–65. doi:10.1016/j.cbi.2010.02.028

Deng, G., Jia, H., Li, Y., Li, J., Wu, C., Shi, H., et al. (2023). Erchen Decoction improves iron homeostasis in mice with non-alcoholic fatty liver disease by regulating iron transport capacity in the spleen. *Nan fang yi ke da xue xue bao = J. South. Med. Univ.* 43 (8), 1287–1296. doi:10.12122/j.issn.1673-4254.2023.08.04

Deng, L., Zhang, X., Dong, Y., Wang, L., Chen, K., Zheng, M., et al. (2020). Erchen decoction combined with Sanziyangqin decoction for chronic obstructive pulmonary disease: a protocol for systematic review and meta-analysis. *Med. Baltim.* 99 (40), e22315. doi:10.1097/md.0000000000022315

Dey, P., Kundu, A., Kumar, A., Gupta, M., Lee, B. M., Bhakta, T., et al. (2020) "Analysis of alkaloids (indole alkaloids, isoquinoline alkaloids, tropane alkaloids)," in *Recent advances in natural products analysis*. doi:10.1016/B978-0-12-816455-6.00015-9

Ding, Q. (2013). Clinical observation of self-formulated Hawthorn Er Chen Decoction in treating mixed hyperlipidemia. *J. Clin. Traditional Chin. Med.* 25 (04), 319–320. doi:10.16448/j.cjtcm.2013.04.035

Ding, S., Chen, Q., Huang, Y., Li, X., Chai, Y., Li, C., et al. (2022). Exploring miRNA-related molecular targets of erchen decoction against lipid metabolism disorder using a network pharmacologic approach. *Comb. Chem. High. Throughput Screen* 25 (6), 986–997. doi:10.2174/1386207324666210302093300

Ding, S., Kang, J., Tong, L., Lin, Y., Liao, L., and Gao, B. (2018). Erchen decoction ameliorates lipid metabolism by the regulation of the protein CAV-1 and the receptors VLDLR, LDLR, ABCA1, and SRB1 in a high-fat diet rat model. *Evid. Based Complement. Altern. Med.* 2018, 5309490. doi:10.1155/2018/5309490

Dong, L., Wang, F., Mao, P. a., and Huang, F. (2021). Effects of modified Er Chen Decoction combined with statins on lipids, hs-CRP, TNF-α, and IL-18 in elderly patients with coronary heart disease and hyperlipidemia. *Chin. J. Traditional Chin. Med. Pharm.* 28 (05), 702–704+768.

Feng, S., Dai, Z., Liu, A. B., Huang, J., Narsipur, N., Guo, G., et al. (2018). Intake of stigmasterol and β-sitosterol alters lipid metabolism and alleviates NAFLD in mice fed a high-fat western-style diet. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* 1863 (10), 1274–1284. doi:10.1016/j.bbalip.2018.08.004

Ference, B. A., Ginsberg, H. N., Graham, I., Ray, K. K., Packard, C. J., Bruckert, E., et al. (2017). Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur. Heart J.* 38 (32), 2459–2472. doi:10.1093/eurheartj/ehx144

Gembe-Olivarez, G., Preciado-Ortiz, M. E., Campos-Perez, W., Rodríguez-Reyes, S. C., Martínez-López, E., and Rivera-Valdés, J. J. (2023). A mix of ginger phenols exhibits anti-adipogenic and lipolytic effects in mature adipocytes derived from 3T3-L1 cells. *Exp. Ther. Med.* 26 (1), 336. doi:10.3892/etm.2023.12035

Geng, X., Liu, Q., and Hua, J. (2023). Progress in research on the chemical components and pharmacological actions of Pinellia. *Shanxi Chem. Ind.* 43 (09), 53–54+61. doi:10.16525/j.cnki.cn14-1109/tq.2023.09.021

Guan, X., Yang, H., Zhang, J., and Xu, J. (2024). Progress in research on the chemical components and pharmacological actions of tangerine peel. *Chin. J. Traditional Chin. Med. Pharm.*, 1–14. doi:10.13193/j.issn.1673-7717.2024.06.008

Gumede, N. M., Lembede, B. W., Nkomozepi, P., Brooksbank, R. L., Erlwanger, K. H., and Chivandi, E. (2020). β-Sitosterol mitigates the development of high-fructose diet-induced nonalcoholic fatty liver disease in growing male Sprague-Dawley rats. *Can. J. Physiol. Pharmacol.* 98 (1), 44–50. doi:10.1139/cjpp-2019-0295

He, X. (2022). Study on the mechanism of Er chen decoction combined with tao hong Si Wu tang regulating p53/slc7a11 mediated oxidative damage and ferroptosis anti-atherosclerosis. *Liaoning Univ. Traditional Chin. Med.* 2022.

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverria, J., Kulić, Ž., McGaw, L. J., et al. (2022). Best Practice in the chemical characterisation of extracts used in pharmacological and toxicological research-The ConPhyMP-Guidelines. *Front. Pharmacol.* 13, 953205. doi:10.3389/fphar.2022.953205

Karalis, D. G. (2021). Editorial commentary: advances in the management of dyslipidemia: the future is bright, but what we do today is what matters most. *Trends Cardiovasc Med.* 31 (7), 425–426. doi:10.1016/j.tcm.2020.08.008

Kim, Y. J., Choi, M. S., Woo, J. T., Jeong, M. J., Kim, S. R., and Jung, U. J. (2017). Long-term dietary supplementation with low-dose nobiletin ameliorates hepatic steatosis, insulin resistance, and inflammation without altering fat mass in diet-induced obesity. *Mol. Nutr. Food Res.* 61 (8). doi:10.1002/mnfr.201600889

Kuang, B., and Huang, L. (2017). Analysis of the therapeutic effects of modified Er Chen Decoction on hyperlipidemia. *World Latest Med. Inf. Dig.* 17 (58), 156. doi:10.19613/j.cnki.1671-3141.2017.58.087

Li, J., Liu, H., and Liao, W. (2019a). Clinical observation of modified Er Chen Decoction and Si Wu Tang in treating hyperlipidemia with carotid atherosclerotic plaques. *Clin. Res. Traditional Chin. Med.* 11 (11), 37–39.

Li, J. J., Zhao, S. P., Zhao, D., Lu, G. P., Peng, D. Q., Liu, J., et al. (2023a). 2023 China guidelines for lipid management. *J. Geriatric Cardiol.* 20 (9), 621–663. doi:10.26599/1671-5411.2023.09.008

Li, J. J., Zhao, S. P., Zhao, D., Lu, G. P., Peng, D. Q., Liu, J., et al. (2023b). 2023 Chinese guideline for lipid management. *Front. Pharmacol.* 14, 1190934. doi:10.3389/fphar.2023.1190934

Li, Q., Zhao, W., Zeng, X., and Hao, Z. (2018). Ursolic acid attenuates atherosclerosis in ApoE(-/-) mice: role of LOX-1 mediated by ROS/NF-κB pathway. *Molecules* 23 (5), 1101. doi:10.3390/molecules23051101

Li, S., and Liu, K. (2017). Professor Li yingdong's treatment for hyperlipidemia from spleen-qi deficiency. *West. Chin. Med.* 30 (03), 53–55.

Li, W., Yu, J., Zhao, J., Xiao, X., Li, W., Zang, L., et al. (2021). Poria cocos polysaccharides reduces high-fat diet-induced arteriosclerosis in ApoE(-/-) mice by inhibiting inflammation. *Phytother. Res.* 35 (4), 2220–2229. doi:10.1002/ptr.6980

Li, X., He, Y., Zeng, P., Liu, Y., Zhang, M., Hao, C., et al. (2019b). Molecular basis for Poria cocos mushroom polysaccharide used as an antitumour drug in China. *J. Cell Mol. Med.* 23 (1), 4–20. doi:10.1111/jcmm.13564

Libby, P., Buring, J. E., Badimon, L., Hansson, G. K., Deanfield, J., Bittencourt, M. S., et al. (2019). Atherosclerosis. *Nat. Rev. Dis. Prim.* 5 (1), 56. doi:10.1038/s41572-019-0106-z

Liu, A., Wu, Q., Guo, J., Ares, I., Rodríguez, J. L., Martínez-Larrañaga, M. R., et al. (2019). Statins: adverse reactions, oxidative stress and metabolic interactions. *Pharmacol. Ther.* 195, 54–84. doi:10.1016/j.pharmthera.2018.10.004

Ll, H. (2016). *Preparation of triterpenoid acids from the cortex of Poria cocos*. Southwest Jiaotong University.

López-Mejías, R., Genre, F., Remuzgo-Martínez, S., González-Juanatey, C., Robustillo-Villarino, M., Llorca, J., et al. (2016). Influence of elevated-CRP level-related polymorphisms in non-rheumatic Caucasians on the risk of subclinical atherosclerosis and cardiovascular disease in rheumatoid arthritis. *Sci. Rep.* 6, 31979. doi:10.1038/srep31979

Lu, H. K., Huang, Y., Liang, X. Y., Dai, Y. Y., and Liu, X. T. (2020). Pinellia ternata attenuates carotid artery intimal hyperplasia and increases endothelial progenitor cell activity via the PI3K/Akt signalling pathway in wire-injured rats. *Pharm. Biol.* 58 (1), 1184–1191. doi:10.1080/13880209.2020.1845748

Lu, J., Zheng, Z., Xu, Z., and Yang, H. (2019). Advances in research on hypolipidemic mechanism of phytosterols. *Chin. J. Traditional Chin. Med.* 44 (21), 4552–4559. doi:10.19540/j.cnki.cjcmm.20190424.401

Lü, L., Zhang, L., and Lü, J. (2024). Chemical components, pharmacological actions, and clinical applications of Poria cocos. *J. Binzhou Med. Univ.* 47 (01), 61–67. doi:10.19739/j.cnki.issn1001-9510.2024.01.013

Luo, H., Xiong, M., Zhu, W., and Shen, T. (2020). Erchen decoction for hyperlipemia: protocol for a systematic review and meta-analysis. *Med. Baltim.* 99 (42), e22374. doi:10.1097/md.0000000000022374

Luo, H. Q., Shen, J., Chen, C. P., Ma, X., Lin, C., Ouyang, Q., et al. (2018). Lipid-lowering effects of oleanolic acid in hyperlipidemic patients. *Chin. J. Nat. Med.* 16 (5), 339–346. doi:10.1016/s1875-5364(18)30065-7

Luo, J. (2012). Treatment of 58 cases of hyperlipidemia with modified Er Chen Decoction. *Contemp. Med. China* 18 (30), 157–158.

Luo, T. (2014). Treatment of hyperlipidemia with Huang qi jian zhong tang combined with Er chen decoction. *Pract. J. Traditional Chin. Intern. Med.* 28 (05), 128–129. doi:10.13729/j.issn.1671-7813.2014.05.66

Ma, J. Q., Ding, J., Zhang, L., and Liu, C. M. (2014). Ursolic acid protects mouse liver against CCl4-induced oxidative stress and inflammation by the MAPK/NF-κB pathway. *Environ. Toxicol. Pharmacol.* 37 (3), 975–983. doi:10.1016/j.etap.2014.03.011

Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., et al. (2020). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur. Heart J.* 41 (1), 111–188. doi:10.1093/eurheartj/ehz455

Milhem, F., Skates, E., Wilson, M., and Komarnytsky, S. (2024). Obesity-resistant mice on a high-fat diet display a distinct phenotype linked to enhanced lipid metabolism. *Nutrients* 16 (1), 171. doi:10.3390/nu16010171

Montaigne, D., Butruille, L., and Staels, B. (2021). PPAR control of metabolism and cardiovascular functions. *Nat. Rev. Cardiol.* 18 (12), 809–823. doi:10.1038/s41569-021-00569-6

Mulvihill, E. E., Burke, A. C., and Huff, M. W. (2016). Citrus flavonoids as regulators of lipoprotein metabolism and atherosclerosis. *Annu. Rev. Nutr.* 36, 275–299. doi:10.1146/annurev-nutr-071715-050718

Opoku, S., Gan, Y., Yobo, E. A., Tenkorang-Twum, D., Yue, W., Wang, Z., et al. (2021). Awareness, treatment, control, and determinants of dyslipidemia among adults in China. *Sci. Rep.* 11 (1), 10056. doi:10.1038/s41598-021-89401-2

Ou, J., Wang, R., Li, X., Huang, L., Yuan, Q., Fang, C., et al. (2020). Comparative analysis of free amino acids and nucleosides in different varieties of mume fructus based on simultaneous determination and multivariate statistical analyses. *Int. J. Anal. Chem.* 2020, 4767605. doi:10.1155/2020/4767605

Pan, L. C., Zhu, Y. M., Zhu, Z. Y., Xue, W., Liu, C. Y., Sun, H. Q., et al. (2020). Chemical structure and effects of antioxidation and against α-glucosidase of natural polysaccharide from Glycyrrhiza inflata Batalin. *Int. J. Biol. Macromol.* 155, 560–571. doi:10.1016/j.ijbiomac.2020.03.192

Park, S. H., Jung, S. J., Choi, E. K., Ha, K. C., Baek, H. I., Park, Y. K., et al. (2020). The effects of steamed ginger ethanolic extract on weight and body fat loss: a randomized, double-blind, placebo-controlled clinical trial. *Food Sci. Biotechnol.* 29 (2), 265–273. doi:10.1007/s10068-019-00649-x

Potue, P., Wunpathe, C., Maneesai, P., Kukongviriyapan, U., Prachaney, P., and Pakdeechote, P. (2019). Nobiletin alleviates vascular alterations through modulation of Nrf-2/HO-1 and MMP pathways in l-NAME induced hypertensive rats. *Food Funct.* 10 (4), 1880–1892. doi:10.1039/c8fo02408a

Ruan, Y., Mo, W., Chen, J., and Yang, K. (2019). Effects of different doses of ursolic acid on liver and kidney functions and levels of blood lipids and blood glucose in diabetic rats. *J. Traditional Chin. Med.* 34 (05), 1007–1011. doi:10.16368/j.issn.1674-8999.2019.05.239

Shang, C., and Bai, Z. (2022). Components and clinical pharmacological value of dark plum. *Mod. Salt Chem. Ind.* 49 (05), 38–40. doi:10.19465/j.cnki.2095-9710.2022.05.042

Shen, Z. (2017). Correlation between lipid levels and major inflammatory factors in patients with coronary heart disease and hyperlipidemia. *J. Cardiovasc. Rehabilitation Med.* 26 (04), 388–390.

Shi, Y., Pu, D., Zhou, X., and Zhang, Y. (2022). Recent progress in the study of taste characteristics and the nutrition and health properties of organic acids in foods. *Foods* 11 (21), 3408. doi:10.3390/foods11213408

Su, R., and Yu, D. (2009). The hazards of hyperlipidemia and its prevention and treatment. *Contemp. Med. China* (8), 128–129.

Su, S., Wu, G., Cheng, X., Fan, J., Peng, J., Su, H., et al. (2018). Oleanolic acid attenuates PCBs-induced adiposity and insulin resistance via HNF1b-mediated regulation of redox and PPARγ signaling. *Free Radic. Biol. Med.* 124, 122–134. doi:10.1016/j.freeradbiomed.2018.06.003

Suk, S., Kwon, G. T., Lee, E., Jang, W. J., Yang, H., Kim, J. H., et al. (2017). Gingerenone A, a polyphenol present in ginger, suppresses obesity and adipose tissue inflammation in high-fat diet-fed mice. *Mol. Nutr. Food Res.* 61 (10). doi:10.1002/mnfr.201700139

Sun, Y., Huang, X., and Liang, W. (2018). Effects of tangerine peel and Pinellia on PI3K-Akt pathway, SOD, MDA, and SA-β-gal levels in atherosclerotic mice. *J. Cap. Med. Univ.* 39 (06), 805–809.

Timmis, A., Aboyans, V., Vardas, P., Townsend, N., Torbica, A., Kavousi, M., et al. (2024). European society of cardiology: the 2023 atlas of cardiovascular disease statistics. *Eur. Heart J.* 45 (38), 4019–4062. doi:10.1093/eurheartj/ehae466

Trinder, M., Vikulova, D., Pimstone, S., Mancini, G. B. J., and Brunham, L. R. (2022). Polygenic architecture and cardiovascular risk of familial combined hyperlipidemia. *Atherosclerosis* 340, 35–43. doi:10.1016/j.atherosclerosis.2021.11.032

Wang, J., Chen, W., and Jia, L. (2019). Study on the effects of Er chen decoction combined with tao hong Si Wu tang on the Nox4/NF-κB/HIF-1α signaling pathway in ApoE-/- atherosclerotic mice. *Chin. J. Traditional Chin. Med.* 34 (06), 2417–2420.

Wang, Q. (2022). *Clinical observation of erchen decoction combined with Jiao sanxian in the treatment of hyperlipidemia of phlegm and turbidity blocking type*. Hubei University of Chinese Medicine.

Wang, Q., Hong, Y., Liu, Z., and Lin, C. (2023). Study on the antioxidant and blood sugar lowering effects of licorice polysaccharides. *Sci. Technol. Food Industry* 44 (01), 398–404. doi:10.13386/j.issn1002-0306.2022030175

Wang, X., Wu, H., Yu, W., Liu, J., Peng, J., Liao, N., et al. (2017). Hepatocyte nuclear factor 1b is a novel negative regulator of white adipocyte differentiation. *Cell Death Differ.* 24 (9), 1588–1597. doi:10.1038/cdd.2017.85

Wang, Y., and Wang, Q. (2020). Progress in research on the chemical components, pharmacological actions, and toxicity of Pinellia. *China Pharm.* 31 (21), 2676–2682.

Wei, W., Xuan, Y., and Huang, X. (2023). Lipid-lowering and gut microbiota modulation effects of Poria cocos polysaccharides on nutritionally obese young mice. *Mod. Food Sci. Technol.* 39 (10), 35–43. doi:10.13982/j.mfst.1673-9078.2023.10.1312

Weng, W., Wang, Q., Wei, C., Adu-Frimpong, M., Toreniyazov, E., Ji, H., et al. (2021). Mixed micelles for enhanced oral bioavailability and hypolipidemic effect of liquiritin: preparation, *in vitro* and *in vivo* evaluation. *Drug Dev. Ind. Pharm.* 47 (2), 308–318. doi:10.1080/03639045.2021.1879839

Wu, J., Wang, X., and Wang, K. (2019). Research progress on the nutritional value and pharmacological effects of ginger. *Food Ind.* 40 (02), 237–240.

Wu, X., Liu, D., and Li, N. (2020). Mechanisms of licorice polysaccharides in repairing inflammation and oxidative damage in mouse lung tissue. *J. Gansu Agric. Univ.* 55 (05), 8–14+30. doi:10.13432/j.cnki.jgsau.2020.05.002

Wu, Y., Yi, L., Li, E., Li, Y., Lu, Y., Wang, P., et al. (2017). Optimization of Glycyrrhiza polysaccharide liposome by response surface methodology and its immune activities. *Int. J. Biol. Macromol.* 102, 68–75. doi:10.1016/j.ijbiomac.2017.04.006

Xia, Q., Chen, Y., Yu, Z., Huang, Z., Yang, Y., Mao, A., et al. (2023). Prevalence, awareness, treatment, and control of dyslipidemia in Chinese adults: a systematic review and meta-analysis. *Front. Cardiovasc Med.* 10, 1186330. doi:10.3389/fcvm.2023.1186330

Xiang, D. (2023). *Study on Er Chen Decoction promoting the browning of white adipose tissue to improve insulin resistance in PCOS rats*. Nanjing University of Chinese Medicine.

Xiao, X., Li, C., and Liu, X. (2023). Research progress on the major chemical components and pharmacological effects of licorice. *J. Xinxiang Med. Univ.* 40 (03), 280–285.

Xin, Y., Li, X., Zhu, X., Lin, X., Luo, M., Xiao, Y., et al. (2023). Stigmasterol protects against steatohepatitis induced by high-fat and high-cholesterol diet in mice by enhancing the alternative bile acid synthesis pathway. *J. Nutr.* 153 (7), 1903–1914. doi:10.1016/j.tjnut.2023.05.026

Ye, H., He, B., Zhang, Y., Yu, Z., Feng, Y., Wen, C., et al. (2023). Herb-symptom analysis of Erchen decoction combined with Xiebai powder formula and its mechanism in the treatment of chronic obstructive pulmonary disease. *Front. Pharmacol.* 14, 1117238. doi:10.3389/fphar.2023.1117238

Yin, J., and Fu, D. (2022a). Clinical observation of modified Er Chen Decoction combined with atorvastatin in treating phlegm-turbidity obstructive hyperlipidemia. *Jiangxi Tradit. Chin. Med.* 53 (05), 39–42.

Yin, J., and Fu, D. (2022b). Effects of modified Er Chen Decoction combined with atorvastatin on inflammatory factors, uric acid, and carotid artery plaques in patients with phlegm-dampness obstructive hyperlipidemia. *Chin. J. Traditional Chin. Med. Pharm.* 29 (04), 528–532.

Zhang, L. (2022). Network pharmacology analysis and experimental study on the mechanism of action of Chen Pi-Pinellia in the treatment of hyperlipidemia. *J. Integr. Traditional Chin. West. Med. Cardio-Cerebrovascular Dis.* 20 (17), 3118–3128.

Zhang, M., Shao, Y., Gao, B., Chen, J., Zhang, P., Hu, Y., et al. (2020a). Erchen decoction mitigates lipid metabolism disorder by the regulation of PPARγ and LPL gene in a high-fat diet C57bl/6 mice model. *Evid. Based Complement. Altern. Med.* 2020, 9102475. doi:10.1155/2020/9102475

Zhang, S., He, Y., Sen, B., and Wang, G. (2020b). Reactive oxygen species and their applications toward enhanced lipid accumulation in oleaginous microorganisms. *Bioresour. Technol.* 307, 123234. doi:10.1016/j.biortech.2020.123234

Zhang, X., Xue, X., Ye, C., Zhao, J., Yang, Z., Li, P., et al. (2024). Study on the effects of Er Chen Decoction in reducing oxidative stress levels in hyperlipidemic mice with phlegm-turbidity obstruction syndrome by regulating the p38MAPK signaling pathway. *J. Liaoning Univ. Traditional Chin. Med.* 26 (04), 38–42. doi:10.13194/j.issn.1673-842x.2024.04.008

Zhang, Y., Gu, Y., Jiang, J., Cui, X., Cheng, S., Liu, L., et al. (2022). Stigmasterol attenuates hepatic steatosis in rats by strengthening the intestinal barrier and improving bile acid metabolism. *NPJ Sci. Food* 6 (1), 38. doi:10.1038/s41538-022-00156-0

Zhao, M., Wu, F., Tang, Z., Yang, X., Liu, Y., Wang, F., et al. (2023). Anti-inflammatory and antioxidant activity of ursolic acid: a systematic review and meta-analysis. *Front. Pharmacol.* 14, 1256946. doi:10.3389/fphar.2023.1256946

Zhu, J., and Wang, S. (2022). Wang Shoufu's experience in treating hyperlipidemia from a phlegm-damp perspective. *Chin. Folk. Remedies* 30 (19), 51–53. doi:10.19621/j.cnki.11-3555/r.2022.1916

Zhu, L., Chen, G., Guo, Y., Zheng, J., Yang, H., Sun, X., et al. (2022a). Structural characterization of Poria cocos oligosaccharides and their effects on the hepatic metabolome in high-fat diet-fed mice. *Food Funct.* 13 (12), 6813–6829. doi:10.1039/d2fo00638c

Zhu, L., Ye, C., Hu, B., Xia, H., Bian, Q., Liu, Y., et al. (2022b). Regulation of gut microbiota and intestinal metabolites by Poria cocos oligosaccharides improves glycolipid metabolism disturbance in high-fat diet-fed mice. *J. Nutr. Biochem.* 107, 109019. doi:10.1016/j.jnutbio.2022.109019

Zhu, Y., Wei, S., Cao, X., Wang, S., Chang, Y., Ouyang, H., et al. (2022c). Multi-component pharmacokinetic study of prunus mume fructus extract after oral administration in rats using UPLC-MS/MS. *Front. Pharmacol.* 13, 954692. doi:10.3389/fphar.2022.954692

Zou, T., Wang, J., Wu, X., Yang, K., Zhang, Q., Wang, C., et al. (2023). A review of the research progress on Pinellia ternata (Thunb.) Breit.: botany, traditional uses, phytochemistry, pharmacology, toxicity and quality control. *Heliyon* 9 (11), e22153. doi:10.1016/j.heliyon.2023.e22153

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 12 December 2024
DOI 10.3389/fphar.2024.1487119

OPEN ACCESS

EDITED BY
Qing Yong He,
China Academy of Chinese Medical Sciences, China

REVIEWED BY
Jiale Zhang,
China Academy of Chinese Medical Sciences, China
Chenyang Ji,
University of Malaya, Malaysia

*CORRESPONDENCE
Xian Wang,
wxian202212@163.com

†These authors have contributed equally to this work.

RECEIVED 27 August 2024
ACCEPTED 25 November 2024
PUBLISHED 12 December 2024

CITATION
Dai S, Ding Y, Guo J and Wang X (2024) Efficacy and safety of danshen class injections in the treatment of coronary heart disease: a network meta-analysis.
Front. Pharmacol. 15:1487119.
doi: 10.3389/fphar.2024.1487119

Efficacy and safety of danshen class injections in the treatment of coronary heart disease: a network meta-analysis

Shuang Dai[1†], Yukun Ding[2†], Jianbo Guo[3] and Xian Wang[1*]

[1]Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [2]Science and Education Departmen, Beijing Fengtai Hospital of Integrated Traditional Chinese and Modern Medicine, Beijing, China, [3]LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China

Background: Danshen [Salvia miltiorrhiza Bunge (Lamiaceae; Salviae miltiorrhizae radix et rhizoma)] class injections (DSCIs) are widely used in the treatment of coronary heart disease (CHD). However, there are various types of DSCIs available on the market, and it remains uncertain which DSCI has the best clinical efficacy, as well as which one is most effective in regulating inflammatory markers and oxidative stress indicators. The aim of this network meta-analysis (NMA) is to compare the therapeutic effects of different DSCIs to identify the optimal DSCI for the treatment of CHD.

Methods: The databases searched to identify randomized controlled trials (RCTs) of DSCIs for CHD included the China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, Web of Science, and Cochrane Library. The search period spanned from the inception of each database up to June 2024. NMA was conducted using RevMan 5.3 and Stata 16.0 software.

Results: A total of 106 studies including 14,979 patients, involving 10,931 patients, with 5,640 in the experimental group and 5,291 in the control group. And ten DSCIs were extracted, namely: Danhong injection (DH), Danshen injection (DS), Danshenchuanxiongqin injection (DSCXQ), Dansenduofensuanyan injection (DSDFSY), Danshenfen injection (DSFZ), Fufang Danshen injection (FFDS), Guanxinning injection (GXN), Sodium Tanshinone IIA Sulfonate injection (STS), Xiangdan injection (XD), Shenxiongputaotang injection (SXPTT). The results of NMA showed that, XD injection significantly enhances clinical efficacy; STS is more effective in reducing hs-CRP levels; DSDFSY shows better efficacy in

Abbreviations: DSCIs, Danshen class injection; CHD, coronary heart disease; NMA, network meta-analysis; RCT, randomized controlled trials; CNKI, China National Knowledge Infrastructure; VIP, China Science and Technology Journal Database; CBM, Chinese Biomedical Literature Database; CCS, chronic coronary syndrome; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; TCM, traditional Chinese medicine; TSN, tanshinones; Tan IIA, Tanshinone IIA; Tan I, Tanshinone I; SAA, Salvia acid A; WM, western medicine; DH, Danhong injection; DS, Danshen injection; DSCXQ, Danshenchuanxiongqin injection; DSDFSY, Dansenduofensuanyan injection; DSFZ, Danshenfen injection; FFDS, Fufang Danshen injection; GXN, Guanxinning injection; STS, Sodium Tanshinone IIA Sulfonate injection; XD, Xiangdan injection; SXPTT, Shenxiongputaotang injection. hs-CRP, high-sensitivity C-reactive protein; IL-1, interleukin-1; IL-6, interleukin-6; NO, nitric oxide; SOD, superoxide dismutase; MDA, malondialdehyde.

decreasing IL-1 and increasing NO levels; DSCXQ has a greater advantage in reducing IL-6 levels; GXN is more effective in regulating SOD levels; and DH is better at reducing MDA levels.

Conclusion: The combined treatment of DSCIs and WM more significant efficacy in patients with CHD compared to WM treatment alone, including clinical efficacy evaluation, inflammatory markers, and oxidative stress markers. Overall, DSDFSY and DSCXQ show better performance in clinical efficacy evaluation and regulation of inflammatory markers, while DH exhibits a more stable effect in regulating oxidative stress. However, larger sample sizes and high-quality RCTs are still necessary to further compare the various DSCIs.

Systematic Review Registration: [PROSPERO], identifier [CRD42024548928].

KEYWORDS

danshen class injections, Chinese medicine injection, coronary heart disease, network meta-analysis, randomized controlled trial

1 Introduction

CHD is one of the most common cardiovascular diseases, with approximately 11.39 million patients in China (National Center for Cardiovascular Disease, 2023). According to the "China Health and Family Planning Statistical Yearbook 2021" (National Health Commission of the People's Republic of China, 2021), the mortality rate of CHD in urban residents in China was 126.91/100,000 and 135.88/100,000 in rural areas in 2020, showing a continuous upward trend. Dyslipidemia (Martin et al., 2014) and inflammation (Hansson, 2005) jointly induce the formation of atherosclerotic plaques, which obstruct the coronary arteries and lead to CHD. CHD is a dynamic process characterized by the accumulation of atherosclerotic plaques and changes in coronary circulation. Clinically, CHD can be divided into chronic coronary syndrome (CCS) and acute coronary syndrome (ACS). The "2019 ESC Guidelines for the Diagnosis and Management of Chronic Coronary Syndromes" (Knuuti et al., 2020) recommend that conventional treatments for CCS include anti-ischemic therapy (Wight et al., 1992; Wei et al., 2011), antiplatelet therapy (Mehta et al., 2010), lipid-lowering therapy (Mach et al., 2020), and revascularization (Neumann et al., 2019). The "2023 ESC Guidelines for the Management of Acute Coronary Syndromes" (Byrne et al., 2023) suggest that the primary treatments for ACS should include percutaneous coronary intervention (PCI) (Huynh et al., 2009), thrombolytic therapy (Fibrinolytic Therapy Trialists FTT, 1994), and antithrombotic therapy (Valgimigli et al., 2018; Eikelboom et al., 2000). Additionally, anti-inflammatory and antioxidant treatments have been studied for decades in CHD patients (Malekmohammad et al., 2019), such as low-dose colchicine (Nidorf et al., 2020), IL-6 inhibitors (Broch et al., 2021), IL-1 inhibitors (Everett et al., 2020), vitamin C (Kaufmann et al., 2000), vitamin E (Riemersma, 1996), and β-carotene (Törnwall et al., 2004). Despite the gradual improvement of current treatment methods, challenges such as angina, antiplatelet drug resistance (Gorog et al., 2009), and microcirculation disorders (Padro et al., 2020) still exist. Therefore, comprehensively improving the quality of life for CHD patients remains a significant challenge.

CHD falls under the categories of "chest impediment and heart pain", "sudden heart pain", and "true heart pain" in traditional Chinese medicine (TCM). The earliest Chinese medicinal text, "Shen Nong's Materia Medica," documented that Danshen could treat evil qi in the heart and abdomen. In ancient China, decoctions and pills were the primary preparations of Danshen [Salvia miltiorrhiza Bunge (Lamiaceae; Salviae miltiorrhizae radix et rhizoma)], with the dried root being the most commonly used part. According to the "Chinese Pharmacopoeia" (2020), Danshen possesses effects such as promoting blood circulation, removing blood stasis, and cooling the blood. Modern research has identified various chemical metabolites in Danshen (Su et al., 2015), which can be categorized into three main types: diterpene quinones, including tanshinone-type diterpenes; hydrophilic phenolic acids, mainly phenolic acids; and essential oil metabolites, with diterpene quinones and hydrophilic phenolic acids being the primary active metabolites (Gao et al., 2012). Modern studies have discovered that Danshen has multiple pharmacological effects, including anti-myocardial ischemia, improvement of atherosclerosis, anti-inflammatory, antihypertensive, lipid-lowering, hypoglycemic, antithrombotic, and anti-tumor effects (Su et al., 2015). Therefore, DSCIs, which are TCM injections with Danshen as the main component, are widely used in treating CHD.

Previous studies have conducted meta-analyses on stable angina, unstable angina, or myocardial infarction (Zhang et al., 2017; Wu et al., 2017; Liu et al., 2018; Li et al., 2022), but no comprehensive meta-analysis on CHD as a whole has been done, and it remains unclear which injection is more effective for CHD. NMA was chosen for this study as it allows for the simultaneous comparison of multiple treatments, even when direct head-to-head trials are unavailable, by combining both direct and indirect evidence. This approach provides a more comprehensive and precise assessment of the relative efficacy of different DSCIs, offering insights that would be difficult to obtain through traditional Meta-Analysis alone. Therefore, we decided to use a network meta-analysis, incorporating both direct comparisons from RCTs and indirect comparisons based on shared control RCTs (Nikolakopoulou et al., 2018). We aim to identify the most reliable DSCIs for the treatment of CHD through relevant RCT-based network meta-analyses and to evaluate the relative efficacy and safety of different DSCIs in CHD patients, providing a reference for

clinical application. This study focuses on patients with coronary heart disease (CHD), addressing a gap in previous research that has primarily focused on other conditions. We extended the search period to include studies from the past 2 years, enhancing the relevance and timeliness of our findings. Additionally, we explored changes in inflammatory markers and oxidative stress indicators, providing deeper insight into the underlying mechanisms of Danshen's therapeutic effects. We also compared different Danshen injections, an area that has not been extensively addressed in previous meta-analyses, offering more precise conclusions about the relative efficacy of various formulations. These distinctive aspects highlight the originality and value of our study in advancing the understanding of Danshen's role in treating CHD.

2 Methods

2.1 Study registering

The review protocol was registered at PROSPERO (No: CRD42024548928, https://www.crd.york.ac.uk/prospero/). The current research procedure was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Hutton et al., 2015).

2.2 Inclusion and exclusion criteria

The inclusion criteria for this study adhered to the PICOS framework, encompassing participants, interventions, comparisons, outcomes, and study design. Therefore, clinical trials meeting the following criteria were included:

(1) Participants: This study included patients diagnosed with CHD, including chronic coronary syndrome and acute coronary syndrome, without restrictions on race, gender, age, or nationality. Study design. Only RCTs mentioned in articles were enrolled.
(2) Interventions and comparisons: The experimental group received DSCIs combined with guideline-recommended Western medicine. Patients in the control group received Western medicine treatment alone, without the use of other Chinese medicine. Commonly used Western medicines included antiplatelet agents, statins, nitrates, β-receptor blockers, and Angiotensin-Converting Enzyme Inhibitors. There were no restrictions on dosage and duration of treatment. Appropriate treatment measures were taken for patients with additional comorbidities.
(3) Outcomes: The primary outcome of this study was the clinical effectiveness rate. Based on changes in clinical symptoms and objective indicators, the effectiveness status was categorized as effective or ineffective. When patients' clinical symptoms showed no significant change or even worsened (e.g., increased frequency, longer duration, more intense pain), and there was no improvement in the electrocardiogram, it was considered ineffective. Secondary outcomes included high-sensitivity C-reactive protein (hs-CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), nitric oxide (NO), superoxide dismutase (SOD), malondialdehyde (MDA), and adverse reactions. Included studies should have at least one outcome measure.
(4) Study design: Only Randomized Controlled Trial (RCT) were enrolled.

We excluded the following studies: (1) studies using other traditional Chinese medicine preparations or external traditional Chinese medicine therapies (such as massage, gua sha, cupping); (2) studies related to percutaneous coronary intervention (PCI) or thrombolytic surgery; (4) studies with incomplete or erroneous data; (5) studies for which the full text could not be obtained.

2.3 Search strategy

A systematic electronic search was conducted across eight databases to identify RCT studies published from their inception up to June 2024. The databases searched included the China National Knowledge Infrastructure Database (CNKI), the Chinese Scientific Journals Full-text Database (VIP), the Wan-Fang Database, the Chinese Biomedical Literature Database (SinoMed), the Cochrane Library, PubMed, Web of Science and Embase. The search was not restricted by language or country. For detailed search strategies, please refer to the appendix.

2.4 Data extraction

Two researchers (DS and DYK) used EndNote X9 for reference management, removing duplicate records and excluding irrelevant or non-compliant studies according to the inclusion and exclusion criteria. Subsequently, a database was established using Microsoft Excel to meticulously record study information, including publication details (title, author names, and publication date), patient information (sample size, mean age and gender composition, classification of coronary artery disease), interventions (name of the injection, dosage, and duration of administration), outcomes (primary and secondary outcomes), and study design (randomization, allocation concealment, and blinding). To ensure data accuracy, two independent researchers entered the data and cross-checked for inconsistencies. For studies with missing data, we contacted the original authors for clarification; if no accurate data was provided, the study was excluded from the analysis.

2.5 Quality assessment

Two researchers independently assessed the quality of all included studies according to the Cochrane Intervention Reviewer's Handbook version 5.1.0 (Cumpston et al., 2019). The assessment criteria included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other

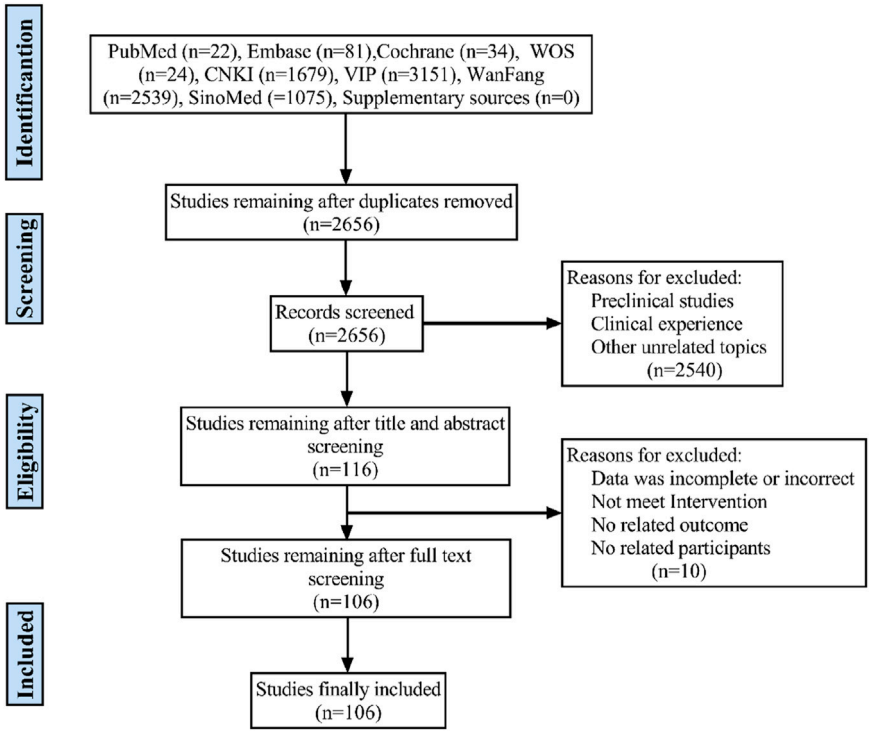


FIGURE 1
Flow diagram of eligible literature selection. CNKI, the China National Knowledge Infrastructure Database; WanFang, Wanfang Database; VIP, the Chinese Scientific Journals Full-text Database; SinoMed, the Chinese Biomedical Literature Database; n, number of publications.

biases. Each criterion could be rated as low, high, or unclear risk of bias.

In cases of discrepancies in data extraction and quality assessment, resolution was achieved through the judgment of a third researcher or consensus.

2.6 Statistical analysis

Statistical and network meta-analysis were conducted using Stata 16.0 software. For dichotomous outcomes, results were presented as odds ratios (OR) with corresponding 95% confidence intervals (95% CI); for continuous variable outcomes, results were shown as mean differences (MD) with 95% CI. Additionally, if a particular outcome had two or more studies directly compared, a pairwise meta-analysis using a random-effects model was employed. Different interventions were compared through network meta-analysis using a frequentist framework and a random-effects model, and the results were presented in a ranking format. The surface under the cumulative ranking curve (SUCRA) was plotted according to the size of the cumulative ranking area under the curve, providing a more intuitive display of the ranking of each treatment measure. SUCRA ranges from 0% to 100%, assigned to the worst and best treatment measures respectively. Since no closed loops were formed in the analysis, inconsistency assessment was not feasible. Furthermore, publication bias of the included RCT was examined by comparing funnel plots corrected by regression lines.

3 Results

3.1 Literature selection

A total of 8,605 articles were retrieved by searching eight databases. After removing duplicate articles, 2,656 articles remained for abstract screening. Excluding reviews, meta-analyses, systematic reviews, animal studies, and other u—elated topics, 116 articles were left for full-text review. Ultimately, 106 RCTs met the criteria for inclusion in this network meta-analysis. The detailed process of article selection is illustrated in Figure 1.

3.2 Study characteristic

A total of 106 RCTs were included in this research, involving 10,931 patients, with 5,640 in the experimental group and 5,291 in the control group. All included studies were conducted in China. The research covered 10 types of DSCIs, including DSDFSY + WM vs. WM (n = 44), DH + WM vs. WM (n = 31), DSCXQ + WM vs. WM (n = 9), STS + WM vs. WM (n = 8), DS + WM vs. WM (n = 2), SXPTT + WM vs. WM (n = 2), GXN + WM vs. WM (n = 4), XD + WM vs. WM (n = 1), DSFZ + WM vs. WM (n = 1), DH + WM vs. DS + WM (n = 1), DH + WM vs. FFDS + WM (n = 1), FFDS + WM vs. DH + WM (n = 1), and DSDFSY + WM vs. DS + WM (n = 1). The control group treatment was WM, mainly consisting of antiplatelet aggregation drugs, β-blockers, statins, nitrates, etc. Detailed

TABLE 1 Characteristics of included studies.

Study ID	Sample size		Sex (M/F)		Average age		Therapy of experiment group	Menstruum	Therapy of control group	Course (days)	Outcomes
	E	C	E	C	E	C					
Guo et al. (2016)	50	50	32/18	36/14	63.2 ± 2.1	62.9 ± 1.8	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	②
Lv (2018)	30	30	20/10	22/8	72.25 ± 8.31	71.29 ± 8.28	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	21d	①②⑤
Wu et al. (2010)	39	33	24/15	19/14	69.5 ± 8.50		DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	③
Zhang et al. (2018)	170	172	88/82	92/80	58.60 ± 10.1	57.90 ± 9.4	DH 40 mL + WM	0.9% NS 250 mL	WM	15d	①③④
Qiu et al. (2017)	40	40	42/38		61.6 ± 11.30		DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	②③
Xi et al. (2015)	35	35	21/14	17/18	55.3 ± 8.7	57.2 ± 10.3	SXPTT 100 mL + WM	—	WM	21d	②
Bi et al. (2011)	62	62	80/44		68.3 ± 7.90		SXPTT 200 mL + WM	—	WM	21d	②
Song et al. (2015)	40	40	20/20	22/18	54.11 ± 5.24	53.42 ± 5.68	DSCXQ 10 mL + WM	0.9% NS 250 mL	WM	14d	①②④
Liu et al. (2015)	62	62	34/28	32/28	67.7 ± 4.3	68.8 ± 5.1	DSCXQ 10 mL + WM	0.9% NS 250 mL	WM	28d	①②
Cai et al. (2014)	54	52	30/24	29/23	77 ± 6.8	76 ± 7.2	DSCXQ 10 mL + WM	0.9% NS 250 mL	WM	15d	①②
Li and Yin (2012)	60	60	69/51		74 ± 7		DSCXQ 10 mL + WM	0.9% NS 250 mL	WM	6d	②
Yu and Fang (2016)	47	47	26/21	27/20	—		DSCXQ 5–10 mL + WM	0.9% NS 250–500 mL	WM	20d	①②
Ji (2013)	40	40	48/32		42.3 ± 6.7		DSCXQ 10 mL + WM	0.9% NS 250 mL	WM	10d	①②
Liu and Xiao (2014)	83	77	48/35	45/32	65.3 ± 12.1	63.8 ± 11.3	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	28d	①②
Chen and Huang (2016a)	25	25	14/11	15/10	61.5 ± 5.7	62.3 ± 6.0	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	③④
Wang and Bi (2017)	61	61	35/26	34/27	59.1 ± 6.6	58.4 ± 6.4	DSDFSY 200 mg + WM	5%GS/0.9%NS 250–500 mL	WM	14d	①③④
Mao et al. (2016)	48	48	32/16	31/17	58.3 ± 7.5	57.4 ± 7.3	DSDFSY 100 mg + WM	5%GS/0.9%NS 250 mL	WM+0.9%NS250 mL	14d	①②
Jiang et al. (2012)	30	30	—		—		DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	10d	①②
Tao et al. (2024)	53	53	39/14	35/18	68.8	67.6	DSDFSY 100 mg + WM	0.9% NS 250 mL	WM	14d	①②
Zhang et al. (2015a)	42	42	48/36		63.1 ± 8.8	65.4 ± 10.2	DSDFSY 100 mg + WM	0.9% NS 250 mL	WM	14d	①②④
Li et al. (2018a)	76	76	49/27	52/24	58.1 ± 7.8	59.3 ± 8.2	DSDFSY 100 mg + WM	0.9% NS 250 mL	WM	1m	①②③
Zhu (2019)	38	38	21/17	20/18	60.37 ± 8.89	59.87 ± 9.87	DSDFSY 150 mg + WM	5% GS 250 mL	WM	15d	②
Liu et al. (2023)	51	51	30/21	28/23	62.98 ± 4.57	63.56 ± 4.89	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM	7d	①②④
Jiang (2022)	52	52	30/22	27/25	62.39 ± 6.43	62.45 ± 6.10	DSDFSY 200 mg + WM	5% GS 250 mL	WM	14d	①③④
Jing (2014)	42	40	31/11	30/10	64.67 ± 7.45	64.33 ± 6.99	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①②

(Continued on following page)

10.3389/fphar.2024.1487119

TABLE 1 (*Continued*) Characteristics of included studies.

Study ID	Sample size		Sex (M/F)		Average age		Therapy of experiment group	Menstruum	Therapy of control group	Course (days)	Outcomes
	E	C	E	C	E	C					
Xia and Zhang (2022)	43	43	23/20	22/21	71.52 ± 1.25	71.59 ± 2.13	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①②④
Jiao and Wang (2019)	40	40	24/16	23/17	49.57 ± 4.39	49.63 ± 4.57	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM	14d	①④
Pan et al. (2024)	66	66	39/27	40/26	61.3 ± 10.8	60.7 ± 10.4	DSDFSY 200 mg + WM	0.9% NS 200 mL	WM	14d	④
Qiu (2020)	31	35	42/24		61.5 ± 11.4	62.1 ± 12.6	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM	14d	①②④
Xie et al. (2020)	53	53	29/24	27/26	57.42 ± 6.45	58.02 ± 6.49	DSDFSY 200 mg + WM	5% GS 250 mL	WM	28d	②④
Yue et al. (2023)	51	51	26/25	28/23	61.53 ± 2.92	61.48 ± 2.81	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM	28d	①④
Chen et al. (2012)	40	40	47/33		53.2 ± 6.8		STS 12 mL + WM	0.9% NS 100 mL	WM	14d	②
Yang and Ren (2010)	32	32	18/14	17/15	59 ± 11	60 ± 10	STS 12 mL + WM	5%GS/0.9%NS 250 mL	WM	7d	①②④
Li et al. (2007)	37	36	39/34		67.4 ± 6.5		DS 20 mL + WM	—	WM	14d	②
Li et al. (2009a)	92	90	55/37	54/36	61 ± 14	63 ± 11	DH 20 mL + WM	0.9% NS 250 mL	WM	14d	①②
Huang (2017)	20	20	11/9	8/12	53.7 ± 6.5	54.3 ± 6.1	DH 20 mL + WM	0.9% NS 250 mL	WM	28d	②
Xie and Cao (2011)	32	32	20/12	18/14	62.8 ± 8.2	63.0 ± 8.5	DH 30 mL + WM	0.9% NS 250 mL	WM	14d	①②
Mei et al. (2006)	22	20	12/10	11/9	61.1 ± 9.5	61.6 ± 9.9	DH 40 mL + WM	5% GS 500 mL	WM	14d	②
Liao et al. (2008)	40	30	19/21	17/13	65.1 ± 13.5	64.2 ± 10.3	DH 20 mL + WM	5%GS/0.9%NS 250 mL	WM	10d	②
Zhao et al. (2015)	54	54	27/27	26/28	61.93 ± 4.41	62.53 ± 4.73	DH 30 mL + WM	0.9% NS 250 mL	WM	14d	①②⑤
Zhang (2011)	60	60	32/28	31/29	61.21 ± 5.02	61.51 ± 7.86	DH 40 mL + WM	5%GS/0.9%NS 250 mL	WM	14d	①②④
Yang and Shi (2009)	60	60	46/14	47/13	62.9 ± 6.9	63.1 ± 7.2	DH 30 mL + WM	5%GS/0.9%NS 250 mL	WM	14d	②④
Peng et al. (2015)	45	45	26/19	27/18	63.2 ± 9.2	63.5 ± 9.0	DH 30 mL + WM	0.9% NS 250 mL	WM	14d	①②
Fu and Jiang (2015)	49	47	27/22	26/21	46.17 ± 5.43	45.81 ± 4.79	DH 30 mL + WM	0.9% NS 250 mL	WM	10d	①②
Wang and Wang (2020)	55	55	33/22	32/23	64.9 ± 7.1	65.3 ± 6.9	DH 20 mL + WM	0.9% NS 250 mL	WM	14d	①④
Li et al. (2008)	80	50	48/32	28/22	60.3 ± 10.10	62.18 ± 10.50	DH 20 mL + WM	0.9% NS 250 mL	WM	14d	①②
Zhao et al. (2011)	36	36	42/30		50.9 ± 8.60	60.2 ± 9.20	DH 40 mL + WM	5% GS 250 mL	WM	14d	①②
Chen et al. (2015a)	65	65	43/22	49/16	68.00 ± 12.00	69.00 ± 14.00	DH 30 mL + WM	5%GS/0.9%NS 100 mL	WM	14d	①②
Liu et al. (2012)	48	48	27/21	25/23	62.50 ± 3.60	62.9 ± 3.10	DH 40 mL + WM	5%GS/0.9%NS 250 mL	WM	15d	①②
Li and Ge (2011)	44	42	50/36		64.5 ± 8		DH 20 mL + WM	10%GS/0.9%NS 250 mL	WM	10d	①②

(Continued on following page)

10.3389/fphar.2024.1487119

TABLE 1 (*Continued*) Characteristics of included studies.

Study ID	Sample size		Sex (M/F)		Average age		Therapy of experiment group	Menstruum	Therapy of control group	Course (days)	Outcomes
	E	C	E	C	E	C					
SHI and Liu (2012)	80	76	40/40	39/37	66–80	65–78	DH 40 mL + WM	0.9% NS 250 mL	WM	14d	①②
Chen et al. (2015b)	94	73	59/35	47/26	64.83 ± 8.45	64.54 ± 9.64	DH 30 mL + WM	5%GS/0.9%NS 250 mL	WM	14d	①②④
Xu et al. (2014)	46	46	30/16	32/14	53.40 ± 8.20	52.20 ± 9.60	GXN 20 mL + WM	5% GS 250 mL	WM	15d	①②
Fu and Meng (2011)	25	22	13/12	11/11	—		GXN 20 mL + WM	5% GS 250 mL	WM	10d	①②
Zhang et al. (2012)	44	44	22/22	26/18	22–41	20–44	DH 20 mL + WM	0.9% NS 250 mL	WM	10d	①
Zhang (2016)	35	35	17/18	18/17	53.70 ± 4.30	54.10 ± 4.50	DSDFSY 100 mg + WM	0.9% NS 250 mL	WM	28d	①②④
Hong et al. (2004)	90	30	52/38	17/13	62.95 ± 9.36	66.00 ± 8.96	XD 20 mL + WM	5%GS/0.9%NS 250 mL	WM	14d	①
Lang (2012)	60	60	38/22	35/25	60.60 ± 8.20	62.50 ± 8.00	DSCXQ 20 mL + WM	—	WM	14d	①②④
Yu and Jiao (2014)	62	62	41/21	40/22	50.30 ± 8.80	51.40 ± 7.90	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM	14d	①②
Lu and Ma (2023)	60	60	38/22	35/25	69.53 ± 5.18	69.34 ± 5.23	DSDFSY 200 mg + WM	5% GS 250 mL	WM	14d	①④
Feng and Ji (2010)	20	20	31/9		55.18 ± 4.35		DSDFSY 100 mg + WM	5% GS 250 mL	WM	14d	①⑤⑥⑦
Mei et al. (2014)	39	39	22/17	23/16	65.40 ± 4.20	66.20 ± 4.10	DSCXQ 10 mL + WM	5% GS 250 mL	WM	14d	②⑤
Xu and Hao (2022)	30	30	20/10	17/13	65.73 ± 4.88	65.75 ± 4.76	DSCXQ 10 mL + WM	0.9% NS 250 mL	WM	28d	⑥
Chen and Huang (2016b)	30	30	18/12	17/13	62.80 ± 6.50	63.10 ± 5.80	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	⑤
Zhang (2010)	30	20	25/5	14/6	70.56 ± 2.25	71.21 ± 5.10	DSDFSY 200 mg + WM	5% GS 250 mL	WM	14d	⑤
Wu et al. (2012)	30	30	19/11	17/13	59.91 ± 10.86	59.92 ± 9.03	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	10d	①⑤
Duan et al. (2010)	28	32	18/14	15/13	62.3	61.5	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	10d	①⑥⑦
Guan et al. (2019)	40	40	24/16	23/17	58.30 ± 7.30	57.90 ± 7.30	DSDFSY 200 mg + WM	5%GS/0.9%NS 250–500 mL	WM	14-28d	⑤⑥⑦
Lin et al. (2020)	93	92	52/41	50/42	62.10 ± 7.20	62.40 ± 7.30	DSDFSY 200 mg + WM	5% GS 250 mL	WM	28d	①⑤
Tan et al. (2009)	42	40	35/7	31/9	71.56 ± 8.25	70.18 ± 8.26	DSDFSY 200 mg + WM	5% GS 250 mL	WM	14d	⑤
Pang et al. (2014)	42	42	26/16	25/17	73.40 ± 7.30	73.80 ± 7.50	DSDFSY 200 mg + WM	5% GS 250 mL	WM	14d	①⑤
Liu (2017)	40	40	23/17	22/18	59.12 ± 2.13	60.29 ± 2.24	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①⑤
Ye et al. (2021)	74	76	43/31	46/30	59.64 ± 6.98	60.17 ± 7.05	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM	10d	⑥
Lun et al. (2011)	30	30	19/11	18/12	60.11 ± 11.00	62.31 ± 8.30	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①⑤
Qiu et al. (2018)	55	55	30/25	31/24	58.93 ± 7.51	59.31 ± 7.29	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM	56d	⑥⑦

(Continued on following page)

10.3389/fphar.2024.1487119

TABLE 1 (*Continued*) Characteristics of included studies.

Study ID	Sample size		Sex (M/F)		Average age		Therapy of experiment group	Menstruum	Therapy of control group	Course (days)	Outcomes
	E	C	E	C	E	C					
Chen et al. (2020)	60	60	33/27	34/26	62.86 ± 4.15	62.55 ± 4.23	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①
Song et al. (2017)	42	31	35/38		63.01 ± 9.25	63.75 ± 11.83	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①④⑤
Yang et al. (2010)	22	20	12/10	12/8	71.56 ± 8.20	70.18 ± 8.26	DSDFSY 100 mg + WM	5% GS 250 mL	WM	14d	①⑤
Zhu and He (2002)	42	40	24/18	24/16	54.00 ± 8.00	55.00 ± 8.00	DSFZ 400 mg + WM	5% GS 500 mL	WM	15d	①⑥
Jin et al. (2012)	50	50	62/48		66 ± 8.5		STS 20 mL + WM	5%GS 250 mL	WM	14d	⑤
Wei and Shen (2014)	60	60	38/22	36/24	49.18 ± 12.50	52.36 ± 10.18	STS 12 mL + WM	—	WM	14d	①⑥⑦
Fang et al. (2018)	33	33	17/16	16/17	58.60 ± 4.80	57.90 ± 5.40	STS 16 mL + WM	0.9% NS 250 mL	WM	14d	⑤
Mou (2011)	34	37	41/30		53.57 ± 12.83		STS 12 mL + WM	5% GS 250 mL	WM	14d	①
Qi et al. (2001)	80	80	42/38		65.59 ± 7.39		DS 10 mL + WM	0.9% NS 100 mL	WM	10d	⑥⑦
Hu and Liu (2011)	36	36	49/23		57.6 ± 4.5		DH 30 mL + WM	0.9% NS 100 mL	WM	14d	②⑤
Luo and Huang (2011)	39	39	48/30		67.8		DH 20 mL + WM	0.9% NS 100 mL	WM	14d	①⑤
Li and Yang (2008)	100	100	52/48	53/47	62.56 ± 6.53	62.53 ± 5.42	DH 40 mL + WM	5% GS 250 mL	WM	14d	①⑤
Su et al. (2011)	50	48	45/5	43/5	73.46 ± 9.34	72.56 ± 9.62	DH 30 mL + WM	—	WM	28d	⑥⑦
Li et al. (2009b)	67	67	34/33	38/29	55.20 ± 4.70	54.80 ± 5.20	GXN 20 mL + WM	5%GS/0.9%NS 250 mL	WM	10d	①⑥⑦
Li and Wang (2007)	58	62	31/27	33/29	66.89 ± 10.79	65.79 ± 9.98	GXN 20 mL + WM	—	WM	10d	⑥⑦
Chen et al. (2009)	44	38	—		—		DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①
Liu et al. (2021)	364	182	407/206	188/117	59.60 ± 6.93	60.01 ± 6.75	DH 40 mL + WM	0.9% NS 250 mL	WM+0.9% NS 250 mL	14d	②
Li et al. (2018b)	80	80	53/27	55/25	56.80 ± 11.40	58.9 ± 12.30	DH 30 mL + WM	5%GS/0.9%NS 250 mL	WM	14d	①
Sun and Zhang (2024)	52	57	32/21	32/25	55.20 ± 7.60	56.20 ± 8.70	DH	—	WM	14d	①
Sun et al. (2014)	36	36	—		—		DH 20 mL + WM	5%GS/0.9%NS 100 mL	WM+5%GS/0.9%NS 100 mL	14d	①
Li et al. (2014)	36	36	—		—		STS 16 mL + WM	—	WM	14d	②
Yao (2022)	40	40	45/72	40/73	—		DSDFSY 200 mg + WM	0.9% NS 200 mL	WM	0.5m	④⑤
Gao et al. (2009)	42	40	—		—		DH 20 mL + WM	0.9% NS 200 mL	WM	14d	②
Chen et al. (2021)	80	80	52/28	46/34	70.06 ± 8.15	70.25 ± 8.17	DSDFSY 200 mg + WM	5%GS/0.9%NS 250 mL	WM	14d	①②④
Zhang (2017)	50	50	30/20	28/22	67.5 ± 5.40	66.2 ± 6.19	STS 12 mL + WM	0.9% NS 250 mL	WM	14d	②

(Continued on following page)

10.3389/fphar.2024.1487119

10.3389/fphar.2024.1487119

TABLE 1 (*Continued*) Characteristics of included studies.

Study ID	Sample size		Sex (M/F)		Average age		Therapy of experiment group	Menstruum	Therapy of control group	Course (days)	Outcomes
	E	C	E	C	E	C					
Wang (2009)	50	50	27/23	29/21	57.2 ± 8.7	56.8 ± 8.7	DH 20 mL + WM	5% GS 200 mL	WM	14d	②
Liu and Wang (2013)	40	40	23/17	25/15	47.3	48.8	DH 30 mL + WM	5%GS/0.9%NS 250 mL	WM	10d	①②
Cao and Liu (2013)	43	43	22/21	19/24	—		DH 30 mL + WM	5%GS/0.9%NS 250 mL	WM + DS 30 mL	14d	②⑤
Yan and Zeng (2009)	30	30	42/18		58.1 ± 10.6		DH 20 mL + WM	5%GS/0.9%NS 500 mL	WM + FFDS 20 mL	28d	①⑤⑥⑦
Zhang et al. (2010)	40	40	—		—		FFDS 20 mL + WM	5% GS 250 mL	WM + DH 30 mL	14d	①②
Zhou and Guo (2018)	96	96	54/42	58/38	54.7 ± 11.6	55.4 ± 10.8	DSDFSY 200 mg + WM	0.9% NS 250 mL	WM + DS 30 mL	14d	①⑥

M, male; F, female; E, experimental group; C, control; ① clinical effectiveness rate; ②high-sensitivity C-reactive protein (hs-CRP); ③interleukin-1 (IL-1); ④interleukin-6 (IL-6); ⑤nitric oxide (NO); ⑥superoxide dismutase (SOD); ⑦malondialdehyde (MDA).

information on the characteristics of the included studies is shown in Table 1.

3.3 Quality evaluation

A risk of bias assessment was conducted on the 106 included studies. (1) Selection bias: Two studies did not mention randomization and were considered "unclear risk," while the remaining studies mentioned random allocation but may not have reported the specific randomization method; these were also evaluated as "low risk". (2) Allocation concealment: One study mentioned using allocation concealment and was considered "low risk", while the rest did not mention this information and were deemed "unclear risk". (3) Performance bias: Four studies explicitly stated that the trial design was "single-blind", thus considered "low risk". Studies that did not report relevant information were deemed "unclear risk". (4) Detection bias: One study mentioned blinding the outcome assessors, considered "low risk", while other studies did not mention this information and were deemed "unclear risk". (5) Attrition bias: All included studies had no incomplete data, so the risk of attrition bias was considered "low risk". (6) Reporting bias: Eight studies reported fewer outcomes, potentially indicating reporting bias, and were evaluated as "unclear risk", while the remaining studies were "low risk." (7) Other biases: Two studies did not report whether the experimental and control groups were comparable at baseline and were evaluated as "unclear risk", while the remaining studies were considered "low risk". Overall, the quality of the included studies was suboptimal, with summary results shown in Figure 2 and ROB 2.0 evaluation results in Supplementary table.

3.4 Results of network meta-analysis

3.4.1 Consistency testing

None of the interventions in this study formed a closed loop, so consistency testing was not required.

3.4.2 Clinical effectiveness rate

A total of 69 randomized controlled trials involving 9 types of DSCIs were included in the analysis of clinical effectiveness rate: DSDFSY + WM vs. WM (n = 30), DSFZ + WM vs. WM (n = 1), DH + WM vs. FFDS + WM (n = 1), FFDS + WM vs. DH + WM (n = 1), DH + WM vs. WM (n = 22), XD + WM vs. WM (n = 1), DSDFSY + WM vs. DS + WM (n = 1), DSCXQ + WM vs. WM (n = 6), GXN + WM vs. WM (n = 3), and STS + WM vs. WM (n = 3). The network relationship diagram is shown in Figure 3. Connections between nodes represent direct comparative evidence between the two interventions, while the absence of a connection indicates no direct comparison. The thickness of the lines indicates the number of included studies comparing each treatment, and the size of the circles represents the sample size of the population using each intervention. Except for the DS + WM and FFDS + WM groups, all other DSCIs combined with WM showed superior clinical efficacy compared to WM alone. Additionally, compared to DS + WM, the clinical efficacy rates of DSCXQ + WM, DSDFSY + WM, XD + WM, and DH + WM were significantly higher. No

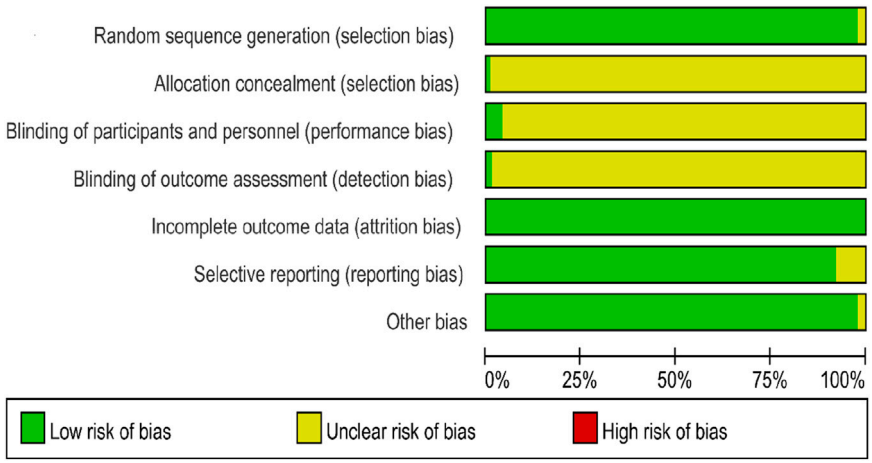


FIGURE 2
Results of risk of bias evaluation of included studies.

significant differences were observed between other interventions (Table 2). According to the SUCRA probabilities ranking, XD + WM (94.0%) was the most likely to be the best intervention to improve the clinical efficacy rate, followed by DSDFSY + WM (73.1%) > DSCXQ + WM (68.7%) > DH + WM (60.7%) > DSFZ + WM (58.4%) > STS + WM (53.7%) > GXN + WM (40.5%) > FFDS + WM (33.7%) > DS + WM (10.9%) > WM (6.2%). The specific results are shown in the Table 3 and Figure 4.

3.4.3 Hs-CRP

A total of 59 randomized controlled trials involving 8 types of DSCIs were analyzed for hs-CRP: DH + WM vs. WM (n = 22), DS + WM vs. WM (n = 1), DSCXQ + WM vs. WM (n = 8), DSDFSY + WM vs. WM (n = 18), GXN + WM vs. WM (n = 2), STS + WM vs. WM (n = 4), SXPTT + WM vs. WM (n = 2), FFDS + WM vs. DH + WM (n = 1), and DH + WM vs. DS + WM (n = 1). The network relationship diagram is shown in Figure 3. DH, DSCXQ, DSDFSY, and STS combined with WM were superior to WM alone in reducing hs-CRP. Moreover, STS + WM was more effective than DH + WM, DS + WM, DSCXQ + WM, DSDFSY + WM, FFDS + WM, or GXN + WM in reducing hs-CRP, with statistically significant differences (Table 2). According to the SUCRA probability ranking, STS + WM (99.6%) is most likely to be the best intervention for reducing hs-CRP, followed by DSCXQ + WM (69.6%) > DSDFSY + WM (65.7%) > GXN + WM (62.4%) > SXPTT + WM (52.7%) > DH + WM (49.9%) > DS + WM (25.4%) > WM (14.9%) > FFDS + WM (9.9%). The specific results are shown in the Table 3 and Figure 4.

3.4.4 IL-1

7 randomized controlled trials involving IL-1, including 2 types of DSCIs [DH + WM vs. WM (n = 1) and DSDFSY + WM vs. WM (n = 6)], were analyzed. The network relationship diagram is shown in Figure 3. DSDFSY + WM was more effective than WM alone in reducing IL-1, with statistically significant differences (Table 2). According to the SUCRA probability ranking, DSDFSY + WM (90.3%) is most likely to be the best intervention for reducing IL-1, followed by DH + WM (34.2%) and WM (25.5%). The specific results are shown in the Table 3 and Figure 4.

3.4.5 IL-6

24 randomized controlled trials involving 4 types of DSCIs were analyzed for IL-6: DH + WM vs. WM (n = 5), DSCXQ + WM vs. WM (n = 2), DSDFSY + WM vs. WM (n = 16), and STS + WM vs. WM (n = 1). The network relationship diagram is shown in Figure 3. DSCXQ and DSDFSY combined with WM were more effective than WM alone in reducing IL-6. DSCXQ + WM was more effective than DH + WM in reducing IL-6, while DSDFSY + WM was less effective than DSCXQ + WM (Table 2). According to the SUCRA probability ranking, DSCXQ + WM (98.9%) is most likely to be the best intervention for reducing IL-6, followed by DSDFSY + WM (64.1%) > DH + WM (36.7%) > STS + WM (32.5%) > WM (17.8%). The specific results are shown in the Table 3 and Figure 4.

3.4.6 NO

24 randomized controlled trials involving 6 types of DSCIs were analyzed for NO: DH + WM vs. WM (n = 4), DSCXQ + WM vs. WM (n = 1), DSDFSY + WM vs. WM (n = 14), STS + WM vs. WM (n = 2), DH + WM vs. FFDS + WM (n = 1), DH + WM vs. DS + WM (n = 1), and DSDFSY + WM vs. DS + WM (n = 1). The network relationship diagram is shown in Figure 3. DSDFSY + WM was more effective than WM alone in increasing NO (Table 2). According to the SUCRA probability ranking, DSDFSY + WM (90.7%) is most likely to be the best intervention for increasing NO, followed by STS + WM (65.7%) > DH + WM (52.1%) > DS + WM (47.7%) > DSCXQ + WM (38.8%) > FFDS + WM (33.5%) > WM (21.5%). The specific results are shown in the Table 3 and Figure 4.

3.4.7 SOD

13 randomized controlled trials involving 8 types of DSCIs were analyzed for SOD: DH + WM vs. WM (n = 1), DS + WM vs. WM (n = 1), DSCXQ + WM vs. WM (n = 1), DSDFSY + WM vs. WM (n = 5), GXN + WM vs. WM (n = 2), STS + WM vs. WM (n = 1),

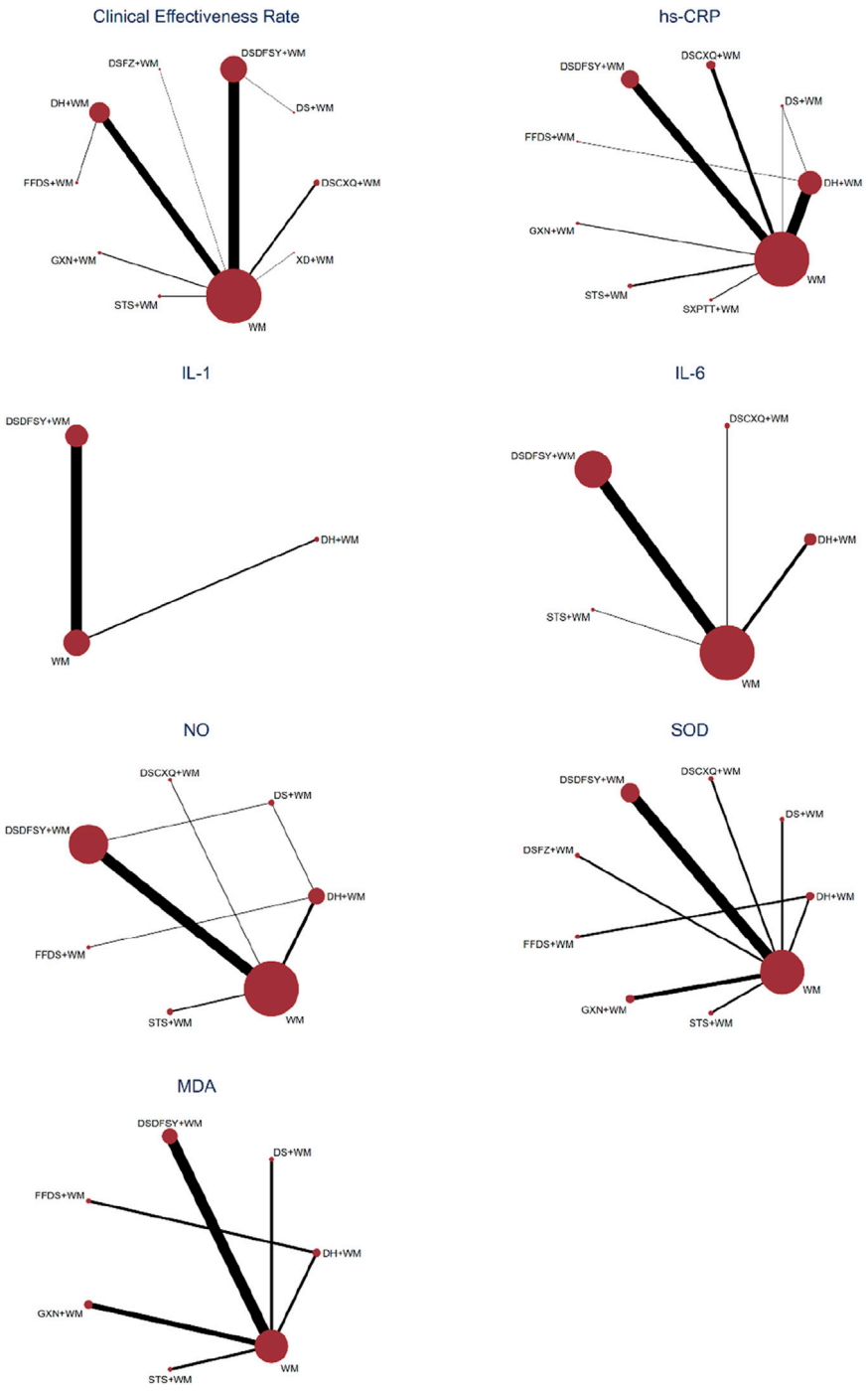


FIGURE 3
Network diagram of various outcomes. WM, western medicine; DH, Danhong injection; DS, Danshen injection; DSCXQ, Danshenchuanxiongqin injection; DSDFSY, Dansenduofensuanyan injection; DSFZ, Danshenfen injection; FFDS, Fufang Danshen injection; GXN, Guanxinning injection; STS, Sodium Tanshinone IIA Sulfonate injection; XD, Xiangdan injection; SXPTT, Shenxiongputaotang injection. hs-CRP, high-sensitivity C-reactive protein; IL-1, interleukin-1; IL-6, interleukin-6; NO, nitric oxide; SOD, superoxide dismutase; MDA, malondialdehyde.

DSFZ + WM vs. WM (n = 1), and FFDS + WM vs. DH + WM (n = 1). The network relationship diagram is shown in Figure 3. Except for DSFZ, FFDS, and DSCXQ, other types of DSCIs combined with WM were more effective than WM alone in increasing SOD (Table 2). According to the SUCRA probability ranking, GXN + WM (94.0%) is most likely to be the best intervention for increasing SOD, followed by DS + WM (74.1%) > DH + WM (70.4%) > STS + WM (69.1%) > DSDFSY + WM (62.8%) > DSFZ + WM (27.8%) > WM (26.3%) > FFDS + WM (22.5%) > DSCXQ + WM (3.00%). The specific results are shown in the Table 3 and Figure 4.

TABLE 2 OR/MD (95%CIs) of all interventions. The bolded and underlined results indicate statistical significance.

Comparison		Clinical effectiveness rate	hs-CRP	IL-1	IL-6	NO	SOD	MDA
DH + WM	vs. WM	**3.82 (2.97, 4.92)**	**−1.42 (-1.98, -0.86)**	0.16 (−141.93, 141.61)	−6.76 (−28.17, 14.66)	9.74 (−5.90, 25.38)	**10.28 (2.17, 18.40)**	**−2.40 (-3.52, -1.28)**
DS + WM		1.11 (0.41, 2.98)	−0.29 (−2.49, 1.91)			6.64 (−17.67, 30.95)	**11.49 (2.31, 20.67)**	−0.25 (−1.29, 0.79)
DSCXQ + WM		**4.27 (2.48, 7.35)**	**−1.94 (-2.83,-1.05)**		**−62.11 (-99.46, -24.77)**	4.55 (−28.67, 37.77)	**−9.39 (-18.24,-0.54)**	
DSDFSY + WM		**4.36 (3.43, 5.56)**	**−1.82 (-2.42, -1.21)**	**−67.20 (-125.44,-8.96)**	**−18.73 (-31.38, -6.08)**	**25.76 (17.05, 34.47)**	**8.92 (4.86, 12.99)**	**−1.52 (-2.11,-0.93)**
DSFZ + WM		**3.60 (1.04, 12.48)**					0.16 (−7.79, 8.11)	
FFDS + WM		2.11 (0.66, 6.73)	0.75 (−1.84, 3.34)			1.23 (−35.51, 37.96)	−1.69 (−13.80, 10.43)	0.18 (−1.37, 1.73)
GXN + WM		**2.63 (1.15, 5.97)**	−1.81 (−3.66, 0.03)				**16.61 (10.15 23.08)**	−0.45 (−1.21, 0.32)
STS + WM		**3.38 (1.82, 6.30)**	**−4.66 (-6.41, -2.92)**		−3.62 (−50.83, 43.59)	16.72 (−6.99, 40.42)	**10.11 (1.04, 19.18)**	**−1.58 (-2.77, -0.39)**
XD + WM		**8.97 (3.23, 24.89)**						
SXPTT + WM			−1.45 (−3.26, 0.36)					
DS + WM	vs. DH + WM	**0.29 (0.10, 0.80)**	1.13 (−1.05, 3.32)			−3.10 (−27.64, 21.43)	1.21 (−11.05, 13.46)	**2.15 (0.62, 3.67)**
DSCXQ + WM		1.12 (0.61, 2.03)	−0.52 (−1.57, 0.53)		**−55.36 (-98.36, -12.35)**	−5.19 (−41.91, 31.53)	**−19.67 (-31.68, -7.66)**	
DSDFSY + WM		1.14 (0.80, 1.62)	−0.39 (−1.22, 0.43)	−67.04 (-220.31, 86.23)	−11.97 (-36.83, 12.88)	16.02 (−1.50, 33.54)	−1.36 (−10.44, 7.72)	0.88 (−0.38, 2.15)
DSFZ + WM		0.94 (0.27, 3.35)					−10.12 (−21.49, 1.24)	
FFDS + WM		0.55 (0.18, 1.71)	2.17 (−0.36, 4.70)			−8.52 (−41.79, 24.76)	**−11.97 (-20.97, -2.97)**	**2.58 (1.50, 3.66)**
GXN + WM		0.69 (0.29, 1.62)	−0.39 (−2.32, 1.54)				6.33 (−4.05, 16.71)	**1.95 (0.60, 3.30)**
STS + WM		0.88 (0.45, 1.73)	**−3.24 (-5.07, -1.41)**		3.14 (−48.70, 54.98)	6.98 (−21.42, 35.38)	−0.17 (−12.34, 12.00)	0.82 (−0.81, 2.45)
XD + WM		2.35 (0.82, 6.71)						
SXPTT + WM			−0.02 (−1.92, 1.87)					
DSCXQ + WM	vs. DS + WM	**3.86 (1.25, 11.97)**	−1.65 (-4.02, 0.72)			−2.09 (−43.26, 39.08)	**−20.88 (-33.64, -8.12)**	
DSDFSY + WM		**3.95 (1.51, 10.33)**	−1.52 (-3.80, 0.75)			19.12 (−5.32, 43.57)	−2.57 (−12.61, 7.48)	**−1.27 (-2.46, -0.07)**
DSFZ + WM		3.26 (0.66, 15.98)					−11.33 (−23.48, 0.82)	
FFDS + WM		1.91 (0.42, 8.78)	1.04 (−2.30, 4.38)			‘-5.41 (−46.74, 35.92)	−13.18 (−28.38, 2.03)	0.43 (−1.44, 2.30)
GXN + WM		2.37 (0.65, 8.61)	−1.52 (−4.39, 1.35)				5.12 (−6.11,16.35)	−0.20 (−1.49, 1.09)

(Continued on following page)

TABLE 2 (*Continued*) OR/MD (95%CIs) of all interventions. The bolded and underlined results indicate statistical significance.

Comparison		Clinical effectiveness rate	hs-CRP	IL-1	IL-6	NO	SOD	MDA
STS + WM		3.06 (0.95, 9.86)	**−4.37 (-7.17, -1.58)**			10.08 (−23.87, 44.03)	−1.38 (−14.28, 11.52)	−1.33 (−2.91, 0.25)
XD + WM		**8.11 (1.95, 33.67)**						
SXPTT + WM			−1.16 (−4.00, 1.69)					
DSDFSY + WM	vs. DSCXQ + WM	1.02 (0.56, 1.85)	0.13 (−0.95, 1.20)		**43.38 (4.28, 82.49)**	21.21 (−13.14, 55.56)	**18.31 (8.57, 28.06)**	
DSFZ + WM		0.84 (0.22, 3.27)					9.55 (−2.35, 21.45)	
FFDS + WM		0.49 (0.14, 1.78)	2.69 (−0.05, 5.43)			−3.32 (−52.86, 46.21)	7.70 (−7.30, 22.71)	
GXN + WM		0.61 (0.23, 1.65)	0.13 (−1.92, 2.18)				**26.00 (15.04,36.97)**	
STS + WM		0.79 (0.35, 1.81)	**−2.72 (-4.67, -0.77)**		58.49 (−1.70, 118.69)	12.17 (−28.65, 52.98)	**19.50 (6.83, 32.17)**	
XD + WM		2.10 (0.66,6.68)						
SXPTT + WM			0.50 (−1.52, 2.51)					
DSFZ + WM	vs. DSDFSY + WM	0.83 (0.23, 2.93)					−8.76 (−17.70, 0.17)	
FFDS + WM		0.48 (0.15, 1.58)	2.56 (−0.10, 5.22)			−24.54 (−62.11, 13.04)	−10.61 (−23.39, 2.17)	**1.70 (0.04, 3.36)**
GXN + WM		0.60 (0.26, 1.42)	0.00 (−1.94, 1.94)				**7.69 (0.05, 15.33)**	**1.07 (0.10, 2.03)**
STS + WM		0.77 (0.40, 1.51)	**−2.85 (-4.69, -1.01)**		15.11 (−33.77, 63.99)	−9.04 (−34.30, 16.21)	1.19 (−8.75, 11.12)	−0.06 (−1.39, 1.26)
XD + WM		2.05 (0.72, 5.87)						
SXPTT + WM			0.37 (−1.54, 2.28)					
FFDS + WM	vs. DSFZ + WM	0.59 (0.11, 3.20)					−1.85 (−16.34, 12.65)	
GXN + WM		0.73 (0.16,3.23)					**16.45 (6.20, 26.70)**	
STS + WM		0.94 (0.23,3.76)					9.95 (−2.11,22.01)	
XD + WM		2.49 (0.50,12.42)						
SXPTT + WM								
GXN + WM	vs. FFDS + WM	1.24 (0.30, 5.14)	−2.56 (−5.74, 0.62)				**18.30 (4.57, 32.03)**	−0.63 (−2.36, 1.10)
STS + WM		1.60 (0.43, 5.96)	**−5.41 (-8.53, -2.29)**			15.49 (−28.23, 59.21)	11.80 (−3.34, 26.93)	−1.76 (−3.72, 0.20)
XD + WM		4.24 (0.91, 19.87)						
SXPTT + WM			−2.19 (−5.35, 0.97)					
STS + WM	vs. GXN + WM	1.29 (0.46, 3.61)	**−2.85 (-5.39, -0.31)**				−6.50 (−17.64, 4.63)	−1.13 (−2.54, 0.28)
XD + WM		3.42 (0.92, 12.67)						

(Continued on following page)

TABLE 2 (*Continued*) OR/MD (95%CIs) of all interventions. The bolded and underlined results indicate statistical significance.

Comparison		Clinical effectiveness rate	hs-CRP	IL-1	IL-6	NO	SOD	MDA
SXPTT + WM			0.37 (−2.22, 2.95)					
XD + WM	vs. STS + WM	2.65 (0.80, 8.76)						
SXPTT + WM			3.22 (0.71, 5.73)					
SXPTT + WM	vs. XD + WM							

TABLE 3 SUCRA (%) of all therapeutic measures. The redder color in the table means the higher the ranking of the corresponding intervention.

	Clinical effectiveness rate	hs-CRP	IL-1	IL-6	NO	SOD	MDA
WM	6.2	14.9	25.5	17.8	21.5	26.3	17.4
DH + WM	60.7	49.9	34.2	36.7	52.1	70.4	95.8
DS + WM	10.9	25.4			47.7	74.1	30.1
DSCXQ + WM	68.7	69.6		98.9	38.8	3	
DSDFSY + WM	73.1	65.7	90.3	64.1	90.7	62.8	75.2
DSFZ + WM	58.4					27.8	
FFDS + WM	33.7	9.9			33.5	22.5	17
GXN + WM	40.5	62.4				94	39.2
STS + WM	53.7	99.6		32.5	65.7	69.1	75.3
XD + WM	94						
SXPTT + WM		52.7					

3.4.8 MDA

10 randomized controlled trials involving 6 types of DSCIs were analyzed for MDA: DH + WM vs. WM (n = 1), DS + WM vs. WM (n = 1), DSDFSY + WM vs. WM (n = 4), GXN + WM vs. WM (n = 2), STS + WM vs. WM (n = 1), and FFDS + WM vs. DH + WM (n = 1). The network relationship diagram is shown in Figure 3. DH, DSDFSY, and STS combined with WM were more effective than WM alone in reducing MDA (Table 2). According to the SUCRA probability ranking, DH + WM (95.8%) is most likely to be the best intervention for reducing MDA, followed by STS + WM (75.3%) > DSDFSY + WM (75.2%) > GXN + WM (39.2%) > DSCXQ + WM (30.1%) > WM (17.4%) > FFDS + WM (17.0%). The specific results are shown in the Table 3 and Figure 4.

3.4.9 Adverse reactions

A total of 49 studies reported adverse reaction events, with 17 studies detailing specific adverse reactions. These included the following manifestations: circulatory system: dizziness, headache, palpitations, fatigue; digestive system: nausea, abdominal distension, vomiting; peripheral vasculature: facial flushing; skin: rash, bruising. The specific results are shown in Table 4.

3.4.10 Publication bias

A funnel plot was used to test for publication bias in this study (Figure 5 and Supplementary Figure). As shown in the figure, most points are concentrated in the middle, with a few at the bottom, indicating that some studies had small sample sizes, which may lead to bias. Additionally, the points in the funnel plot are asymmetrically distributed relative to the centerline, and the regression line forms an angle with the centerline, suggesting the presence of publication bias in this study.

4 Discussion

Although DSCIs are widely used in China to treat CHD, they are mostly used as adjunctive therapies and rarely used alone. Their acceptance in other countries is relatively poor. The reasons for this may include: ① Although multiple clinical studies have confirmed the efficacy of DSCIs, the trial designs are not rigorous enough, and there is still a lack of large-scale, high-quality evidence-based medical evidence to verify their efficacy and safety. ② Most DSCIs are compound preparations containing various active metabolites, making their mechanisms of action complex. Notably, current basic research is often focused on simple target points and pathways, lacking in-depth studies on pharmacokinetics and pharmacological and toxicological mechanisms. ③ The complex composition of traditional Chinese medicine injections increases the probability of adverse reactions when used in combination with other drugs, limiting their clinical use by

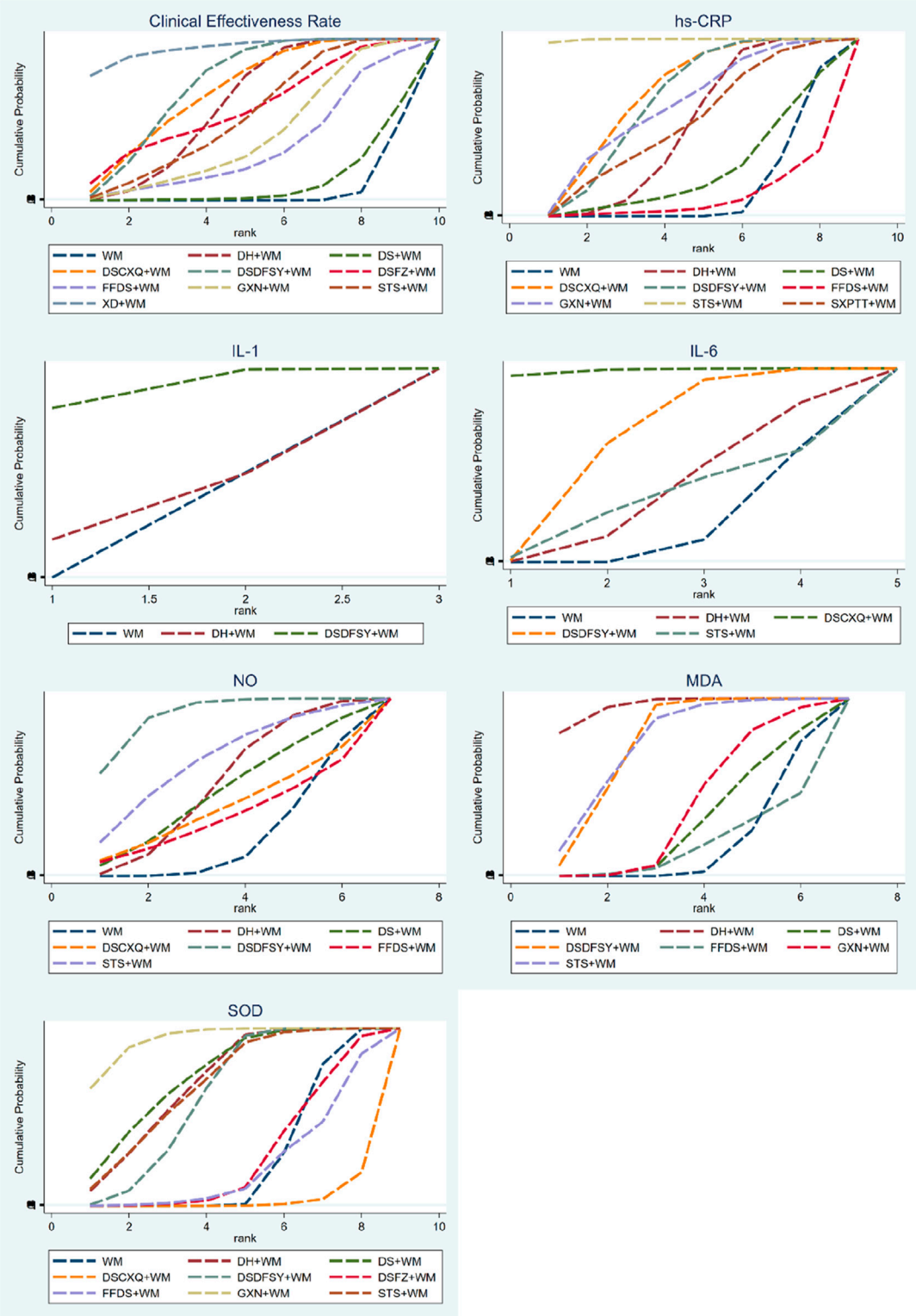


FIGURE 4
SUCRA for different outcomes.

physicians. ④ There are many types of DSCIs, with both similarities and differences, making clinical drug selection challenging.

Based on these issues, this study employs the NMA method to fully utilize existing clinical research and compare the efficacy and safety of multiple DSCIs. By pooling small sample data, we expand the sample size, reduce bias and errors, improve statistical power, and obtain more reliable results. Additionally, the NMA results provide efficacy rankings for different outcome indicators, offering

TABLE 4 Adverse reactions.

	Number	Dizziness	Headache	Palpitations	Fatigue	Nausea	Abdominal distension	Vomiting	Facial flushing	Rash	Bruising	Others
Zhang et al. (2018)	35					5					6	
Jiang et al. (2012)	48	1										
Li et al. (2018a)	76					1	1					4
Jiao and Wang (2019)	40					1						
Xie et al. (2020)	53		1		1							
Yue et al. (2023)	51	2	1			2						
Xie and Cao (2011)	32		1						1			
SHI and Liu (2012)	80	8	3	6								
Lu and Ma (2023)	60	1						2		2		
Duan et al. (2010)	28				1							
Guan et al. (2019)	40			1		1	1					
Fang et al. (2018)	33		1									
Mou (2011)	80	3			1	1						
Chen et al. (2009)	44			2					1			
Li et al. (2018b)	80	1							2			
Yao (2022)	40	1		1		1						
Zhou and Guo (2018)	96			2		2	4			4		
Summary		17	7	12	3	14	6	2	4	6	6	4

10.3389/fphar.2024.1487119

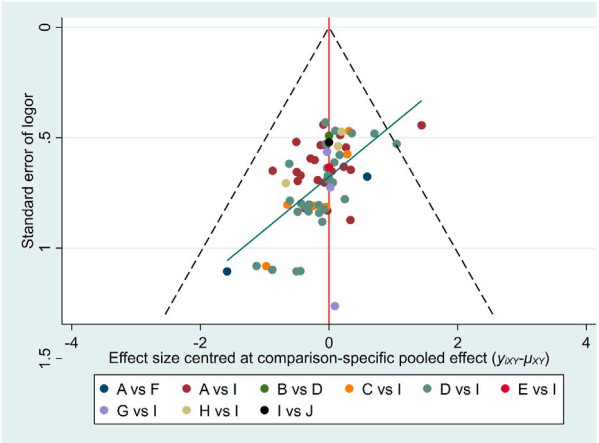


FIGURE 5
Funnel plots of clinical effectiveness rate. The vertical axis represents "standard error of effect size" and horizontal axis represents "effect size centred at comparison-specific pooled effect (y_{ixy}-μ_{xy})." A, DH + WM; B, DS + WM; C, DSCXQ + WM; D, DSDFSY + WM; E, DSFZ + WM; F, FFDS + WM; G, GXN + WM; H, STS + WM; I, WM; J, XD + WM.

reference suggestions for clinical drug selection and helping clinicians understand the associations and differences between various treatment options.

This study used the NMA method to evaluate 106 randomized controlled trials that met the inclusion and exclusion criteria, involving 10 types of DSCIs. The outcomes included clinical efficacy, inflammatory markers (hs-CRP, IL-1, IL-6), oxidative stress markers (NO, SOD, MDA), and safety. The NMA results indicate that seven types of DSCIs combined with WM achieved better efficacy than WM alone. According to the SUCRA probability ranking, XD + WM showed the most significant improvement in clinical efficacy, followed by DSDFSY + WM and DSCXQ + WM. However, the relatively small sample size for XD + WM might lead to greater errors, potentially interfering with the results. Additionally, due to differences in the active ingredients of each DSCIs, their effects vary among different types of patients. Clinically, the appropriate injection can be chosen based on the patient's symptoms and signs to achieve better clinical efficacy. In reducing inflammatory markers, STS + WM had an advantage in lowering hs-CRP, DSDFSY + WM was more effective in reducing IL-1, and DSCXQ + WM was better at reducing IL-6. Regarding the impact on oxidative stress markers, DSDFSY + WM had a more significant effect on NO regulation, GXN + WM was more evident in SOD regulation, and DH + WM had an advantage in MDA regulation.

This study found that 49 RCTs included adverse reactions as an observed outcome, with 17 RCTs reporting specific adverse reactions. Clinical manifestations were mainly concentrated in the circulatory system, digestive system, peripheral vessels, and skin. The most common adverse reactions were dizziness, nausea, and palpitations (n = 17, n = 14, n = 12), followed by headache (n = 7), abdominal distension, rash, bruising (n = 6), facial flushing (n = 4), and fatigue (n = 3). The active ingredients in Danshen have vasodilatory effects (Deng et al., 2014; Lin et al., 2022), which may cause dizziness, headache, and facial flushing in users. These conditions are generally tolerable and can resolve with reduced infusion speed or discontinuation of the drug. Traditional Chinese medicine injections, containing large molecular metabolites, are prone to allergic reactions, such as rashes. Rapid infusion of multiple drugs can increase the incidence of allergic reactions (Zou et al., 2023) Therefore, we recommend the following precautions when using injections: ① Infusion speed should not be too fast and can be slowed down according to the patient's age and tolerance. ② Do not combine with other injections, especially other traditional Chinese medicine injections. ③ Strictly follow the instructions, and do not arbitrarily change the dosage or frequency of administration. We recommend that future studies place greater emphasis on safety monitoring, including: ① Routine monitoring of liver and renal function, especially in patients with pre-existing conditions, due to the known effects of herbal treatments. ② Observation for allergic reactions, particularly during the initial stages of treatment. ③ Careful monitoring for bleeding risks, given the potential anticoagulant effects of Danshen injections, particularly when used alongside antiplatelet or anticoagulant drugs.

Danshen, a commonly used herbal medicine in TCM for the treatment of CHD, has a long history of clinical application due to its blood-activating and stasis-removing properties, which promote blood circulation and remove blood stasis. Danshen contains two major metabolites: hydrophilic phenolic acids and lipophilic tanshinones, both of which possess anti-oxidative stress, anti-inflammatory, and anti-thrombotic effects (Li et al., 2020; Ke et al., 2023). Among these, tanshinones (TSN) have potent cardiovascular protective effects (Li ZM. et al., 2018). TSN modulates multiple pathways to inhibit the development of atherosclerosis. For instance, study (Ma et al., 2023) has shown that Tanshinone IIA (Tan IIA) can reduce vascular endothelial inflammation and prevent plaque formation through the COX-2/TNF-α/NF-κB signaling pathway. Tanshinone I (Tan I) can inhibit oxidative stress and oxidative stress-induced cardiomyocyte damage by regulating the Nrf2 signaling pathway (Wu et al., 2021). Salvia acid A (SAA) inhibits TLR2/TLR4-mediated Myd88 activation and its downstream molecules TRAF6 and IRAK4, thereby reducing the release of pro-inflammatory cytokines and mediators (Dawuti et al., 2023). Additionally, research indicates that SAA significantly enhances the expression of Nrf2 and HO-1 in a dose-dependent manner, improving atherosclerosis (Song et al., 2019). Furthermore, study has demonstrated that intraperitoneal injection of Danshen in chronic iron overload mice can decrease MDA levels, increase SOD activity, and reverse oxidative stress-induced damage (Zhang Y. et al., 2015). DSCIS inhibits endothelial cell autophagy via the miR-19a/SIRT1 pathway, mitigating the effects of oxidative stress (Guo et al., 2021). Study has found that DSCIS reduces MDA levels and increases SOD activity in a dose-dependent manner, reducing oxidative stress (Du et al., 2021). Other research has shown that DSCIS has a disease-specific bidirectional regulatory effect on angiogenesis, promoting the repair of ischemic vascular injury through angiogenic activity while inhibiting tumor growth through anti-angiogenic activity (He et al., 2022). The observed differences in efficacy among the various DSCIs may be attributed to differences in their active ingredients, formulations, and mechanisms of action. However, the complex composition of

traditional Chinese medicine injections warrants further investigation to fully understand the underlying mechanisms.

However, this study has several limitations. Firstly, the quality of the included literature is not high, with most RCTs not detailing the methods of random allocation and blinding, potentially leading to selection bias and detection bias, thus reducing the accuracy of the study. Secondly, there is heterogeneity in this study, which may be related to various factors such as different WM treatment methods, inclusion of populations at different stages of CHD, and varying doses and intervention times of DSCIs. Thirdly, the studies included are concentrated in different regions of China, and the efficacy in other countries and ethnic groups has not been evaluated, which may affect the generalizability of the results. Fourthly, this study focuses on the overall CHD population, and the recommendations for individualized treatment for patients at different stages of the disease are not sufficiently accurate. To reduce potential biases, we established transparent inclusion and exclusion criteria to ensure consistency across studies. For missing data, we applied multiple imputation techniques, and studies of low quality were excluded to improve the overall reliability of the results.

Therefore, we believe that to improve the accuracy of NMA results and provide more effective treatment recommendations, future clinical studies should adhere to RCT standard designs, improve methodological quality, and describe methodological key points in detail when publishing results to enhance the quality of evidence-based medicine. We hope future research directions that emphasize the need for larger, multicenter trials involving diverse populations across different countries and ethnic groups. This approach will enhance the robustness of our findings and contribute to a more comprehensive understanding of the studied phenomena. Despite certain limitations, the NMA analysis in this study evaluates the effects of different treatment regimens on various outcome indicators, providing recommendations for clinical treatment of CHD.

5 Conclusion

In summary, this study demonstrates that the combination of DSCIs and WM treatment is more effective than WM treatment alone for patients with CHD. This includes improvements in clinical symptoms, electrocardiogram efficacy evaluation, and hematological parameters (inflammatory markers and oxidative stress markers). Overall, DSDFSY and DSCXQ showed favorable performance in clinical efficacy evaluation and inflammatory marker modulation, while DH exhibited stable performance in oxidative stress regulation. Although this study partially confirmed the efficacy of DSCIs, there are still shortcomings in the level of evidence and clinical application. In the future, we hope to conduct rigorous, high-quality randomized controlled trials to further clarify the efficacy and mechanisms of DSCIs, thereby facilitating their clinical use.

Author contributions

SD: Conceptualization, Data curation, Investigation, Software, Validation, Visualization, Writing–original draft. YD: Data curation, Investigation, Software, Validation, Visualization, Writing–original draft. JG: Formal Analysis, Methodology, Supervision, Writing–review and editing. XW: Formal Analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by Grants from the National Natural Science Foundation of China (No. 8227142388), the National Administration of Traditional Chinese Medicine (No. ZYYZDXK-2023259 and No. 2024-JYB-KYPT-10).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1487119/full#supplementary-material

References

Bi, C. W., Chen, Z. L., and Bi, C. F. (2011). The effect of Shenxiong glucose injection on high-sensitivity C-reactive protein, endothelin, and quality of life in elderly patients with unstable angina pectoris. *Shandong Med. J.* 51 (41), 65–66.

Broch, K., Anstensrud, A. K., Woxholt, S., Sharma, K., Tøllefsen, I. M., Bendz, B., et al. (2021). Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. *J. Am. Coll. Cardiol.* 77 (15), 1845–1855. doi:10.1016/j.jacc.2021.02.049

Byrne, R. A., Rossello, X., Coughlan, J. J., Barbato, E., Berry, C., Chieffo, A., et al. (2023). 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur. Heart J.* 44 (38), 3720–3826. doi:10.1093/eurheartj/ehad191

Cai, L. L., Li, J. H., Xu, J. G., and Li, D. M. (2014). Effect of Danshen ligustrazine for injection on blood rheology, hs-CRP and fat metabolism on elderly patients with unstable angina pectoris. *Pract. Pharm. Clin. Remedies* 17 (3), 267–270.

Cao, X. F., and Liu, C. R. (2013). The effect of Danhong injection on blood lipids, endothelial function, and inflammatory markers in patients with coronary heart disease and angina pectoris. *China Rural. Health*, 103.

Chen, F. L., Wang, X. L., and Ma, B. (2020). Evaluation for the treatment effect of salvianolate and its influence on the hemorheology and oxidative stress in angina pectoris patients. *Chin. J. Disaster Med.* 8 (3), 137–141.

Chen, J. H., Han, Y., and Wang, X. F. (2015b). Danhong injection for the treatment of 94 cases of unstable angina pectoris with blood stasis type. *Henan Tradit. Chin. Med.* 35 (7), 1525–1527.

Chen, J. L., Wan, J., and Wang, A. L. (2012). Influence of sodium tanshinon IIasilate on high sensitivity C-reactive protein and matrix metalloproteinase-9 of patients with unstable angina pectoris. *Shandong Med. J.* 52 (29), 41–42.

Chen, S., Zhang, J., Yan, F. D., Yan, J. F., Yuan, B., and He, S. H. (2009). Changes in serum levels of nitric oxide, endothelin, and vascular endothelial growth factor in patients with stable angina pectoris and the intervention effect of salvianolic acid salts. *Chin. J. Clin. Pharmacol. Ther.* 14 (10), 1160–1163.

Chen, S. L., and Huang, S. B. (2016a). Effect of Salvia miltiorrhiza on cytokines in patients with unstable angina pectoris. *J. Hainan Med. Univ.* 22 (8), 744–746.

Chen, S. L., and Huang, S. B. (2016b). Effects of Salvia miltiorrhiza on hemorheology and vascular endothelial function in patients with unstable angina pectoris. *J. Hainan Med. Univ.* 22 (10), 954–956.

Chen, S. Q., Li, L. P., Ning, P., and Wang, B. D. (2015a). The therapeutic effect and pharmacological analysis of Danhong injection in the treatment of unstable angina pectoris. *J. China Prescr. Drug* 13 (07), 37–38.

Chen, Y. J., Jian, F., and Chen, Y. K. (2021). Effeet of salvianolate on serum IL-6 and hs-CRP in patients with unstable angina pectoris. *Chongqing Med. J.* 50 (S1), 28–31.

Cumpston, M., Li, T., Page, M. J., Chandler, J., Welch, V. A., Higgins, J. P., et al. (2019). Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst. Rev.* 10 (10), ED000142. doi:10.1002/14651858.ED000142

Dawuti, A., Sun, S., Wang, R., Gong, D., Liu, R., Kong, D., et al. (2023). Salvianolic acid A alleviates heart failure with preserved ejection fraction via regulating TLR/Myd88/TRAF/NF-κB and p38MAPK/CREB signaling pathways. *Biomed. Pharmacother.* 168, 115837. doi:10.1016/j.biopha.2023.115837

Deng, Y., Ng, E. S., Kwan, Y. W., Lau, C. B. S., Cheung, D. W. S., Koon, J. C. M., et al. (2014). Cerebral vasodilator properties of Danshen and Gegen: a study of their combined efficacy and mechanisms of actions. *Phytomedicine* 21 (4), 391–399. doi:10.1016/j.phymed.2013.09.016

Du, H., Li, C., Wang, Z., He, Y., Wang, Y., Zhou, H., et al. (2021). Effects of Danhong injection on dyslipidemia and cholesterol metabolism in high-fat diets fed rats. *J. Ethnopharmacol.* 274, 114058. doi:10.1016/j.jep.2021.114058

Duan, X. L., Ji, X. W., Zhang, A. Y., Zhang, J. G., Zhao, C. H., and Yang, L. L. (2010). The effect of Salvianolate on unstable angina pectoris and its influence on the levels of SOD and MDA. *Acta Acad. Med. Weifang* 32 (1), 23–25.

Eikelboom, J. W., Anand, S. S., Malmberg, K., Weitz, J. I., Ginsberg, J. S., and Yusuf, S. (2000). Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 355 (9219), 1936–1942. doi:10.1016/S0140-6736(00)02324-2

Everett, B. M., MacFadyen, J. G., Thuren, T., Libby, P., Glynn, R. J., and Ridker, P. M. (2020). Inhibition of interleukin-1β and reduction in atherothrombotic cardiovascular events in the CANTOS trial. *J. Am. Coll. Cardiol.* 76 (14), 1660–1670. doi:10.1016/j.jacc.2020.08.011

Fang, Y., Yang, K. P., and Jin, D. (2018). The effects of vascular endothelial growth factor, serum brain natriuretic peptide precursor, and soluble signaling hormone 4D. *Mod. J. Integr. Traditional Chin. West. Med.* 27 (35), 3964–3967.

Feng, Z. H., and Ji, X. W. (2010). Clinical study of salvianolate in early admission period in patients with unstable angina. *J. Liaoning Univ. Traditional Chin. Med.* 12 (4), 54–56.

Fibrinolytic Therapy Trialists (FTT) (1994). Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet* 343 (8893), 311–322.

Fu, T., and Jiang, C. H. (2015). Effects of Danhong injection on serum sICAM-1 and hs-CRP in patients with unstable angina pectoris. *J. Electrocardiol. Circulation* 34 (4), 256–258, 278.

Fu, Y. C., and Meng, L. Q. (2011). Clinical observation on the treatment of coronary heart disease and angina pectoris with Guanxinning injection. *New Chin. Med.* 43 (8), 8–9.

Gao, S., Liu, Z., Li, H., Little, P. J., Liu, P., and Xu, S. (2012). Cardiovascular actions and therapeutic potential of tanshinone IIA. *Atherosclerosis* 220 (1), 3–10. doi:10.1016/j.atherosclerosis.2011.06.041

Gao, W., Shi, Y. Y., and Suo, D. M. (2009). Clinical efficacy observation of Beitong Danhong injection in the treatment of unstable angina pectoris. *Liaoning J. Traditional Chin. Med.* 36 (2), 235–236.

Gorog, D. A., Sweeny, J. M., and Fuster, V. (2009). Antiplatelet drug 'resistance'. Part 2: laboratory resistance to antiplatelet drugs-fact or artifact? *Nat. Rev. Cardiol.* 6 (5), 365–373. doi:10.1038/nrcardio.2009.13

Guan, J. S., Zhou, Y., Miao, Z. J., Gao, S. Z., and Chen, J. (2019). Effect of salvianolate on endothelial function and oxidative stress in patients with coronary heart disease. *China Pharm.* 28 (24), 75–77.

Guo, G. l., Li, C. H., and Sun, L. Q. (2016). The effects of visfatin. matrix metalloproteinases-9 and hypersensitive C-reactive protein by the treatment of depside salt from salvia miltiorrhiza in ST-segment elevation myocardial infarction patient. *J. Clin. Intern Med.* 33 (9), 614–616.

Guo, Y., Yang, J. H., Cao, S. D., Gao, C. X., He, Y., Wang, Y., et al. (2021). Effect of main ingredients of Danhong Injection against oxidative stress induced autophagy injury via miR-19a/SIRT1 pathway in endothelial cells. *Phytomedicine* 83, 153480. doi:10.1016/j.phymed.2021.153480

Hansson, G. K. (2005). Inflammation, atherosclerosis, and coronary artery disease. *N. Engl. J. Med.* 352 (16), 1685–1695. doi:10.1056/NEJMra043430

He, S., Chen, R., Peng, L., Jiang, Z., Liu, H., Chen, Z., et al. (2022). Differential action of pro-angiogenic and anti-angiogenic components of Danhong injection in ischemic vascular disease or tumor models. *Chin. Med.* 17 (1), 4. doi:10.1186/s13020-021-00557-5

Hong, Y. D., Wu, H., Mo, H. H., and Li, F. Y. (2004). Effeet of xiangdan injection in treating acute coronary syndrome and inflammatory markers. *Traditional Chin. Drug Res. Clin. Pharmacol.* 15 (6), 425–428.

Hu, A. Y., and Liu, L. (2011). The effect of Danhong injection on vascular endothelial function and inflammatory factors in patients with unstable angina pectoris. *Her. Med.* 30 (3), 319–321.

Huang, D. P. (2017). The therapeutic effect of Danhong injection on unstable angina pectoris patients and its effect on serum CRP, Cys-C, and Hcy. *World Clin. Med.* 11 (21), 74–75.

Hutton, B., Salanti, G., Caldwell, D. M., Chaimani, A., Schmid, C. H., Cameron, C., et al. (2015). The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann. Intern Med.* 162 (11), 777–784. doi:10.7326/M14-2385

Huynh, T., Perron, S., O'Loughlin, J., Joseph, L., Labrecque, M., Tu, J. V., et al. (2009). Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocardial infarction: bayesian hierarchical meta-analyses of randomized controlled trials and observational studies. *Circulation* 119 (24), 3101–3109. doi:10.1161/CIRCULATIONAHA.108.793745

Ji, S. L. (2013). Clinical efficacy analysis of Danshen Chuanxiong Injection in the treatment of acute coronary syndrome. *Mod. Diagnosis Treat.* 24 (4), 794–795.

Jiang, X. (2022). Effect of salvianolate adjuvant therapy on hemodynamics, inflammatory factors and cardiomyocyte apoptosis in patients with unstable angina pectoris. *Med. Innovation China* 19 (13), 58–63.

Jiang, Z. P., Ji, X. W., Zhang, A. Y., Zhang, J. G., Zhao, C. H., Chen, Y. B., et al. (2012). The effect of salvianolic acid salts on inflammatory response in patients with unstable angina pectoris. *Chin. J. Clin. Electron. Ed.* 6 (19), 6097–6098.

Jiao, W. P., and Wang, Q. F. (2019). Clinical effect of salvianolate in the treatment of unstable angina pectoris. *Clin. Res. Pract.* 4 (5), 29–30.

Jin, J., Liu, L., and Du, L. J. (2012). The effect of tanshinone IIA on plasma endothelin and nitric oxide levels in patients with unstable angina pectoris. *Inf. Traditional Chin. Med.* 29 (6), 62–63.

Jing, L. X. (2014). Effects of Salvianolate intervention on heart rate turbulence and myocardial injury serum index in patients with unstable angina. *Med. J. Chin. People's Health* 26 (21), 8–10.

Kaufmann, P. A., Gnecchi-Ruscone, T., di Terlizzi, M., Schäfers, K. P., Lüscher, T. F., and Camici, P. G. (2000). Coronary heart disease in smokers: vitamin C restores coronary microcirculatory function. *Circulation* 102 (11), 1233–1238. doi:10.1161/01.cir.102.11.1233

Ke, L., Zhong, C., Chen, Z., Zheng, Z., Li, S., Chen, B., et al. (2023). Tanshinone I: pharmacological activities, molecular mechanisms against diseases and future perspectives. *Phytomedicine* 110, 154632. doi:10.1016/j.phymed.2022.154632

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., et al. (2020). 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* 41 (3), 407–477. doi:10.1093/eurheartj/ehz425

Lang, X. F. (2012). 60 cases of unstable angina treated with integrated traditional Chinese and Western medicine. *Acta Chin. Med. Pharmacol.* 40 (6), 96–98.

Li, C., Kang, D., and Wu, Y. S. (2008). Clinical research of Danhong injection for amelioration of microcirculation in patients with unstable angina. *Clin. J. Med. Officers* 36 (3), 402–404.

Li, H., Chai, H., Wang, L. Z., Yang, H. Y., and Ma, D. M. (2009b). Observation of guanxinning injection on antioxidant damage in initial type of exercised angina pectoris. *China Med. Her.* 30 (24), 24–25.

Li, H., Li, X. C., Jia, X. R., Wei, C., Xu, Z. R., and Huang, Y. Q. (2009a). The effect and therapeutic effect of Danhong injection on hypersensitive C-reactive protein in patients with unstable angina pectoris. *Shaanxi Med. J.* 37 (8), 1054–1055.

Li, H., and Wang, L. Z. (2007). Clinical observation of the anti free radical effect of Guanxinning injection on patients with worsening fatigue angina pectoris. *Clin. Med. China* 23 (10), 874–876.

Li, H., and Yang, H. Y. (2008). The therapeutic effect and endothelial function of Danhong injection on elderly patients with unstable angina pectoris. *Shandong Med. J.* 48 (32), 92–93.

Li, H. D., Lin, X. Y., Liu, Q. W., and Zhang, Y. (2018b). Curative effect of Danhong injection on the clinical symptoms, adverse reactions and electrocardiogram of angina pectoris of coronary heart disease. *Int. J. Clin. Exp. Med.* 11 (2), 910–915.

Li, M., Li, H., Liu, H., Lai, X., and Xing, W. (2022). Efficacy and safety of eight types Salvia miltiorrhiza injections in the treatment of unstable angina pectoris: a network meta-analysis. *Front. Pharmacol.* 13, 972738. doi:10.3389/fphar.2022.972738

Li, S. M., Shang, Q. H., Chen, K. J., and Hao, X. (2014). GW25-e4351 sodium tanshinone IIA sulfate reduces elevated serum high sensitivity C-reactive protein in patients with coronary heart disease: a prospective randomized open-label blinded end point trial. *J. Am. Coll. Cardiol.* 64 (16), C206. doi:10.1016/j.jacc.2014.06.956

Li, X., Wang, W. B., Cao, S. J., and Zhang, Y. (2018a). The effects of salvianolic acid salts on TNF - alpha, hs - CRP, IL - 1, and cardiac function in patients with unstable angina pectoris. *J. Clin. Exp. Med.* 17 (5), 499–503.

Li, Y. F., and Yin, G. (2012). The effect of Salvia miltiorrhiza ligustrazine injection in UAP for aged people. *Qingdao Med. J.* 44 (2), 130–132.

Li, Y. H., and Ge, H. Y. (2011). Observation on the treatment of acute coronary syndrome with Danhong injection. *J. Med. Forum* 32 (11), 150–152.

Li, Y. M., Chen, X. H., Li, J., Hu, J. P., Bian, Y. L., and Wu, Y. J. (2007). Clinical study on danshen injection in the treatment of acute coronary syndrome. *Chin. J. Traditional Med. Sci. Technol.* 14 (6), 392–393.

Li, Z., Zou, J., Cao, D., and Ma, X. (2020). Pharmacological basis of tanshinone and new insights into tanshinone as a multitarget natural product for multifaceted diseases. *Biomed. Pharmacother.* 130, 110599. doi:10.1016/j.biopha.2020.110599

Li, Z. M., Xu, S. W., and Liu, P. Q. (2018c). Salvia miltiorrhizaBurge (Danshen): a golden herbal medicine in cardiovascular therapeutics. *Acta Pharmacol. Sin.* 39 (5), 802–824. doi:10.1038/aps.2017.193

Liao, Y. H., Liu, X., Deng, Y. M., and Hu, J. J. (2008). The effect of Danhong injection on serum high-sensitivity C-reactive protein in patients with unstable angina pectoris. *China Med.* 3 (6), 334–335.

Lin, Q. W., Wei, Z. B., Yao, C. Y., and Lu, Y. L. (2020). Effect of salvianolic acid salt on endothelial function in patients with coronary atherosclerotic heart disease. *Chin. J. Mod. Drug Appl.* 14 (21), 147–148.

Lin, Y. K., Chen, Y. J., Li, J. Y., Chen, Y. L., He, D., Zuo, R., et al. (2022). Salvianolic acid A from Danhong Injection induces vasorelaxation by Regulating L-type calcium channel in isolated mouse arteries. *J. Ethnopharmacol.* 296, 115431. doi:10.1016/j.jep.2022.115431

Liu, B., and Wang, B. J. (2013). Observation on the therapeutic effect of Danhong injection in the treatment of unstable angina pectoris. *Guide China Med.* 11 (1), 606–607.

Liu, G. D., and Xiao, G. L. (2014). Effect of the salvia phenolic acid on high sensitivity C reactive protein and hemorheology in patients with unstable angina. *J. Emerg. Traditional Chin. Med.* 23 (1), 3–5.

Liu, J., Li, D. D., Dong, W., Liu, Y. Q., Wu, Y., Tang, D. X., et al. (2021). Detection of an anti-angina therapeutic module in the effective population treated by a multi-target drug Danhong injection: a randomized trial. *Signal Transduct. Target Ther.* 26 (1), 329. doi:10.1038/s41392-021-00741-x

Liu, J. Z., Wang, T., Zhao, Y. G., Pan, Z. X., and Yuan, X. Q. (2015). The therapeutic effect of Danshen Chuanxiong Injection on elderly patients with unstable angina pectoris and its effects on serum hs-CRP and blood lipids. *Pharmacol. Clin. Chin. Materia.* 31 (4), 237–239.

Liu, L. L., Yan, Y. J., and Gu, S. Z. (2023). Evaluation of the efficacy of salvianolate adjuvant therapy in patients with unstable angina pectoris. *Northwest Pharm. J.* 38 (4), 169–173.

Liu, M. Y. (2017). Study on the effect and therapeutic effect of salvianolic acid salts on hemorheology in elderly patients with unstable angina pectoris. *Pract. Clin. J. Integr. Traditional Chin. West. Med.* 17 (1), 15–16.

Liu, S., Wu, J., Zhang, D., and Tan, D. (2018). What are the best Salvia miltiorrhiza injection classes for treatment of unstable angina pectoris? A systematic review and network Meta-analysis. *J. Tradit. Chin. Med.* 38 (3), 321–338. doi:10.1016/s0254-6272(18)30623-x

Liu, Y. F., Xu, L. J., Xu, Z. X., Zhao, W. H., and Liu, X. T. (2012). Danhong injection in the treatment of 48 cases of unstable angina pectoris with coronary atherosclerotic heart disease. *China Pharm.* 21 (20), 109–110.

Lu, J., and Ma, P. X. (2023). Observation on the clinical effect of injectable salvianolic acid salts in the treatment of coronary heart disease angina pectoris. *Pract. Clin. J. Integr. Traditional Chin. West. Med.* 23 (6), 11–13.

Lun, J., Ji, X. W., Zhang, A. Y., Zhao, C. H., Zhang, J. G., and Chen, Y. B. (2011). Effect of Salvianolate on unstable angina and its influence on NO and ET. *Chin. J. Clin. Ration. Drug Use.* 4 (2), 1–2.

Luo, X. C., and Huang, T. (2011). The effect of Danhong injection on vascular endothelial function and cardiac function in unstable angina pectoris. *J. Mil. Surg. Southwest China* 13 (03), 469–470.

Lv, X. S. (2018). Influence of salvianolate on endothelial function and homocysteine level in elderly patients with unstable angina pectoris. *J. Electrocardiol. Circulation* 37 (2), 117–120.

Ma, X., Zhang, L., Gao, F., Jia, W., and Li, C. (2023). Salvia miltiorrhiza and Tanshinone IIA reduce endothelial inflammation and atherosclerotic plaque formation through inhibiting COX-2. *Biomed. Pharmacother.* 167, 115501. doi:10.1016/j.biopha.2023.115501

Mach, F., Baigent, C., Catapano, A. L., Koskinas, K. C., Casula, M., Badimon, L., et al. (2020). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur. Heart J.* 41 (1), 111–188. doi:10.1093/eurheartj/ehz455

Malekmohammad, K., Sewell, R. D. E., and Rafieian-Kopaei, M. (2019). Antioxidants and atherosclerosis: mechanistic aspects. *Biomolecules* 9 (8), 301. doi:10.3390/biom9080301

Mao, Y. Y., Wang, J. Q., Wang, C. X., and Wang, C. X. (2016). Effect of salvianolate on serum levels of hs-CRP and TNF a in unstable angina patients. *Clin. Focus* 31 (2), 191–192, 197.

Martin, S. S., Blaha, M. J., Blankstein, R., Agatston, A., Rivera, J. J., Virani, S. S., et al. (2014). Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. *Circulation* 129 (1), 77–86. doi:10.1161/CIRCULATIONAHA.113.003625

Mehta, S. R., Bassand, J. P., Chrolavicius, S., Diaz, R., Eikelboom, J. W., Fox, K. A., et al. (2010). Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N. Engl. J. Med.* 363 (10), 930–942. doi:10.1056/NEJMoa0909475

Mei, F. G., Wang, Z. L., Zhang, Y. Q., and Zhao, G. (2014). Clinical study on the effect of Danshen Chuanxiong Injection on endothelial function in patients with unstable angina pectoris. *Chin. J. Traditional Med. Sci. Technol.* 21 (z2), 17.

Mei, F. G., Zhang, Y. Q., Wang, Z. L., and Zhao, G. (2006). The effect of Danhong injection on serum hypersensitive C-reactive protein in patients with unstable angina pectoris. *Pract. J. Cardiac Cereb. Pneumal Vasc. Dis.* 14 (12), 972–973.

Mou, L. N. (2011). Clinical observation of sodium tanshinone IIA sulfonate in the treatment of coronary heart disease angina pectoris. *Guide China Med.* 9 (27), 252–253.

National Center for Cardiovascular Disease (2023). *China cardiovascular Health and disease report 2022*. Beijing: Science Press.

National Health Commission of the People's Republic of China (2021). *China Health statistics Yearbook 2021*. Beijing: Peking Union Medical College Press.

Neumann, F. J., Sousa-Uva, M., Ahlsson, A., Alfonso, F., Banning, A. P., Benedetto, U., et al. (2019). 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur. Heart J.* 40 (2), 87–165. doi:10.1093/eurheartj/ehy394

Nidorf, S. M., Fiolet, A. T. L., Mosterd, A., Eikelboom, J. W., Schut, A., Opstal, T. S. J., et al. (2020). Colchicine in patients with chronic coronary disease. *N. Engl. J. Med.* 383 (19), 1838–1847. doi:10.1056/NEJMoa2021372

Nikolakopoulou, A., Mavridis, D., Furukawa, T. A., Cipriani, A., Tricco, A. C., Straus, S. E., et al. (2018). Living network meta-analysis compared with pairwise meta-analysis in comparative effectiveness research: empirical study. *BMJ* 360, k585. doi:10.1136/bmj.k585

Padro, T., Manfrini, O., Bugiardini, R., Canty, J., Cenko, E., De Luca, G., et al. (2020). ESC Working Group on Coronary Pathophysiology and Microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease. *Cardiovasc Res.* 116 (4), 741–755. doi:10.1093/cvr/cvaa003

Pan, D. M., Liu, Q. P., and Yang, C. J. (2024). Clinical efficacy and safety analysis of salvianolate in treatment of coronary heart disease. *Med. Innovation China* 15 (35), 50–53.

Pang, Z., Zha, G., and Xu, E. F. (2014). Influence of salvia miltiorrhiza phenolic acid salt on blood rheology and endothelial function in elderly patients with unstable angina. *Pract. Geriatr.* 17 (1), 38–40.

Peng, H. S., Liu, C. Y., Yang, Y. P., and Lai, Y. W. (2015). Influence study of danhong injection in the serum GDF-15, hs-CRP and NT-proBNP of unstable angina pectoris patients. *China and Foreign Med. Treat.* 34 (23), 108–110.

Qi, L. P., Wang, T. P., Shi, X. G., and Li, Q. (2001). Study on the antioxidant effect of Danshen injection on patients with stable angina pectoris. *Acta Univ. Med. Anhui* 36 (4), 287–288.

Qiu, C. Z., Lu, Y. G., Huang, J. Z., Chen, L. Y., He, D. M., and Chen, L. (2017). Changes and significance of serum inflammatory factors and endothelial cell microparticle levels in unstable angina patients treated with salvianolic acid salts as adjunctive therapy. *Shandong Med. J.* 57 (7), 52–54.

Qiu, D., Wang, F., and Zhao, T. (2018). Treatment effect of salvianolateand its influence on the hemorheology and oxidative stress in angina pectoris patients. *Anhui Med. Pharm. J.* 22 (1), 147–151.

Qiu, Y. H. (2020). Clinical efficacy analysis of salvianolic acid salts in the treatment of stable angina pectoris. *Chin. J. Urban Rural Enterp. Hyg.* (1), 158–159.

Riemersma, R. A. (1996). Coronary heart disease and vitamin E. *Lancet* 347 (9004), 776–777. doi:10.1016/s0140-6736(96)90861-2

Shi, Y. P., and Liu, B. (2012). Efficacy observation of 156 cases of senile unstable angina pectoris treated with danhong injection. *World J. Integr. Traditional West. Med.* 7 (10), 883–886.

Song, G. M., Li, Y., and Gao, Y. (2015). Effect of Salvia TMP on laboratory indicators and its efficacy on patients with unstable angina pectoris. *Chin. J. Biochem. Pharm.* 35 (12), 102–104, 107.

Song, J. J., Yang, Y. J., Su, T., and Zhao, Q. X. (2017). Effect of salvia miltiorrhiza injection on unstable angina pectoris, serum inflammatory factors and metabonomics. *Zhejiang J. Integr. Traditional Chin. West. Med.* 27 (12), 1026–1031.

Song, Q. T., Zhang, Y. Y., Han, X., Zhang, Y., Zhang, X., Gao, Y. G., et al. (2019). Potential mechanisms underlying the protective effects of salvianic acid A against atherosclerosis *in vivo* and vitro. *Biomed. Pharmacother.* 109, 945–956. doi:10.1016/j.biopha.2018.10.147

Su, C. Y., Ming, Q. L., Rahman, K., Han, T., and Qin, L. P. (2015). Salvia miltiorrhiza: traditional medicinal uses, chemistry, and pharmacology. *Chin. J. Nat. Med.* 13 (3), 163–182. doi:10.1016/S1875-5364(15)30002-9

Su, X. M., Zhi, X. W., Liu, J. X., He, Y. J., Ma, Y., and Wang, Y. X. (2011). Impact of danhong injection on paraoxonase 1, superoxide dismutase activity and malondialdehyde levels in aged patients with coronary heart disease. *Chin. General Pract.* 14 (33), 3804–3806.

Sun, K., Fu, C., Nie, S. H., and You, Y. (2014). The index and improvement effect of using Danhong injection to patients with atherosclerosis symptoms of coronary heart disease (CHD). *Pak J. Pharm. Sci.* 27 (5), 1699–1704.

Sun, L., and Zhang, S. H. (2024). Sixty cases with chronic heart failure treated with shenmai rongxin decoction. *Henan Tradit. Chin. Med.* 35 (7), 1520–1521.

Tan, S. J., Guo, H. F., and Lu, Y. (2009). The effect of salvianolic acid salts on endothelial function in elderly patients with unstable angina pectoris. *Pract. Geriatr.* 23 (2), 126–128.

Tao, L., Song, C. Y., and Chen, D. (2024). Efficacy of salvianolate in the treatment of patients with unstable angina pectoris and its effect on hs - CRP. *Chin J Clin. Ration. Drug Use* 7 (2), 46–47.

Törnwall, M. E., Virtamo, J., Korhonen, P. A., Virtanen, M. J., Taylor, P. R., Albanes, D., et al. (2004). Effect of alpha-tocopherol and beta-carotene supplementation on coronary heart disease during the 6-year post-trial follow-up in the ATBC study. *Eur. Heart J.* 25 (13), 1171–1178. doi:10.1016/j.ehj.2004.05.007

Valgimigli, M., Bueno, H., Byrn, R. A., Collet, J. P., Costa, F., Jeppsson, A., et al. (2018). 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* 39 (3), 213–260. doi:10.1093/eurheartj/ehx419

Wang, N., and Bi, Y. (2017). The effect of salvianolic acid salts on related cytokines in patients with unstable angina pectoris. *Mod. J. Integr. Traditional Chin. West. Med.* 26 (2), 184–186.

Wang, S. (2009). Observation on the therapeutic effect of Danhong injection in the treatment of unstable angina pectoris. *Guide China Med.* 11 (5), 113.

Wang, S. J., and Wang, Y. H. (2020). Study on the effect of Danhong injection on endothelial glycocalyx in patients with coronary heart disease. *J. Med. Theory Pract.* 33 (16), 2648–2650.

Wei, J., Wu, T., Yang, Q., Chen, M., Ni, J., and Huang, D. (2011). Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *Int. J. Cardiol.* 146 (1), 4–12. doi:10.1016/j.ijcard.2010.05.019

Wei, Q., and Shen, X. J. (2014). Effects of tanshinone Ⅱ on clinical symptoms and vascular aging factor in angina pectoris of coronary heart disease patients. *J. Basic Chin. Med.* 20 (6), 783–785.

Wight, L. J., VandenBurg, M. J., Potter, C. E., and Freeth, C. J. (1992). A large scale comparative study in general practice with nitroglycerin spray and tablet formulations in elderly patients with angina pectoris. *Eur. J. Clin. Pharmacol.* 42 (3), 341–342. doi:10.1007/BF00266360

Wu, J. R., Liu, S., Zhang, X. M., and Zhang, B. (2017). Danshen injection as adjuvant treatment for unstable angina pectoris: a systematic review and meta-analysis. *Chin. J. Integr. Med.* 23 (4), 306–311. doi:10.1007/s11655-016-2272-0

Wu, X. L., Pei, X., Li, D. Y., Li, J. M., Yang, D. Y., Gao, Y. L., et al. (2010). Effect of salvianolate on serum cytokins level in elderly patients with unstable angina pectoris. *Chin. J. Integr. Med. Cardio-Cerebrovascular Dis.* 8 (2), 158–160.

Wu, Y. T., Xie, L. P., Hua, Y., Xu, H. L., Chen, G. H., Han, X., et al. (2021). Tanshinone I inhibits oxidative stress-induced cardiomyocyte injury by modulating Nrf2 signaling. *Front. Pharmacol.* 12, 644116. doi:10.3389/fphar.2021.644116

Wu, Z. M., Luo, X. Y., and Wang, S. H. (2012). The therapeutic effect of salvianolic acid salts on unstable angina pectoris and their effects on CRP, NO, and ET-1. *Henan Tradit. Chin. Med.* 32 (7), 864–865.

Xi, H. W., Liu, G. F., and Yang, W. (2015). Influence of Shenxiong glucose injection on heart function, blood lipid and inflammatory factors in patients with unstable angina. *J. Liaoning Univ. Traditional Chin. Med.* 17 (9), 82–84.

Xia, L., and Zhang, H. L. (2022). Efficacy of salvia polyphenolic acid salt in elderly patients with coronary artery disease and its effect on blood lipids. *Med. Innovation China* 19 (26), 56–59.

Xie, Q. T., Liu, J. L., Wang, H. R., Yuan, S. F., Zhao, J., and Yang, X. H. (2020). Clinical trial of salvianolate in the treatment of patients with angina pectoris. *Chin. J. Clin. Pharmacol.* 36 (1), 3–6.

Xie, S., and Cao, C. (2011). Affection of hemorrheology and hyper - sensitive C – RP of danhong injection on unstable angina. *Heilongjiang Med. J.* 35 (9), 660–662.

Xu, L. J., Liu, X. K., and Liu, Y. F. (2014). Treatment of 46 cases of coronary heart disease and angina pectoris with guanxinning injection. *China Pharm.* 23 (14), 107.

Xu, Z. J., and Hao, S. Y. (2022). Effects of salviae miltiorrhizae and ligustrazine hydrochloride injection on cardiovascular function and antioxidant function in patients with unstable angina pectoris of coronary heart disease. *Clin. Res. Pract.* 7 (10), 122–125.

Yan, C. G., and Zeng, J. Q. (2009). The effect of Danhong injection on vascular endothelial function in patients with unstable angina pectoris. *Shandong Med. J.* 49 (8), 78–79.

Yang, C. P., and Shi, G. (2009). The effect of Danhong injection on inflammatory factors in patients with unstable angina pectoris. *J. Pingxiang Univ.* 26 (3), 99–101.

Yang, L. L., Ji, X. W., Zhang, A. Y., Zhang, J. G., and Duan, X. L. (2010). Clinical observation of salvianolic acid injection in the treatment of unstable angina pectoris. *Chin. J. Clin. Ration. Drug Use.* 3 (2), 1–2.

Yang, N., and Ren, F. X. (2010). Sulfotanshinone sodium for unstable angina pectoris: a study of clinical application. *China Mod. Dr.* 48 (21), 47–49.

Yao, H. (2022). Treatment methods and clinical application analysis of coronary heart disease in elderly people over 60 years old. *Med. Health* (4), 5–8.

Ye, T. H., Li, X. H., Zhong, Y. T., and Chen, H. X. (2021). The effect of salvianolic acid salts as adjunctive therapy for coronary heart disease angina pectoris and their impact on oxidative stress. Inner Mongolia. *J. Traditional Chin. Med.* 40 (1), 58–60.

Yu, M. H., and Fang, S. (2016). Clinical curative effect observation of salvia miltiorrhiza ligustrazine injection in treating angina pectoris of coronary heart disease. *Clin. J. Chin. Med.* 8 (6), 44–45.

Yu, M. K., and Jiao, L. Q. (2014). Effect of salvianolate injection on plasma high-sensitivity C reactive protein and tumor necrosis factor and soluble cell apoptosis factor in unstable angina patients. *Hebei J. Traditional Chin. Med.* 36 (1), 11–13.

Yue, H. J., Yang, P. P., and Li, L. M. (2023). Effect of salvianolic acid on ischemic cardiomyopathy. *Henan Med. Res.* 32 (13), 2447–2450.

Zhang, B. H. (2011). The effects of Danhong injection on inflammatory factors, thromboxane B2, and hemorheology in patients with unstable angina pectoris. *Chin. J. Integr. Med. Cardio-Cerebrovascular Dis.* 9 (9), 1055–1057.

Zhang, C. J., An, Q. H., and Zheng, Y. M. (2018). Expression and intervention study of NF-κB, TNF-α, IL-1 and IL-6 in patients with unstable angina pectoris. *J. Binzhou Med. Univ.* 41 (3), 168–170.

Zhang, L. L., Jiang, N., Qu, G., and Gao, S. S. (2010). A comparative study of three commonly used traditional Chinese medicine preparations combined with conventional Western medicine therapy for the treatment of unstable angina pectoris. *Chin. J. Integr. Med. Cardio-Cerebrovascular Dis.* 8 (4), 388–390.

Zhang, R. H. (2010). Influence of salvianolate on clinical efficacy, endothelial function and C-reactive protein in patients with unstable angina pectoris. *Mod. Hosp.* 10 (5), 35–37.

Zhang, S. G., He, L. M., Liu, S. Y., Li, Q. Y., and Tan, R. R. (2012). Clinical observation on the efficacy and safety of traditional Chinese medicine for promoting blood circulation and removing blood stasis in the treatment of acute coronary syndrome. *China and Foreign Med. Treat.* 31 (13).

Zhang, W., Ji, N. J., Mei, Y. B., and Hu, C. S. (2015a). The effect of salvianolic acid salts on serum Ang Ⅱ, IL-6, and hs CRP in elderly patients with unstable angina pectoris. *Chin. J. Traditional Med. Sci. Technol.* 22 (6), 683–684.

Zhang, X. Y. (2016). Effect discussion of salvianolic acid on blood lipid and inflammatory factors of patients with unstable angina pectoris of coronary heart disease. *World Latest Med. Inf.* 16 (59), 13–14.

Zhang, Y., Wang, H., Cui, L. J., Zhang, Y. Y., Liu, Y., Chu, X., et al. (2015b). Continuing treatment with Salvia miltiorrhiza injection attenuates myocardial fibrosis in chronic iron-overloaded mice. *PLoS One* 10 (4), e0124061. doi:10.1371/journal.pone.0124061

Zhang, Y., Xie, Y., Liao, X., Jia, Q., and Chai, Y. (2017). A Chinese patent medicine Salvia miltiorrhiza depside salts for infusion combined with conventional treatment for patients with angina pectoris: a systematic review and meta-analysis of randomized controlled trials. *Phytomedicine* 25, 100–117. doi:10.1016/j.phymed.2017.01.002

Zhang, Z. J. (2017). The effect of tanshinone IIA sodium sulfonate injection on inflammatory factors in unstable angina pectoris. *all Health* 11 (2), 130–131.

Zhao, B., Wang, J., and Song, Y. B. (2015). Effects of Danhong Iniection on unstable factors and vascular endothelial function of inflammation in patients with angina pectoris. *J. Liaoning Univ. Traditional Chin. Med.* 17 (9), 182–184.

Zhao, H., Zhang, Y. C., and Pu, S. J. (2011). Clinical application and evaluation of Danhong injection for patients with unstable angina. *Sichuan J. Anat.* 19 (4), 10–12.

Zhou, S. N., and Guo, H. (2018). The effect of salvianolic acid salts in the treatment of coronary heart disease and their impact on ET-1 and NO levels. *Laboratory Med. Clin.* 15 (11), 1680–1683.

Zhu, Q. K. (2019). The effect of salvianolic acid salts as adjunctive therapy for unstable angina on inflammatory response and angina attacks. *J. Med. Theory Pract.* 32 (13), 2015–2016.

Zhu, Y., and He, Y. H. (2002). Clinical observation of Danshen powder injection in the treatment of unstable angina pectoris. *J. Emerg. Traditional Chin. Med.* 11 (4), 253–254.

Zou, F., Du, Q., Zhang, Y., Zuo, L., and Sun, Z. (2023). Pseudo-allergic reactions induced by Chinese medicine injections: a review. *Chin. Med.* 18 (1), 149. doi:10.1186/s13020-023-00855-0

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 16 December 2024
DOI 10.3389/fphar.2024.1447546

OPEN ACCESS

EDITED BY
Jie Wang,
China Academy of Chinese Medical Sciences, China

REVIEWED BY
Yongsheng Chen,
Jinan University, China
Qiqi Yang,
Massachusetts General Hospital and Harvard Medical School, United States

*CORRESPONDENCE
Xindong Wang,
wangxd@njucm.edu.cn
Jianping Shen,
shenjp@jsatcm.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 11 June 2024
ACCEPTED 25 November 2024
PUBLISHED 16 December 2024

CITATION
Xu Q, Liu X, Chen Z, Guo C, Lu P, Zhang S, Wang X and Shen J (2024) Combination decoction of Astragalus mongholicus and *Salvia miltiorrhiza* mitigates pressure-overload cardiac dysfunction by inhibiting multiple ferroptosis pathways.
Front. Pharmacol. 15:1447546.
doi: 10.3389/fphar.2024.1447546

Combination decoction of Astragalus mongholicus and *Salvia miltiorrhiza* mitigates pressure-overload cardiac dysfunction by inhibiting multiple ferroptosis pathways

Qiyao Xu[1,2†], Xuan Liu[1,2†], Zhaoyang Chen[1,2†], Can Guo[1,2], Pengyu Lu[1,2], Sujie Zhang[1], Xindong Wang[1*] and Jianping Shen[1*]

[1]Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China, [2]Graduate School, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

Background: Astragalus mongholicus (AM) and Salvia miltiorrhiza (SM) are commonly used in traditional Chinese medicine to treat heart failure (HF). Ferroptosis has been studied as a key factor in the occurrence of HF. It remains unclear whether the combined use of AM and SM can effectively improve HF and the underlying mechanisms.

Objective: This study aims to explore whether the combined use of AM and SM can improve HF by inhibiting ferroptosis. It also examines the roles and interactions of the pathways associated with GPX4, FSP1, and DHODH.

Methods: *In vitro* experiments used angiotensin II-induced (4 μM for 48 h) hypertrophic H9c2 cells, while *in vivo* studies employed a rat model of transverse aortic constriction-induced (to 1 mm for 8 weeks) HF. Interventions included decoctions of AM and SM (for animal experiments) and medicated serum (for cell experiments), along with specific pathway inhibitors such as erastin, FSP1 inhibitor and brequinar. Subsequently, various molecular biology methods were used to measure the protein levels of GPX4, FSP1, and DHODH, as well as each sample group's ferroptosis-related and HF-related indicators, to elucidate the underlying mechanisms.

Results: The combined use of AM and SM can effectively restore the levels of GPX4, FSP1, and DHODH that are reduced after HF, as well as improve indicators related to ferroptosis and HF. When GPX4, FSP1, or DHODH is inhibited, the ferroptosis-inhibiting effect and the ability of AM and SM to improve HF are both weakened. When two of the three proteins are inhibited, the protective effect of HDC is strongest when GPX4 is retained, followed by FSP1, and weakest when DHODH is retained.

Conclusion: This study confirms that the combined use of AM and SM inhibits ferroptosis and alleviates HF by increasing GPX4, FSP1, and DHODH levels. It

shows that the protective effect is strongest through GPX4, followed by FSP1, and weakest through DHODH. These findings provide new insights into the therapeutic mechanisms of this combination of botanical drugs.

KEYWORDS

ferroptosis, heart failure, Astragalus mongholicus, Salvia miltiorrhiza, GPX4, FSP1, DHODH

1 Introduction

Heart failure (HF) is a prevalent and debilitating cardiac condition, involves the pathophysiological process of diminished cardiac pumping function, leading to systemic tissue ischemia and hypoxia. While modern medicine has made significant strides in the treatment of HF, it continues to pose a serious threat to health, diminishing the quality of life and significantly reducing patients' life expectancy. The research (Owen et al., 2023) suggests that HF can reduce the average life expectancy by 12.38 years. In a 5-year follow-up of acute HF patients, the median survival time was only 34 months (Li et al., 2021). The recurring exacerbation and worsening of the condition, resulting in repeated hospitalizations, also place a substantial burden on patients' families and the healthcare system. The study indicates a 30-day readmission rate of 13.2% and a 1-year readmission rate of 23.3% among global HF patients (Foroutan et al., 2023). Therefore, to mitigate the global burden imposed by HF, beyond managing underlying conditions contributing to HF such as coronary artery disease and hypertension, further controlling the symptoms of established HF, improving the prognosis of HF, thereby enhancing patients' quality of life, and reducing the readmission rate, remain viable and effective measures.

Ferroptosis is a form of programmed cell death that was identified in 2012. Distinguished from other programmed cell death mechanisms such as apoptosis and necroptosis, ferroptosis is characterized by iron-dependent lipid peroxidation (Dixon et al., 2012). Currently, the main regulatory pathways identified in lipid peroxidation during ferroptosis in the cytoplasm include the nuclear factor erythroid 2-related factor 2 (Nrf2)/cytosolic glutathione peroxidase 4 (cGPX4)/reduced glutathione (GSH) pathway, the ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10)/reduced nicotinamide adenine dinucleotide phosphate (NADPH) pathway, and the mitochondria-localized dihydroorotate dehydrogenase (DHODH)/CoQ10 pathway and GPX4/GSH pathway (Mao et al., 2021). Numerous animal studies on HF/myocardial injury and ferroptosis have consistently observed an increase in ferroptosis, whether induced by physical pressure overload (Wang et al., 2020) drug-induced pressure overload (Chen et al., 2023), cardiotoxic drugs (Liu J. et al., 2022), or myocardial infarction models (Hou et al., 2021). Concurrently, HF also induces alterations in ferroptosis-related regulatory pathways, primarily manifested by the downregulation of GPX4 and FSP1 (Liu B. et al., 2018; Chen et al., 2019; Liang et al., 2023; Zhang et al., 2023). Upregulating GPX4 (Zhang et al., 2023), FSP1(Zhang et al., 2023), or directly inhibiting lipid peroxidation (Zhang et al., 2022; Chen et al., 2023) can also reduce ferroptosis and inhibit the development of HF. This further confirms that ferroptosis is a crucial factor in the occurrence and progression of HF. DHODH was confirmed in 2021 to participate in the regulation of ferroptosis, serving as an inhibitor of ferroptosis (Mao et al., 2021). However, whether DHODH is involved in the occurrence and progression of HF through the regulation of ferroptosis remains unexplored.

Astragalus mongholicus Bunge [Fabaceae; Astragali radix] (AM) [checked with http://www.worldfloraonline.org on (2024-06-05)] and *Salvia miltiorrhiza* Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] (SM) [checked with http://www.worldfloraonline.org on (2024-06-05)] are both traditional Chinese botanical drugs commonly used in the treatment of HF. AM, belonging to the legume family under the Astragalus genus (Chinese Pharmacopeia Commission, 2020) (The official website of Pharmacopoeia of the People's Republic of China: https://ydz.chp.org.cn/#/main), is extensively utilized in traditional Chinese medicine (TCM). Its primary active metabolites include various flavonoids, saponins (such as Astragaloside IV, AS-IV), polysaccharides, among others, endowing it with diverse pharmacological activities such as immunomodulation, antioxidant, anti-inflammatory, anti-tumor, and cardiovascular protection (Zhang et al., 2021). SM belongs to the Lamiaceae family under the Salvia genus (Chinese Pharmacopeia Commission, 2020). Its major active metabolites include tanshinone and salvianolic acids (such as Salvianolic Acid B, SAB), exhibiting various pharmacological activities (Ma et al., 2022). Clinically, SM is utilized for the treatment of various ailments, particularly demonstrating significant effects in the cardiovascular system and blood circulation. It is considered to have multiple actions such as promoting blood circulation, vasodilation, lowering blood pressure, and antioxidant effects and has therapeutic effects in conditions like diabetes, liver diseases, and tumors (Ding et al., 2021). AS-IV and SAB are designated as quality control metabolites of AM and SM in the Chinese Pharmacopeia, respectively.

TCM holds that the fundamental pathogenesis of HF involves Qi and blood stasis. Treatment for HF in TCM primarily focuses on invigorating Qi and promoting blood circulation (Project Group of Traditional Chinese Medicine Guideline for Diagnosis and Treatment of Chronic Heart Failure and China Association of Chinese Medicine, 2023). Currently, among the commercial Chinese polyherbal preparation recommended for treating HF, those with the highest evidence grade and recommendation strength are Qishen Yiqi Dripping Pills and Qili Qiangxin Capsules (Project Group of Traditional Chinese Medicine Guideline for Diagnosis and Treatment of Chronic Heart Failure and China Association of Chinese Medicine, 2023). Both of these commercial Chinese polyherbal preparation contain AM (In Chinese, it is called HuangQi) for Qi invigoration and SM (In Chinese, it is called Danshen) for promoting blood circulation. It is evident that the combined use of AM and SM demonstrates significant efficacy in treating HF and is foundational in TCM

treatment for this condition (Guo et al., 2022; Wei et al., 2022). Numerous studies have confirmed that AM or its active metabolites can improve myocardial hypertrophy, inhibit myocardial fibrosis, and promote blood vessel generation, thereby ameliorating HF (Liu Z. H. et al., 2018; Sui et al., 2020; Lin et al., 2021). SM, as one of the most commonly used botanical drugs in TCM for treating HF, has its active metabolites similarly confirmed by various studies to further improve ejection fraction, reduce N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, and exhibit positive therapeutic effects on HF (Chen et al., 2014; Chung et al., 2018; Li et al., 2023).

In this study, we aim to simplify the complex formula to a combination of AM and SM, using a series of molecular biology techniques to explore whether this simplified combination can effectively improve cardiac function, and to investigate the therapeutic mechanisms of the AM-SM combination (HDC) in HF treatment, particularly in the context of ferroptosis. We will examine the regulatory effects of HDC on the three known pathways involved in inhibiting lipid peroxidation during ferroptosis (GPX4, FSP1, DHODH), and investigate potential interactions among these pathways during the treatment process with HDC.

2 Materials and methods

All manuals or guidelines mentioned in the procedures or methods can be found in Supplementary Material 1.

2.1 Materials and reagents

Astragalus mongholicus Bunge [Fabaceae; Astragali radix] (Batch No. 2301001, Wan Zhen Chinese Herbal Pieces Factory, Bozhou, China; procured via Jiangsu Province Academy of Traditional Chinese Medicine), *S. miltiorrhiza* Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] (Batch No. 20230202-01, Guizhou Tongde Pharmaceutical Co., Ltd., Guizhou, China; procured via Jiangsu Province Academy of Traditional Chinese Medicine), Angiotensin II (AngII) (S25704, Yuanye, China), Ferrostatin-1 (Fer-1) (S7243, Selleck, United States), Brequinar (BQR) (HY108325, MedChemExpress), Erastin (Era) (S7242, Selleck, United States), inhibitor of ferroptosis suppressor protein 1 (iFSP1) (MFCD01572665, Macklin, China), dimethyl sulfoxide (DMSO) (D8371, Solarbio, China). Sodium Penicillin for injection (42220302, Shandong Lukang, China), anhydrous ethanol (100092683, Sinopharm Chemical Reagent Co., Ltd., China), xylene (1002341922, Sinopharm Chemical Reagent Co., Ltd., China), 0.1 M phosphate buffer (PB) (T16865, saint-Bio, China), 1% osmium tetroxide (18,456, Ted Pella Inc), ×5 loading buffer (P0015L, P0285, Beyotime, China), Quick Color Pre-Stained Gel kit 12.5% (S6172, Uelandy, China), Tris-glycine SDS-PAGE running buffer (G2027-1L, Solarbio, China), NC membrane (66,485, Bio Trace, United States), non-fat milk powder (P0216, Beyotime, China), TBST (T1085, Solarbio, China), Anti-GPX4 mAb (67763-1-Ig, Proteintech, China), Anti-FSP1 mAb (68049-1-Ig, Proteintech, China), Anti-DHODH mAb (67977-1-Ig, Proteintech, China), Anti-GAPDH Rabbit pAb (GB11002, Servicebio, China), Horseradish Peroxidase-conjugated secondary antibody (A0208, A0216, Beyotime, China), SuperSignal ECL chemiluminescence kit (P0018M, Beyotime, China), Antibody Stripping Solution (WB6200, NCM biotech, China).

2.2 Animal sources and routine husbandry

The animal experiments in this study were conducted in accordance with the guidelines and international standards for animal welfare issued by the Ethics Committee of the Jiangsu Province Academy of Traditional Chinese Medicine (Ethical Review Number: AEWC-20230310-272, approved on 10 March 2023). Specific Pathogen Free (SPF)-grade Sprague-Dawley (SD) rats used in this research were uniformly acquired from Nantong University [Production License Number: SCXK (Su) 2019-0001] or SiPeiFu (Beijing) Biotechnology Co., Ltd. [Production License Number: SCXK (Jing) 2019-0010], under the management of the Experimental Animal Center of the Jiangsu Province Academy of Traditional Chinese Medicine [Use License Number: SYXK (Su) 2021-0025]. These rats were free to move within their cages and had unrestricted access to food and water.

2.3 Cell source and routine culture

The cells used in this research were H9c2 cells, obtained from Procell (Catalog number CL-0089, China). Routine culture was carried out in a medium composed of 89% Dulbecco's Modified Eagle's Medium ($NaHCO_3$ 1.5 g/L) (iCell-128-0001, Cellverse, China), 10% fetal bovine serum (10,270-106, Gibco, Thermo Fisher Scientific, United States), and 1% penicillin/streptomycin (C0222, Beyotime, China) in an incubator set at 37°C with 5% CO_2.

2.4 Preparation of HDC decoction and HDC drug-containing serum

Both AM and SM were procured by the pharmacy department of the Jiangsu Province Academy of Traditional Chinese Medicine from manufacturers of Chinese herbal pieces, with quality control managed by the manufacturer, in compliance with the quality control standards for AM and SM specified in the *Chinese Pharmacopeia* (Chinese Pharmacopeia Commission, 2020). According to the recommended human dosages, these two botanical drugs were combined at a 2:1 weight ratio of AM to SM (Chinese Pharmacopeia Commission, 2020). To closely align with clinical medication practices, the AM-SM mixture was prepared as a decoction rather than as a freeze-dried powder. After two rounds of decoction and rotary evaporation, the final concentration of the decoction is 0.938 g/mL, equivalent to 0.625 g of AM and 0.313 g of SM per mL. The decoction at 0.938 g/mL concentration was considered a high-dose HDC (HDC-H). A suitable amount of this high-dose decoction was then diluted with an equal volume of distilled water to obtain a low-dose preparation (HDC-L) with a concentration of 0.469 g/mL. The Astragalus-Salvia decoction was analyzed using liquid chromatography-mass spectrometry to determine the content of

AS-IV and SAB. The content of AS-IV was 36.86 ± 0.21 μg/mL, and the content of SAB was 7.72 ± 0.05 μg/mL.

SPF-grade SD rats were stratified by sex and then randomly assigned to three groups: control, low-dose, and high-dose. The maximum human dose for a 60 kg individual, which is 30 g/day of AM and 15 g/day of SM (Chinese Pharmacopeia Commission, 2020), was used as the high dose. Accordingly, 15.00 g/day of AM and 7.50 g/day of SM constituted the low dose. Based on the dosage conversion methods for experimental animals in "*Experimental Methodology of Pharmacology (4th edition)*" (Wei et al., 2020) the drug dosage per kg body weight for SD rats was determined to be 6.25 times that of the human dosage. As a result, the daily required dose for the SD rats in the high-dose group was HDC-H 5 mL/kg, and for the low-dose group, it was HDC-L 5 mL/kg. The daily dose was administered by gavage twice per day for 7 consecutive days. After the dosing period, rats were anesthetized with isoflurane, and blood was collected from the abdominal aorta. After centrifugation, the serum was collected and pooled within the same experimental group, resulting in three types of serum: control rat serum, low-dose HDC-containing serum (HDCL-S), and high-dose HDC-containing serum (HDCH-S).

2.5 Metabolite identification of HDC and molecular docking of the main active metabolites with target proteins

The obtained serum and the HDC decoction were both subjected to liquid chromatography-mass spectrometry for metabolite identification. Liquid chromatography-mass spectrometry data acquisition method referenced previous literature (Yuan et al., 2023), with some methods or parameters slightly modified. Detection was performed using an Orbitrap Exploris 120 mass spectrometer (Thermo Fisher Scientific). Detailed parameters are as follows: Sheath gas flow rate: 35 Arb, Aux gas flow rate: 15 Arb, Ion Transfer Tube Temp: 350°C, Vaporizer Temp: 350°C, Full ms resolution: 60,000, MS/MS resolution: 15,000, Collision energy: 16/32/48 in NCE mode, Spray Voltage: 5.5 kV (positive) or −4 kV (negative). Additionally, multiple reaction monitoring (MRM) was used to detect AS-IV and SAB in the Astragalus-Salvia decoction. Carbamazepine and salidroside, both at concentrations of 1 μg/mL, were used as internal standards for positive and negative ion modes, respectively. AS-IV standard (HY-N0431R, MCE, United States) was used at a concentration of 1,088 μg/mL, and SAB standard (HY-N1362R, MCE, United States) was used at a concentration of 1,136 μg/mL. For AS-IV detection, the conditions were as follows: parent ion mass-to-charge ratio (m/z) of 802.6, daughter ion m/z of 785.1, declustering potential (DP) of 136.1 V, collision energy (CE) of 11.32 eV, and collision cell exit potential (CXP) of 35.11 V. The second condition for AS-IV was parent ion m/z 802.4, daughter ion m/z 785.4, DP 135.93 V, CE 10.63 eV, and CXP 30.92 V. The third condition was parent ion m/z 807.5, daughter ion m/z 627.5, DP 249.78 V, CE 61.76 eV, and CXP 26.94 V. For SAB detection, the first condition was parent ion m/z 717.5, daughter ion m/z 519.3, DP -175.7 V, CE -25.29 eV, and CXP -19.93 V. The second condition was parent ion m/z 717.1, daughter ion m/z 519.4, DP -152.13 V, CE -27.3 eV, and CXP -20.38 V. The third condition was parent ion m/z 717.3, daughter ion m/z 519.6, DP -160.3 V, CE -30 eV, and CXP -21.3 V. This complies with the ConPhyMP requirements (Heinrich M, et al., 2022).

Select the main metabolites of AM (AS-IV, CAS: 84,687-43-4) and SM (SAB, CAS: 121,521-90-2) for molecular docking with target proteins FSP1 (PDB ID: 8JSC), DHODH (PDB ID: 5K9D), and GPX4 (PDB ID: 6ELW). First, convert the 2D structures of AS-IV and SAB obtained from PubChem into 3D structures using Open Babel (version 3.1.0, Open Babel Development Team). Then, preprocess the protein structures using AutoDockTools (version 1.5.7, Scripps Research), including removing water molecules, adding polar hydrogen atoms, and assigning Gasteiger charges. In AutoDockTools, select the entire protein as the grid region and set appropriate grid sizes to cover the whole protein. Perform molecular docking using AutoDock Vina (version 1.2.5, Scripps Research) with 10 iterations and an exhaustiveness of 1.0, outputting the 9 lowest binding energy modes. Finally, analyze the docking results to select the conformation with the lowest binding energy as the optimal binding mode, and visualize the binding mode using PyMOL (version 2.6.0 Open-Source, Schrodinger LLC) to evaluate the interactions between the metabolites and proteins.

2.6 Cell intervention methods

Twenty-four hours after cell passage, cells were cultured for 24–72 h with AngII at different concentrations (0μM, 1μM, 2μM, 4μM, 8μM, 12μM, and 16 μM). A combination of AngII concentration and incubation time that caused significant cell enlargement without notable cytotoxicity (4 μM for 48 h, Supplementary Figures 1A–C) was chosen for subsequent modeling of a HF cell model. After model establishment, drug interventions were performed. The serum in the intervention culture medium was replaced with an equal volume of the corresponding rat serum (blank serum, HDCL-S, or HDCH-S), each constituting 10% of the culture medium volume. The final concentrations of other intervention substances in the culture medium were as follows: AngII at 4 μM, Fer-1 at 1 μM, Era at 5 μM, iFSP1 at 1 μM, and BQR at 10 μM. The concentrations of the aforementioned agents were determined based on similar dosages used in previous research studies (Dixon et al., 2012; Sykes et al., 2016; Horwath et al., 2017; Cheu et al., 2023; Nakamura et al., 2023). All substances were dissolved in DMSO, with the maximum concentration in the culture medium being 0.1%. An appropriate amount of DMSO was added to each of the other culture media to standardize the DMSO concentration to 0.1% across all groups, ensuring comparability. Detailed medium preparation methods are provided in the Supplementary Table 1.

2.7 Animal model and intervention method

After 1 week of acclimatization, 78 SPF-grade mature male SD rats (180–200 g) were randomly assigned into two groups using a random number method: the sham operation group (n = 6) and the transverse aortic constriction (TAC) model group (n = 72). The TAC model group underwent TAC surgery as previously described (Garrott et al., 2017; Carley et al., 2021). In this study, the aortic arch

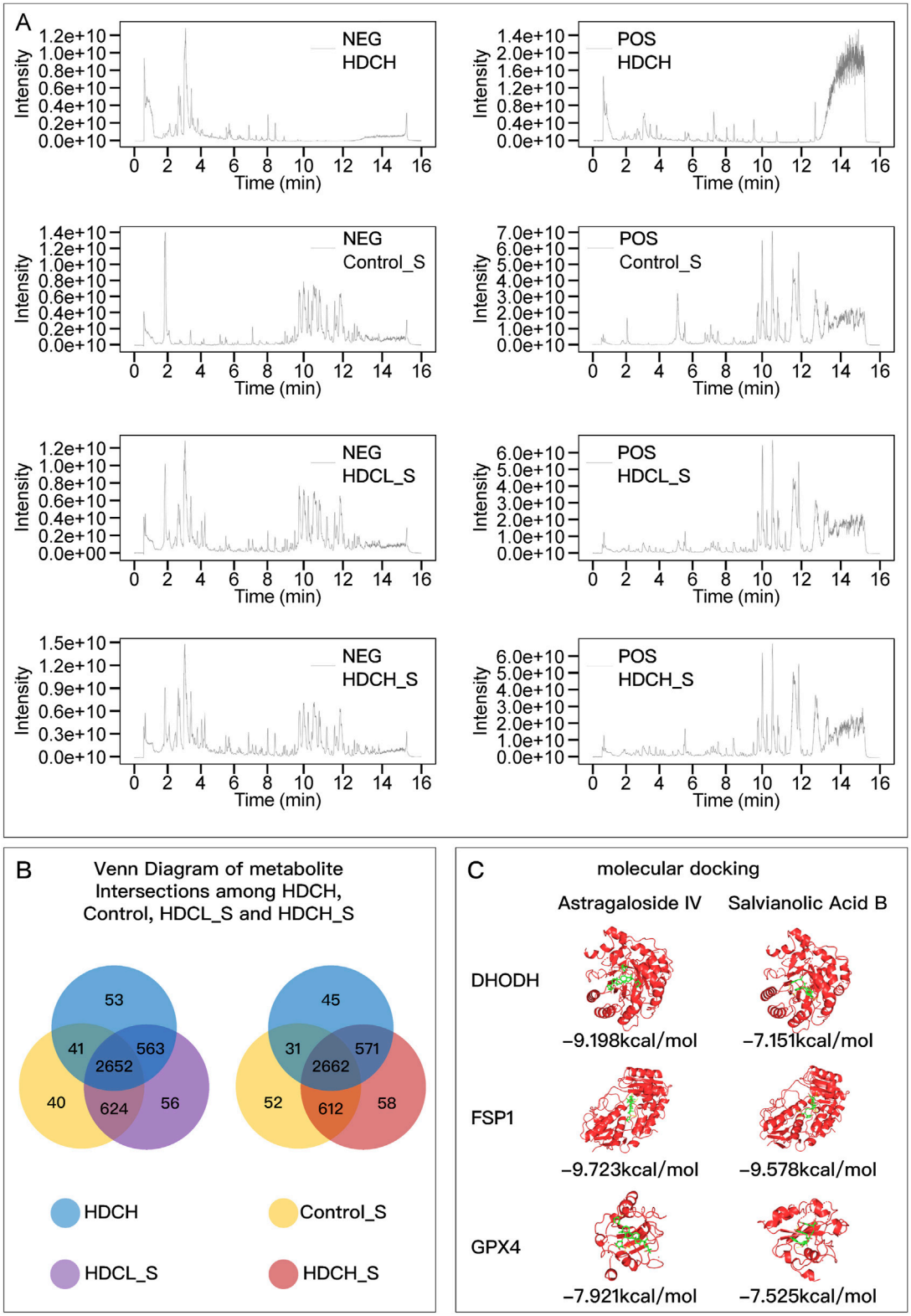


FIGURE 1
HDC metabolite identification and molecular docking. **(A)** Chromatograms of HDCH, Control_S, HDCH_S, and HDCL_S under NEG and POS ion modes; **(B)** Venn diagram of metabolites in different samples. **(C)** Molecular Docking Results of Astragaloside IV and Salvianolic Acid B with DHODH, FSP1, and GPX4. HDCH, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; Control_S, Normal Rat Serum; HDCH_S, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; HDCL_S, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; NEG, Negative Ion Mode; POS, Positive Ion Mode.

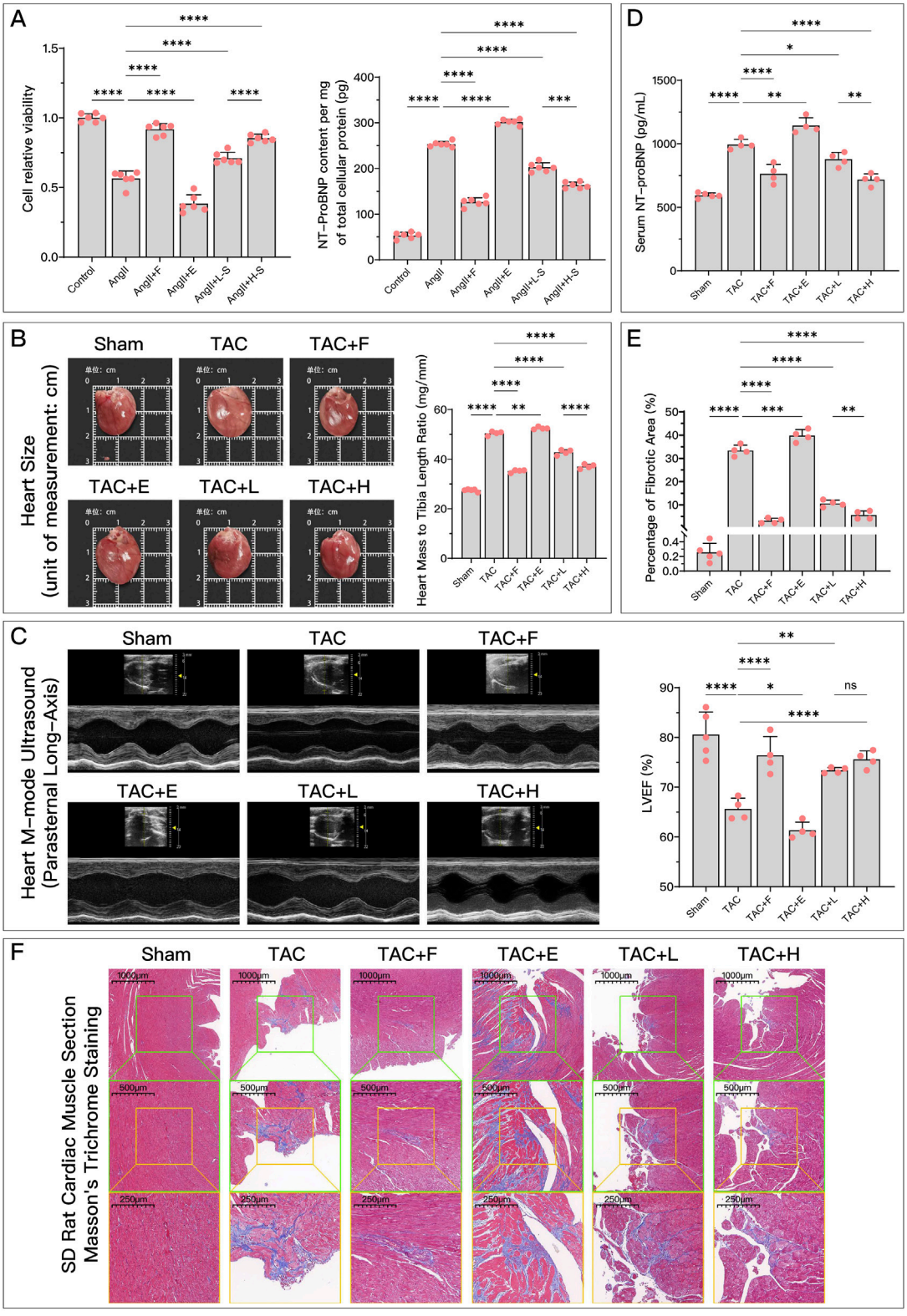


FIGURE 2
HDC effectively improves AngII-induced cell dysfunction and HF due to TAC. **(A)** Relative cell viability of different groups of H9c2 cells compared to the control group, and NT-proBNP content per mg of total cellular protein; **(B)** Gross images of rat hearts from each group for direct comparison of heart size, and comparison of heart weight to tibia length ratio in each group; **(C)** Parasternal long-axis M-mode echocardiographic images of the left ventricle in rats from each group, and quantitative comparison of LVEF; **(D)** Comparison of serum NT-proBNP levels in rats from each group; **(F)** Microscopic images of Masson's trichrome-stained myocardium in rats from each group (×50, ×100, ×200), where the blue-stained areas represent collagen deposition, indicating myocardial fibrosis; **(E)** Quantification of myocardial fibrosis as indicated by Masson's trichrome staining, expressed as the percentage of fibrotic area. $p^{ns} \geq 0.05$, $p^{*} < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$, $p^{****} < 0.0001$. ● represents an individual sample data point. HDC, Astragalus
(*Continued*)

FIGURE 2 (Continued)
mongholicus and Salvia miltiorrhiza Combination; AngII, Angiotensin II; HF, Heart failure; F, Ferrostatin-1; E, Erastin; L-S, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; H-S, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; TAC, Transverse Aortic Constriction; L, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; H, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction.

was transversely constricted to 1.0 mm. The sham operation group underwent the same procedures without the final step of transverse aortic arch ligation. All rats were administered an intramuscular injection of 100,000 units of penicillin for anti-infection on the second and third days post-operation.

After 2 months of standard rearing, left ventricular ejection fraction (LVEF) and serum (from the tail vein) NT-proBNP was assessed in all rats. The sham-operated rats formed one group, while the TAC model rats were stratified based on LVEF and then randomly grouped using a random number method, aiming to ensure comparability between groups as much as possible. Except for HDC-L and HDC-H, which were administered via gavage at a volume of 5 mL/kg as described in Section 2.4 of the methods, other intervention agents were administered via intraperitoneal injection. The injection concentrations and dosages of each agent were as follows: Fer-1 (0.21875 mM, 0.875 μmol/kg), Era (2.1875 mM, 8.75 μmol/kg), BQR (2.1875 mM, 8.75 μmol/kg), and iFSP1 (0.21875 mM, 0.875 μmol/kg). The dosages used for the aforementioned agents were based on the amounts referenced from previous studies (Sykes et al., 2016; Li et al., 2022; Cheon et al., 2023; Zhou et al., 2023). Based on the dosages, the aforementioned preparation concentrations were adopted to ensure that each agent was administered at a volume of 4 mL/kg. The TAC + HDC-H + Era + iFSP1+BQR group required injection of all three formulations, thus having the highest total injection volume at 12 mL/kg. Therefore, for the other groups, the injection volume was supplemented with solvent to reach 12 mL/kg. Intraperitoneal injections were given every other day for 4 weeks. The Sham group receiving pure water by gavage according to body weight for 4 weeks. The detailed preparation methods of reagents are provided in Supplementary Table 2.

2.8 Cell size determination

Following the completion of H9c2 cell culture, crystal violet staining was performed using the crystal violet staining kit (C0121, Beyotime, China) according to the manufacturer's instructions. Subsequently, under an inverted microscope, 6 fields of view at ×100 and ×400 magnification were randomly selected for photography. The images at ×400 magnification were used for direct visual observation, while the images at ×100 magnification were used for calculating cell size. The ImageJ 1.54f software (Wayne Rasband, National Institutes of Health, United States, https://imagej.nih.gov/ij/) was utilized to select all purple regions as the total cell area. Additionally, deeply stained purple cell nuclei were selected for nucleus counting, representing the cell count. The average cell area within each field was determined by dividing the total area by the cell count.

2.9 Cell viability and vitality determination

The cell viability and vitality of each group relative to the control group were measured using the widely used cell counting kit-8 (C0042, Beyotime, China). The specific procedures were carried out according to the manual provided with the kit.

2.10 Enzyme-linked immunosorbent assay (Elisa) detection of substance levels

The levels of NT-proBNP in cells and rat serum were measured using a rat NT-proBNP Elisa kit (DreamBio, China). $CoQ10H_2$ levels were determined using a rat $CoQ10H_2$ Elisa kit (DreamBio, China). The specific procedures were carried out according to the manual provided with the kit.

2.11 Determination of GSH, MDA, and Fe^{2+} content

The contents of GSH, MDA, and Fe^{2+} were measured using commercial assay kits. Specifically, the GSH and GSSG assay kit (S0053, Beyotime, China), lipid peroxidation (MDA) assay kit (S0131S, Beyotime, China), tissue Fe^{2+} colorimetric assay kit (E-BC-K773-M, Elabscience, China), and cellular Fe^{2+} colorimetric assay kit (E-BC-K881-M, Elabscience, China) were employed. The specific operations were conducted according to the instructions provided in the manuals. It should be noted that for MDA measurement, the manual recommended mixing the sample with reagent and boiling it sealed for 15 min. However, preliminary experiments indicated that boiling for 15 min was ineffective; therefore, the boiling duration was extended to 1 h, which was also adopted for subsequent measurements.

2.12 Determination of LVEF in rats

After anesthetization with isoflurane, rats were placed in a supine position on the ultrasound examination table. The chest area was prepared by shaving and applying coupling gel. Echocardiography was performed by the same operator using a high-resolution ultrasound system (Vevo 3,100, VisualSonics, Canada) equipped with a specialized small animal ultrasound probe (21 MHz). Measurements were taken from both the short-axis and parasternal long-axis, capturing at least three consecutive cardiac cycles. The ventricular wall thickness and internal diameter during systole and diastole were manually selected, following which the ejection fraction was automatically calculated by the ultrasound machine.

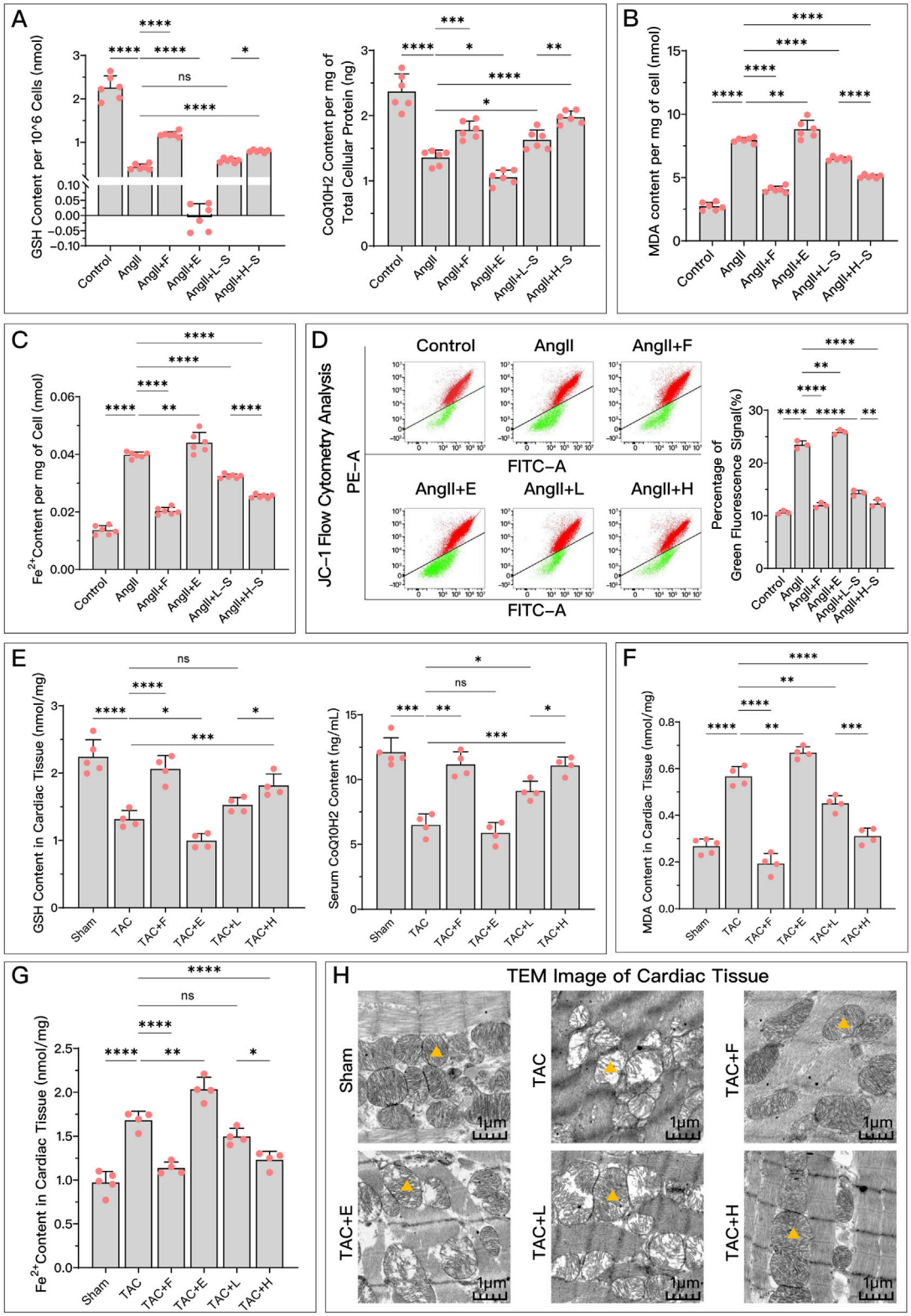


FIGURE 3
HDC effectively inhibits ferroptosis in HF. **(A)** Levels of antioxidants GSH and CoQ10H2 in H9c2 cells of each group; **(B)** Extent of lipid peroxidation (MDA content) in H9c2 cells of each group; **(C)** Levels of Fe^{2+} in H9c2 cells of each group; **(D)** Flow cytometry plots showing red and green fluorescence intensities after JC-1 staining of H9c2 cells from each group, and quantitative analysis of the proportion of green fluorescence signal; **(E)** GSH levels in myocardial tissue homogenates and serum CoQ10H2 levels in SD rats from each group; **(F)** MDA content in myocardial tissue homogenates of SD rats from each group; **(G)** Levels of Fe^{2+} in myocardial tissues of SD rats from each group; **(H)** TEM images of myocardial tissue from each group, with ▲ indicating one of the mitochondria in the image. $p^{ns} \geq 0.05$, $p^{*} < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$, $p^{****} < 0.0001$. ● represents an individual sample data point. HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; HF, Heart failure; AngII, Angiotensin II; F, Ferrostatin-1; E, Erastin; L-S, Low
(*Continued*)

FIGURE 3 (Continued)
Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; H-S, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; TAC, Transverse Aortic Constriction; L, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; H, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; GSH, Reduced Glutathione; CoQ10H2, Reduced Coenzyme Q10; MDA, Malondialdehyde; PE-A, Phycoerythrin Area; FITC-A, Fluorescein Isothiocyanate Area.

2.13 Masson's trichrome staining

For tissue preparation, The ventricle was divided into three sections along the longitudinal axis of the heart, namely, upper, middle, and lower. Approximately 2 mm thick myocardial tissue was obtained from the middle section. This tissue sample was then fixed in 4% paraformaldehyde at ten times its volume. The fixed tissue was embedded in paraffin wax, and sections of 5 μm thickness were prepared using a microtome. masson's trichrome staining was performed using a masson's trichrome stain kit (G1340, Solarbio, China). Additionally, anhydrous ethanol, xylene, a constant temperature oven, glycerol gelatin sealing tablets, and cover slips were prepared. Following the instructions provided in the masson's trichrome stain kit. The prepared slides were observed under a upright optical microscope (E100, Nikon, Japan) for pathological analysis and imaging. The left ventricular section was divided into four parts (upper, lower, left, right), and one image (×20) was randomly selected from each part for fibrosis area quantification. Quantitative analysis of the fibrosis area was performed using ImageJ software (version 1.53t, National Institutes of Health, United States), and the average value of these four measurements was used to represent the fibrosis level for that sample. The same procedure was applied to all samples within the same group, and the average of these individual sample values was calculated to represent the fibrosis level for the entire group. This quantitative fibrosis data was then used to select representative images that accurately reflect the fibrosis extent, allowing for more intuitive visualization of fibrosis severity.

2.14 Detection of mitochondrial membrane potential in cells

Mitochondrial membrane potential was assessed using JC-1 staining and flow cytometry analysis. Post-cultivation, H9c2 cells were harvested into tubes, and a pre-prepared JC-1 staining solution (C2006, Beyotime, China) was added to each tube. The cells were then incubated at 37°C for 30 min. This was followed by centrifugation and resuspension of the cells in phosphate buffered saline (PBS). After a second round of centrifugation to pellet the cells, the precipitate was resuspended in 1 mL of PBS to reconstitute a single-cell suspension. Cell concentration was adjusted to approximately 1*10̈6 cells/mL based on cell counting and the addition of varying volumes of PBS. Analysis was performed using a CytoFLEX S flow cytometer (Beckman Coulter, United States). The fluorescein isothiocyanate (FITC) channel detected green fluorescence of JC-1 monomers, while the phycoerythrin (PE) channel detected red fluorescence of JC-1 aggregates. The degree of reduction in mitochondrial membrane potential was quantified using the formula: Green Fluorescence/(Red Fluorescence + Green Fluorescence).

2.15 Transmission electron microscopy (TEM) analysis

Transmission electron microscopy is used to examine the morphological structure of rat cardiac mitochondria. In brief, Myocardial tissue samples (approximately 2–3 mm in length, 1 mm in diameter) were excised from rat hearts' apical region and fixed in electron microscopy fixative (G1102, Servicebio, China) for 24 h. After fixation, tissues were rinsed thrice with 0.1 M PB for 15 min each. Next, samples were incubated in 1% osmium tetroxide in 0.1 M PB for 2 h, followed by three rinses in 0.1 M PB. Dehydration was done in graded ethanol series (30%-100%) and two immersions in 100% acetone. Infiltration was performed with acetone and EPON812 epoxy resin, followed by embedding in EPON812 epoxy resin. Ultra-thin sections (80 nm) were prepared using an ultramicrotome (PT-PC, RMC, United States) and stained with uranyl acetate and lead citrate. The mitochondrial ultrastructure in myocardial tissue was observed under a transmission electron microscope (HT7800, HITACHI, Japan).

2.16 Western blotting (WB)

After cultivation, H9c2 cells were lysed using lysis buffer. The supernatant, representing the cellular protein, was collected post-centrifugation. Total protein concentration was determined using a BCA assay. After quantification, 1/4 volume of ×5 loading buffer was added to the remaining protein samples, followed by boiling for 5 min to prepare for WB loading. Unused samples were stored at −80°C for future use.

Cardiac muscle tissue was harvested from the same region of each rat heart, homogenized, lysed, and then centrifuged to collect the supernatant, following the same procedure as for cell samples.

The WB process was conducted according to the Bio-Rad company protein blotting guide (Supplementary Material 2), with specific reagents and parameters as follows: The gel concentration was 5% stacking gel +12.5% separating gel. The electrophoresis conditions are as follows: constant voltage of 80 V for the stacking gel and constant voltage of 120 V for the resolving gel. The semi-dry transfer conditions are as follows: GPX4 transferred at 20 V for 10 min, while GAPDH, FSP1, and DHODH transferred at 25 V for 15 min. Antibodies (GPX4 diluted 1:1,000, FSP1 1:5,000, DHODH 1:2000, GAPDH 1:2000) were incubated overnight at 4°C. The horseradish peroxidase-conjugated secondary antibodies were diluted 1,000 times. For DHODH and FSP1, imaging of one

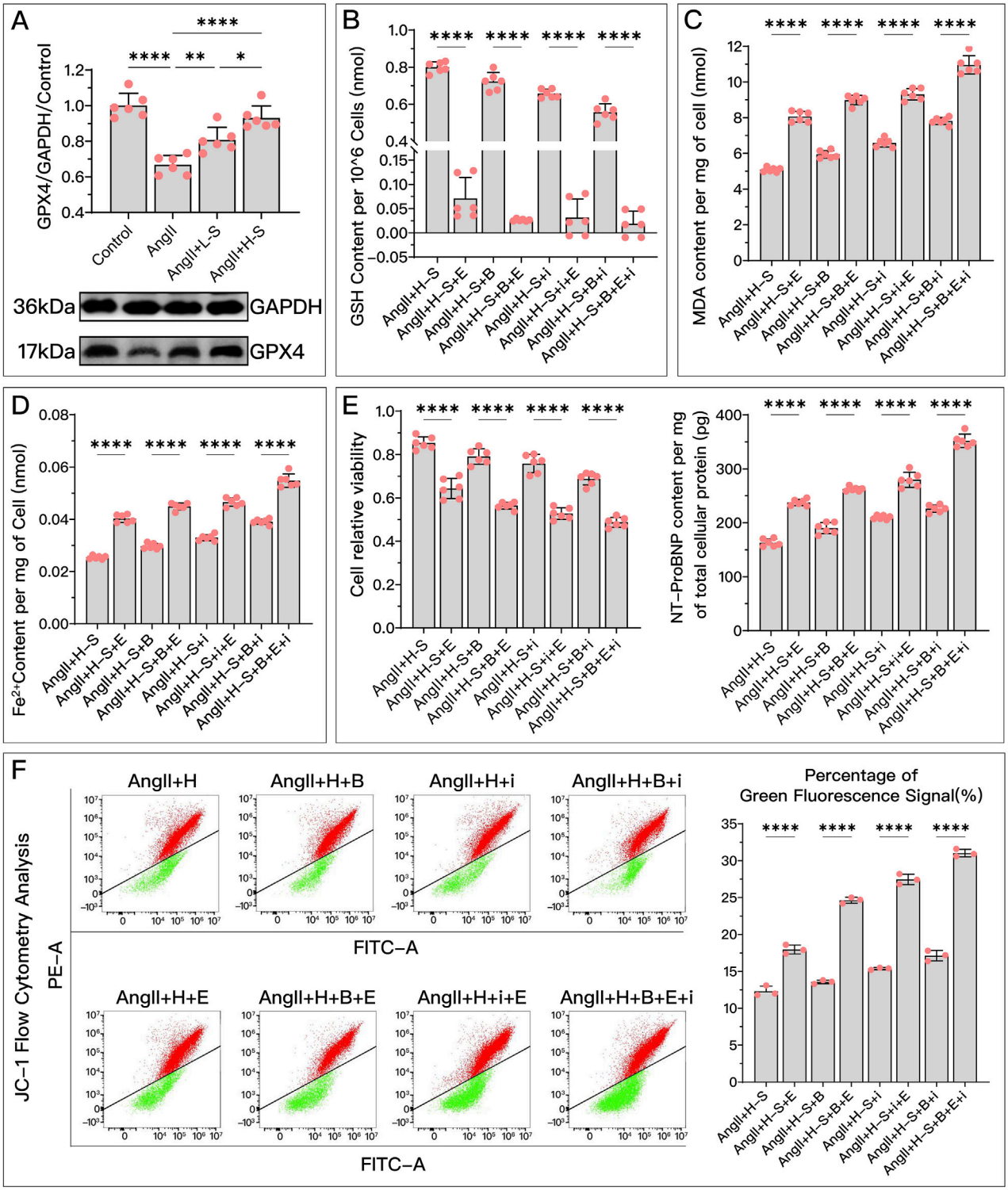


FIGURE 4
HDC ameliorates H9c2 cell dysfunction by inhibiting ferroptosis through the elevation of GPX4 levels. **(A)** Western blotting analysis of GPX4 levels in H9c2 cells from various groups to evaluate the effect of AngII and various doses of HDC on GPX4 content. **(B–F)** All panels represent the conditions of H9c2 cells under HDC intervention, assessing the effects of GPX4 inhibition and non-inhibition in varying FSP1 and DHODH states. **(B–E)** Measurements in H9c2 cells include GSH levels, MDA content, Fe^{2+} levels, cell viability, and NT-proBNP levels. **(F)** Flow cytometry images of H9c2 cells post JC-1 staining and quantitative analysis of the proportion of green fluorescence signal in flow cytometry. $p^* < 0.05$, $p^{**} < 0.01$, $p^{****} < 0.0001$. ● represents an individual sample data point. HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; GPX4, Glutathione Peroxidase 4; GAPDH, Glyceraldehyde 3-Phosphate Dehydrogenase; AngII, Angiotensin II; L-S, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; H-S, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; GSH, Reduced Glutathione; FSP1, Ferroptosis Suppressor Protein 1; DHODH, Dihydroorotate Dehydrogenase; E, Erastin; B, Brequinar; i, Inhibitor of FSP1; MDA, Malondialdehyde; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; PE-A, Phycoerythrin Area; FITC-A, Fluorescein Isothiocyanate Area.

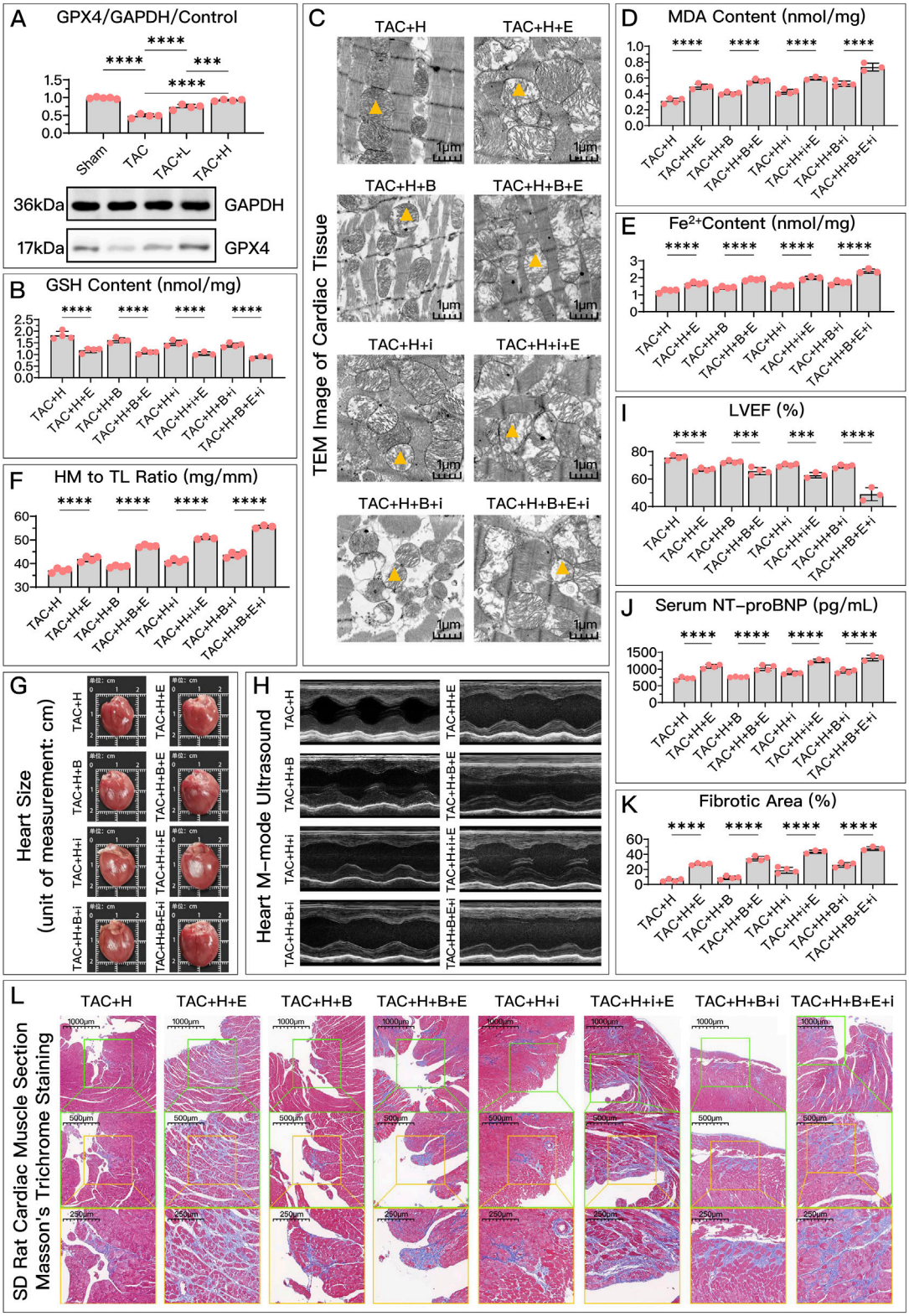


FIGURE 5
HDC improves HF by inhibiting ferroptosis via an increase in GPX4 levels. **(A)** Western blotting analysis of GPX4 levels in the myocardium from SD rats of various groups to evaluate the impact of HDC on GPX4 content. **(B–L)** All panels depict the effects of GPX4 inhibition and non-inhibition under HDC treatment in rats with various FSP1 and DHODH states. **(B–E, J)** In HF rats, measurements include myocardial GSH levels, mitochondrial morphology (TEM images, ▲ indicates one of the mitochondria), MDA levels, Fe^{2+} content, and serum NT-proBNP levels. **(F, G)** The heart mass to tibia length ratio and gross cardiac images in HF rats. **(H, I)** M-mode echocardiography images of the left ventricle adjacent to the sternum and quantitative analysis of LVEF in HF rats. **(L)** Masson's trichrome staining of myocardial tissue in HF rats (×50, ×100, ×200 magnifications), with blue staining indicating collagen deposition, suggestive of myocardial fibrosis. **(K)** Quantitative analysis of fibrotic area based on Masson's trichrome staining. $p^{***} < 0.001$, $p^{****} < 0.0001$. ●
(*Continued*)

FIGURE 5 (Continued)
represents an individual sample data point. HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; HF, Heart failure; GPX4, Glutathione Peroxidase 4; GAPDH, Glyceraldehyde 3-Phosphate Dehydrogenase; TAC, Transverse Aortic Constriction; L, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; H, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; FSP1, Ferroptosis Suppressor Protein 1; DHODH, Dihydroorotate Dehydrogenase; GSH, Reduced Glutathione; E, Erastin; B, Brequinar; i, Inhibitor of FSP1; TEM, Transmission Electron Microscopy; MDA, Malondialdehyde; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; HM, Heart Mass; TL, Tibia Length; LVEF, Left Ventricular Ejection Fraction.

protein was done first, followed by antibody stripping on the NC membrane, re-blocking, incubation with the other antibody, and re-imaging. When performing whole-membrane development, it is also necessary to develop one protein at a time, followed by antibody stripping. Then, the membrane is re-blocked and incubated with another antibody, developed again, and this process is repeated until all target proteins on the membrane have been developed.

2.17 Statistical analysis

In this study, data are reported as the mean ± SD (standard deviation) of multiple sample data, with each experiment being repeated three times to ensure reproducibility. Statistical analysis was conducted using GraphPad Prism 9.0 (GraphPad Software, Inc., United States) and SPSS 26.0 software (IBM, United States). For comparisons between two independent groups, an unpaired two-tailed Student's t-test was used. When assessing differences among multiple groups, one-way analysis of variance (ANOVA) was utilized. A p-value of less than 0.05 was considered statistically significant.

3 Results

3.1 HDC metabolite identification and molecular docking

The main metabolites of the HDC decoction and the drug-containing serum were detected using liquid chromatography-mass spectrometry (Figure 1A; Supplementary Table 3). These primarily include various flavonoids, isoflavones, terpenes, alkaloids, saponins, phenols, amino acids, steroids, and their derivatives. Notably, this includes the main metabolites of AM, such as Astragalus polysaccharides, Astragaloside I-IV, and Cycloastragenol, as well as the key metabolites of SM, including Salvianolic acid A, B, C, Tanshinone I, and Tanshinone IIA. The Venn diagram (Figure 1B) indicates that 3,215 metabolites found in the low-dose drug-containing serum were also present in the decoction. Of these, 563 metabolites not found in the control group's serum suggest direct entry into the blood from the HDC decoction, including major active metabolites of AM and SM. Additionally, 56 metabolites, not present in both the decoction and the control serum, might be metabolites produced in the body from HDC. In the high-dose drug-containing serum, 3,233 metabolites were identified as same as those in the decoction, with 571 metabolites directly entering the blood from the decoction, including major active metabolites of AM and SM, and another 58 metabolites possibly being metabolites produced in the body from HDC.

Using MRM under different parameter settings, chromatographic fingerprinting analysis was performed for AS-IV and SAB in both standard samples and the HDC-H. Three different detection conditions were applied, ensuring a complete and comprehensive characterization of the main active metabolites in the decoction from multiple perspectives. The MRM chromatograms for both the standard samples and the decoction samples are shown in Supplementary Figure 2. The results clearly demonstrate the separation and quantification of AS-IV and SAB, effectively illustrating the content characteristics of these two key metabolites in the decoction, ensuring a thorough evaluation of the chemical composition of the preparation.

Figure 1C shows the lowest binding energy modes of AS-IV and SAB when docked with DHODH, FSP1, and GPX4, respectively. The binding energies were all less than −7 kcal/mol, indicating that the active metabolites of AM and SM can stably bind to the key regulatory proteins of ferroptosis.

3.2 Optimal concentration and induction time of AngII in H9c2 cells

The relative viability of H9c2 cells induced by different concentrations of AngII for varying durations was assessed using the cell counting kit-8, and changes in cell size were observed. There was no significant toxicity at any concentration after 24–48 h of culture, but apparent cell death was observed after 72 h (Supplementary Figure 1A). Concentrations of 4μM, 8μM, and 12 μM AngII caused hypertrophy in H9c2 cells within 24–72 h of culture, while 2 μM required at least 48 h, and 1 μM required at least 72 h (Supplementary Figures 1B, C). Ultimately, this study selected 4 μM AngII concentration with 48 h of induction as the optimal conditions for subsequent experiments.

3.3 Reduction in cardiac function and subsequent grouping in TAC model rats

Eight weeks post-TAC surgery in SD rats, 55 rats survived (6 in sham group and 49 in TAC model group). Standard M-mode echocardiography was used for assessment, revealing significantly reduced left ventricular contractility in the TAC model group compared to the Sham group (Supplementary Figure 1D). Measurement of LVEF further confirmed a significant reduction in cardiac function in SD rats 8 weeks post-TAC surgery (Supplementary Figure 1E). After modeling, the rats were stratified and randomized into groups based on LVEF. Comparison of LVEF and NT-proBNP among groups revealed that the LVEF in the Sham group was significantly higher than in any other group, and the NT-proBNP was significantly

10.3389/fphar.2024.1447546

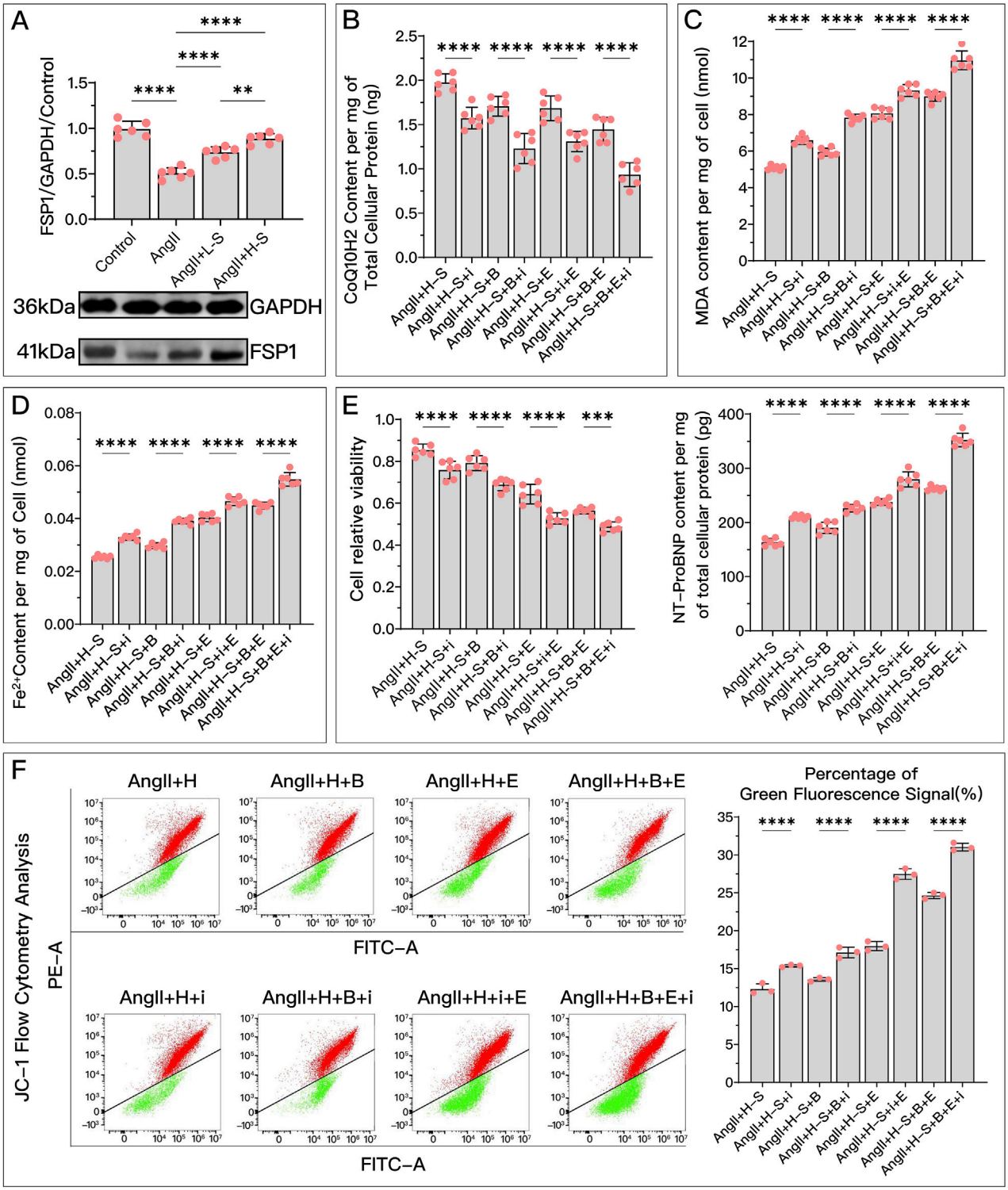


FIGURE 6
HDC ameliorates H9c2 cell dysfunction by increasing FSP1 levels to inhibit ferroptosis. **(A)** Western blotting analysis of FSP1 levels in H9c2 cells from various groups to assess the effects of AngII and different doses of HDC on FSP1 content. **(B–F)** These panels represent the HDC-treated cells, examining the effects of FSP1 inhibition and non-inhibition under varying GPX4 and DHODH states. **(B–E)** Measurements in H9c2 cells include CoQ10H2 levels, MDA levels, Fe^{2+} content, cell viability, and NT-proBNP levels. **(F)** Flow cytometry images of H9c2 cells post JC-1 staining and quantitative analysis of the green fluorescence signal proportion in flow cytometry charts. $p^{**} < 0.01$, $p^{****} < 0.0001$. ● represents an individual sample data point. HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; FSP1, Ferroptosis Suppressor Protein 1; GAPDH, Glyceraldehyde 3-Phosphate Dehydrogenase; AngII, Angiotensin II; L-S, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; H-S, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; CoQ10H2, Reduced Coenzyme Q10; GPX4, Glutathione Peroxidase 4; DHODH, Dihydroorotate Dehydrogenase; i, Inhibitor of FSP1; B, Brequinar; E, Erastin; MDA, Malondialdehyde; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; PE-A, Phycoerythrin Area; FITC-A, Fluorescein Isothiocyanate Area.

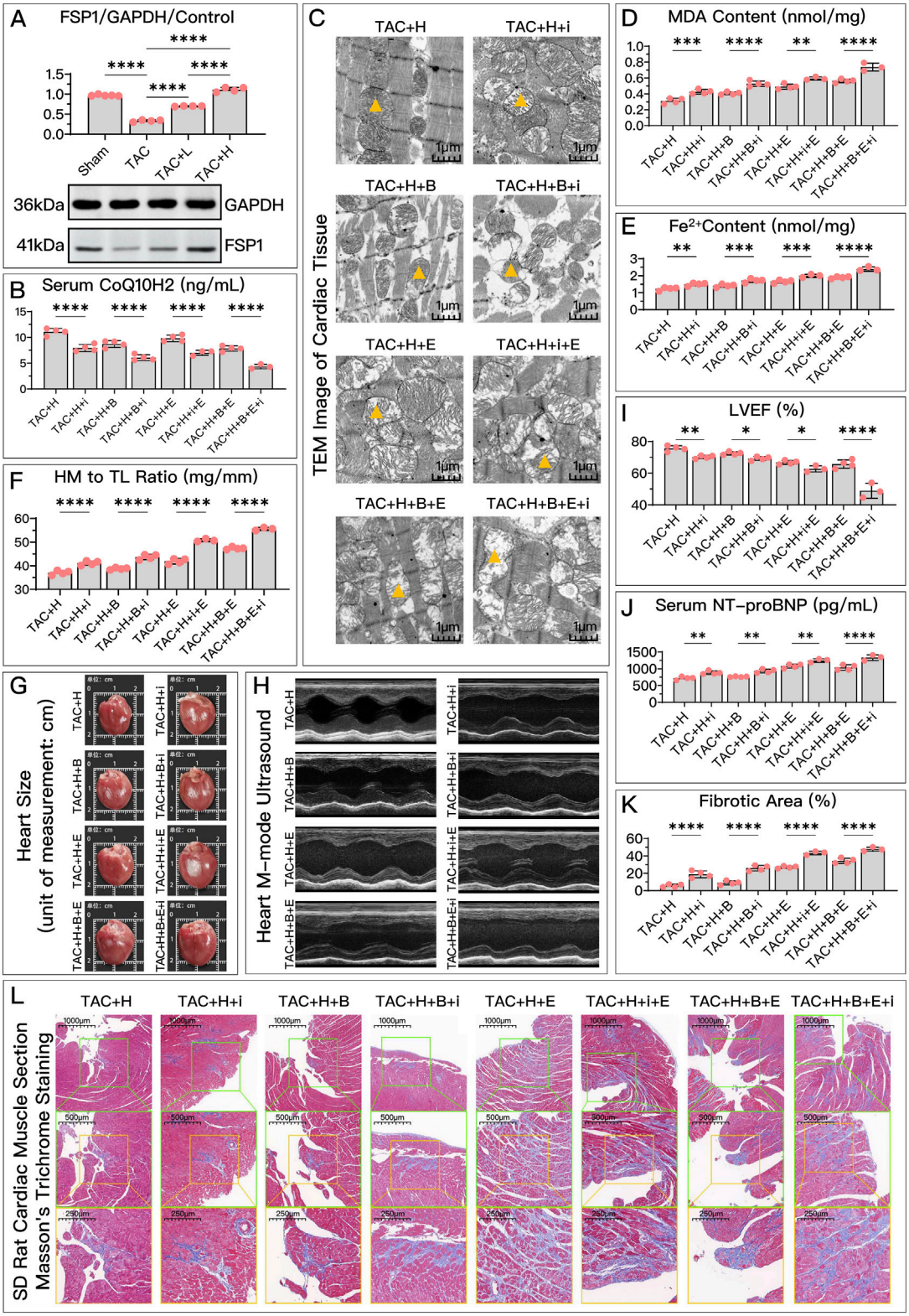


FIGURE 7
HDC improves HF by inhibiting ferroptosis through the elevation of FSP1 levels. **(A)** Western blotting analysis of FSP1 levels in the myocardium from SD rats of various groups to evaluate the impact of HDC on FSP1 content. **(B–K)** Analysis in HDC-treated rats under various GPX4 and DHODH states, assessing the effects of both FSP1 inhibition and non-inhibition. **(B–E, J)** Measurements in HF rats include myocardial CoQ10H2 levels, mitochondrial morphology (TEM images, ▲ indicates one of the mitochondria), MDA levels, Fe^{2+} content, and serum NT-proBNP levels. **(F, G)** Heart mass to tibia length ratio and gross cardiac images in HF rats. **(H, I)** Parasternal long-axis M-mode echocardiography images of the left ventricle and quantitative
(*Continued*)

FIGURE 7 (Continued)
analysis of LVEF in rats. **(L)** Masson's trichrome staining of myocardial tissue in HF rats (×50, ×100, ×200 magnifications), where blue staining indicates collagen deposition, indicative of myocardial fibrosis. **(K)** Quantitative analysis of the fibrotic area based on Masson's trichrome staining. $p^* < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$, $p^{****} < 0.0001$. ● represents an individual sample data point. HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; HF, Heart failure; FSP1, Ferroptosis Suppressor Protein 1; GAPDH, Glyceraldehyde 3-Phosphate Dehydrogenase; TAC, Transverse Aortic Constriction; L, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; H, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; CoQ10H2, Reduced Coenzyme Q10; GPX4, Glutathione Peroxidase 4; DHODH, Dihydroorotate Dehydrogenase; i, Inhibitor of FSP1; B, Brequinar; E, Erastin; TEM, Transmission Electron Microscopy; MDA, Malondialdehyde; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; HM, Heart Mass; TL, Tibia Length; LVEF, Left Ventricular Ejection Fraction.

lower, while there was no inter-group difference in LVEF and NT-proBNP in all TAC model groups (Supplementary Figure 1F), indicating a consistent level of HF across groups.

3.4 HDC effectively inhibits increased ferroptosis associated with worsening HF

As shown in Figure 2, both in animal and cell experiments, the model group exhibited significant HF compared to the control or Sham group. This was manifested by decreased cell viability, increased NT-ProBNP, enlarged heart, reduced LVEF, and aggravated myocardial fibrosis. When the ferroptosis inducer Era was used, HF symptoms further worsened, while the ferroptosis inhibitor Fer-1 alleviated these symptoms. Different concentrations of HDC had similar effects to the ferroptosis inhibitor Fer-1, with high-dose HDC generally being more effective than low-dose HDC, although there was no significant difference in improving LVEF between the doses. This validated that increased ferroptosis is a key factor in HF, and inhibiting ferroptosis can improve HF. Additionally, HDC effectively improved HF.

As shown in Figure 3, compared to the control or Sham group, the model group exhibited significant changes in ferroptosis-related indicators. Antiferroptosis-related GSH and CoQ10H2 levels (Figures 3A, E) were significantly reduced, while ferroptosis-related lipid peroxidation indicator MDA (Figures 3B, F) and F^{2+} (Figures 3C, G) increased. Additionally, mitochondrial membrane potential significantly decreased (Figure 3D), and mitochondria became smaller with cristae fusion loss (Figure 3H), which are signs of ferroptosis. Compared to the model group, different concentrations of serum containing HDC generally improved these ferroptosis-related indicators, confirming that HDC, like the positive control drug Fer-1, has an inhibitory regulatory effect on ferroptosis. The regulatory effect of high-dose HDC was better than that of low-dose HDC, mainly because low-dose serum could not effectively restore GSH levels or significantly reduce iron deposition in myocardial tissue.

3.5 HDC's GPX4-dependent role in improving HF via ferroptosis inhibition

Both *in vivo* and *in vitro*, HDC significantly restored the decreased GPX4 levels after HF, with the effect of high-dose HDC being more pronounced (Figures 4A, 5A).

Compared to the high-dose HDC group, the inhibition of GPX4 pathway using Era significantly weakened the ferroptosis inhibition and HF protection effects of HDC. To explore whether different states of FSP1 and DHODH affect the mediation of HDC's protective effects by GPX4, we compared the HF protection effects of HDC when GPX4 was inhibited, under the conditions of FSP1 inhibition with iFSP1 and/or DHODH inhibition with BQR. The results showed that, compared to the groups without Era, blocking the GPX4 pathway led to reduced GSH (Figures 4B, 5B), increased MDA (Figures 4C, 5D), elevated Fe^{2+} (Figures 4D, 5E), increased mitochondrial membrane potential (Figure 4F), decreased cell viability and elevated NT-proBNP (Figures 4E, 5J), enlarged heart (Figure 5G), increased heart mass (Figure 5F), reduced LVEF (Figures 5H, I), and increased myocardial fibrosis (Figures 5K, L), with aggravated mitochondrial shrinking and cristae fusion (Figure 5C). This confirmed the important role of GPX4 in HDC's inhibition of ferroptosis and improvement of HF.

3.6 HDC's FSP1-dependent role in improving HF via ferroptosis inhibition

Both *in vivo* and *in vitro* experiments, as shown in Figures 6A, 7A, the FSP1 levels in the model group were significantly reduced compared to the control or sham group. After treatment with HDC, FSP1 levels were restored, with the high-dose HDC group showing more significant effects than the low-dose HDC group.

Compared to the high-dose HDC group, inhibiting FSP1 with iFSP1 significantly weakened the inhibitory effects of HDC on ferroptosis and its protective effects on HF. Under the conditions of Era inhibiting the GPX4 pathway and/or BQR inhibiting DHODH, the protective effects of HDC were still significantly suppressed due to the inactivation of FSP1. Specifically, after inhibiting FSP1, there was a significant decrease in CoQ10H2 (Figures 6B, 7B), an increase in MDA (Figures 6C, 7D), an increase in Fe^{2+} (Figures 6D, 7E), a greater reduction in mitochondrial membrane potential (Figure 6F), decreased cell viability, and elevated NT-proBNP (Figures 6E, 7J), increased myocardial hypertrophy (Figures 7F, G), reduced LVEF (Figures 7H, I), increased myocardial fibrosis (Figures 7K, L), and aggravated mitochondrial shrinkage and cristae fusion (Figure 7C). Both cell and animal experiments indicate that HDC can restore FSP1 levels after HF, and FSP1 plays an important role in the inhibition of ferroptosis and the improvement of HF by HDC.

3.7 HDC's conditionally DHODH-dependent role in improving HF via ferroptosis inhibition

As shown in Figures 8A, 9A, compared to the control group, the DHODH content in the model group significantly decreased. HDC

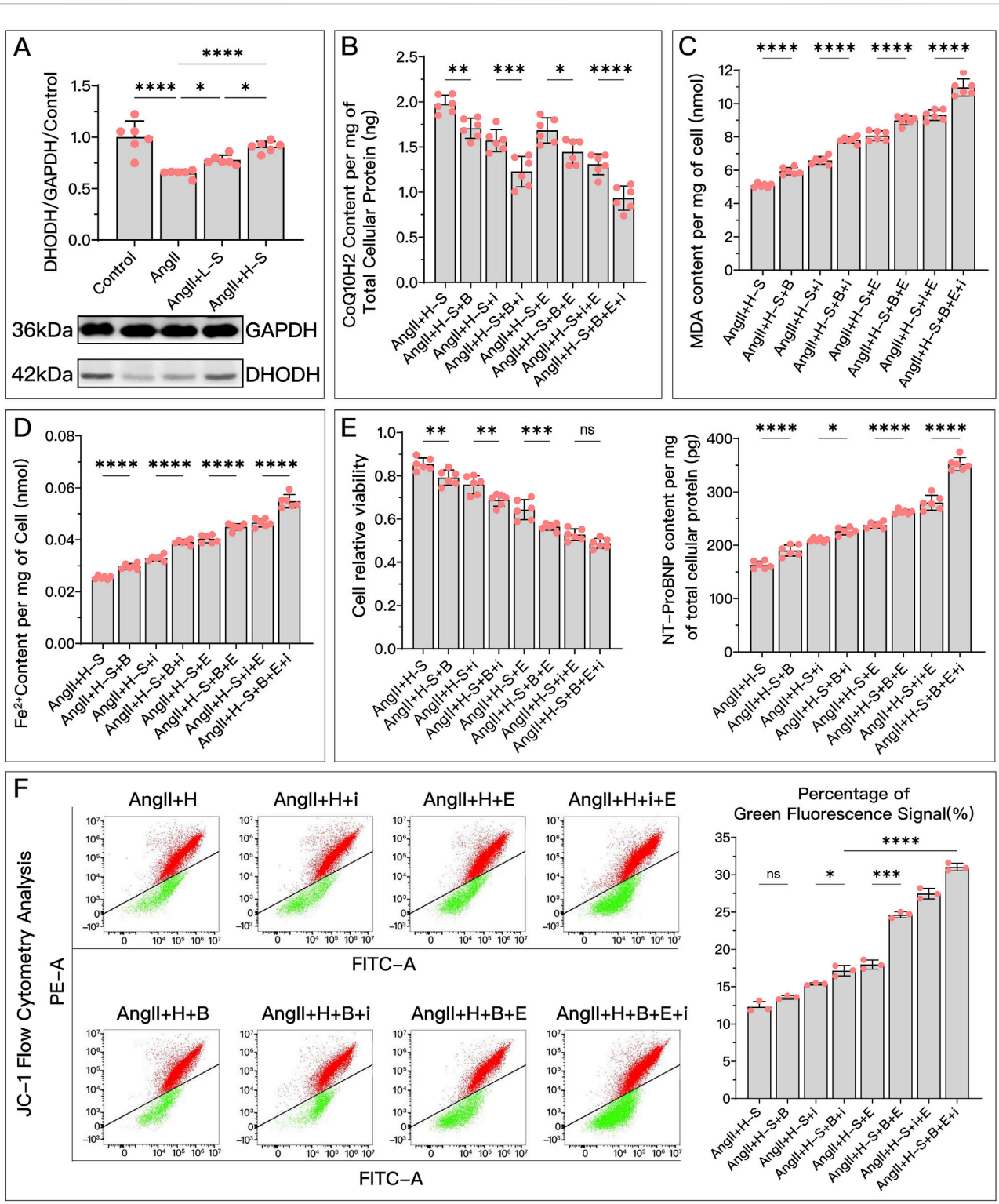


FIGURE 8
HDC ameliorates H9c2 cell dysfunction by inhibiting ferroptosis through the elevation of DHODH levels. **(A)** "Western blotting analysis of DHODH levels in H9c2 cells from various groups, assessing the effects of AngII and different doses of HDC on DHODH content. **(B–F)** Experiments conducted on cells treated with HDC, evaluating the impact of inhibiting or not inhibiting DHODH under different GPX4 and iFSP1 states. **(B–E)** Measurements in H9c2 cells include CoQ10H2 levels, MDA levels, Fe^{2+} content, cell viability, and NT-proBNP levels. Flow cytometry images of H9c2 cells post JC-1 staining and quantitative analysis of the green fluorescence signal proportion in flow cytometry charts. $p^{ns} \geq 0.05$, $p^{*} < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$, $p^{****} < 0.0001$. ● represents an individual sample data point. HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; DHODH, Dihydroorotate Dehydrogenase; WB, Western blotting; GAPDH, Glyceraldehyde 3-Phosphate Dehydrogenase; AngII, Angiotensin II; L-S, Low Dosage
(*Continued*)

FIGURE 8 (Continued)
Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; H-S, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; CoQ10H2, Reduced Coenzyme Q10; GPX4, Glutathione Peroxidase 4; FSP1, Ferroptosis Suppressor Protein 1; B, Brequinar; i, Inhibitor of FSP1; E, Erastin; MDA, Malondialdehyde; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; PE-A, Phycoerythrin Area; FITC-A, Fluorescein Isothiocyanate Area.

treatment effectively restored DHODH levels, but the restorative effect of low-dose HDC on DHODH was not apparent in *in vivo* experiments. Inhibiting DHODH with BQR did not always weaken all of HDC's protective effects.

Specifically, in *in vitro* experiments, HDC's ability to increase CoQ10H2 (Figure 8B), reduce MDA (Figure 8C), lower Fe^{2+} (Figure 8D), and decrease NT-proBNP (Figure 8E) was diminished due to DHODH inhibition. In *in vivo* experiments, HDC's effects in increasing CoQ10H2 (Figure 9B), reducing MDA (Figure 9D), and improving mitochondrial morphology and structure (Figure 9C) were also inhibited. Regardless of whether the FSP1 and GPX4 pathways were blocked, HDC's protective effects mentioned above were weakened due to DHODH inhibition.

As shown in Figure 8E, in terms of improving cell viability, DHODH inhibition could weaken HDC's effect, but this inhibitory effect was no longer obvious when both the FSP1 and GPX4 pathways were blocked. As shown in Figure 8F, inhibiting DHODH alone could not weaken HDC's effect on restoring mitochondrial membrane potential, but when the FSP1 and/or GPX4 pathways were blocked, HDC's effect on restoring mitochondrial membrane potential was weakened due to DHODH inhibition.

In *in vivo* experiments, DHODH's mediating ability in HDC's inhibition of ferroptosis and improvement of HF was more unstable. DHODH inactivation alone did not weaken HDC's effects in reducing Fe^{2+} (Figure 9E), alleviating myocardial hypertrophy (Figures 9F, G), reducing myocardial fibrosis (Figures 9K, L), and improving LVEF (Figures 9H, I). However, DHODH's role was not completely ineffective. As shown in Figures 9F, G, K, L, when the FSP1 and/or GPX4 pathways were blocked, compared to when DHODH was not inhibited, inhibiting DHODH aggravated myocardial hypertrophy and myocardial fibrosis. As shown in Figure 9E, once the GPX4 pathway was blocked, inhibiting DHODH weakened HDC's effect on reducing Fe^{2+}. As shown in Figure 9I, when both the GPX4 and FSP1 pathways were blocked, DHODH's mediating role in HDC's improvement of ejection fraction became apparent. As shown in Figure 9J, in terms of reducing serum NT-proBNP, regardless of the status of the FSP1 and GPX4 pathways, DHODH inhibition did not weaken HDC's effect on lowering NT-proBNP.

Overall, DHODH's mediating role in HDC's inhibition of ferroptosis and subsequent improvement of HF seems to depend on the status of the pathways involving GPX4 and FSP1. It is possible that DHODH's mediating role is weaker and is overshadowed by the strong mediating roles of GPX4 and FSP1. Therefore, we hope to further compare the strengths of the mediating roles of these three key proteins.

3.8 In the process of HDC improving HF by inhibiting ferroptosis, the mediating strengths of GPX4, FSP1, and DHODH vary

As shown in Figures 10, 11, each group uses two of the three protein inhibitors to retain the function of one pathway, minimizing the influence of the other two pathways. By comparing the three groups, we can determine the relative strength of the three key proteins in mediating HDC's inhibition of ferroptosis and improvement of HF.

In *in vitro* experiments, Figures 10A, C–E show that in terms of HDC increasing GSH, decreasing MDA, reducing Fe^{2+}, and improving cell viability, the mediating effect of GPX4 (AngII + H + B + i) is stronger than that of FSP1 (AngII + H + B + E) and DHODH (AngII + H + i + E), while the mediating ability of FSP1 and DHODH is similar. Figure 10B shows that there is no significant difference among the three proteins in mediating HDC's ability to increase COQ10H2. Figure 10E shows that GPX4 has a stronger mediating effect on HDC's improvement of cell viability compared to FSP1. GPX4 has a stronger mediating effect on HDC's reduction of NT-proBNP (Figure 10F) and restoration of mitochondrial membrane potential (Figure 10G) compared to FSP1, and FSP1 is stronger than DHODH.

In vivo experiments, Figures 11A, D, G show that in terms of HDC increasing GSH, reducing Fe^{2+}, and improving mitochondrial structure, the mediating effect of GPX4 (TAC + H + B + i) is stronger than that of FSP1 (TAC + H + B + E) and DHODH (TAC + H + i + E), while the mediating ability of FSP1 and DHODH is similar. In mediating HDC's increase of CoQ10H2 (Figure 11B), FSP1's mediating effect is stronger than that of GPX4, and DHODH's mediating effect is intermediate, but there is no statistical difference between GPX4 and FSP1. As shown in Figures 11C, E, H, GPX4 has a stronger mediating effect on HDC's reduction of MDA and improvement of LVEF compared to DHODH, with FSP1's effect being intermediate but not significantly different from GPX4 and DHODH. Figures 11F, I, K, L show that in mediating HDC's improvement of myocardial hypertrophy and myocardial fibrosis, GPX4 is stronger than FSP1 and DHODH, and FSP1 is stronger than DHODH. As shown in Figure 11J, in mediating HDC's reduction of serum NT-proBNP, DHODH is weaker than GPX4 and FSP1, with no significant difference between GPX4 and FSP1.

4 Discussion

Currently, HF remains a serious global health challenge. One of the fundamental pathological mechanisms of HF is myocardial remodeling, which, once established, is difficult to reverse (Zhang

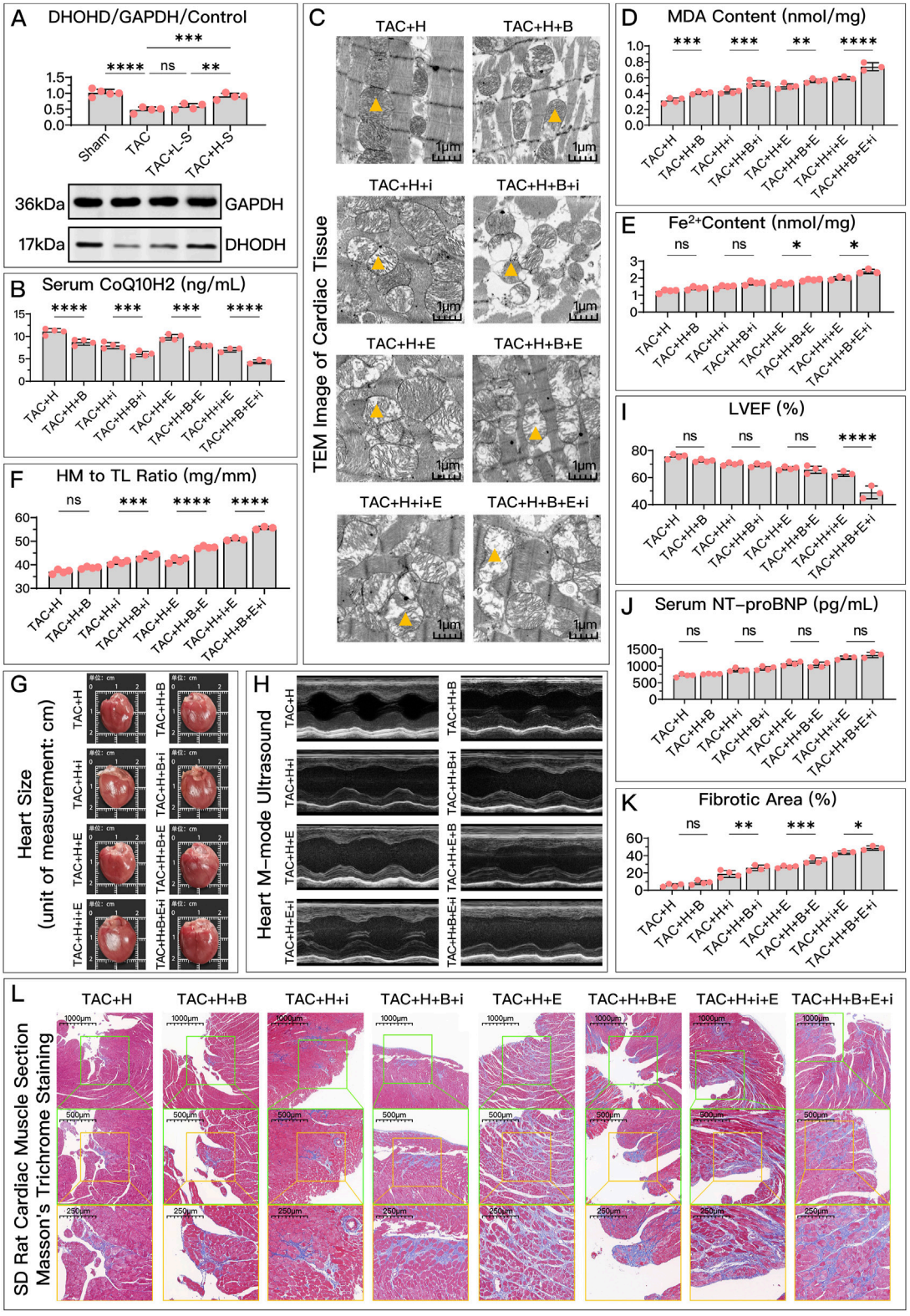


FIGURE 9
HDC mitigates HF by inhibiting ferroptosis through the elevation of DHODH levels. **(A)** Western blotting analysis of DHODH levels in the myocardium from SD rats of various groups to assess the impact of HDC on DHODH content. **(B–L)** Analysis in HDC-treated rats under different GPX4 and FSP1 states, evaluating the effects of DHODH inhibition and non-inhibition. **(B–E, J)** Measurements in HF rats include myocardial CoQ10H2 levels, mitochondrial morphology (TEM images, ▲ indicates one of the mitochondria), MDA levels, Fe^{2+} content, and serum NT-proBNP levels. **(F, G)** Heart mass to tibia length ratio and gross cardiac images in HF rats. **(H, I)** Parasternal long-axis M-mode echocardiography images of the left ventricle and quantitative analysis of LVEF in rats. **(L)** Masson's trichrome staining of myocardial tissue in HF rats (×50, ×100, ×200 magnifications), where blue staining indicates collagen deposition, suggestive of myocardial fibrosis. **(K)** Quantitative analysis of the

(*Continued*)

FIGURE 9 (Continued)
fibrotic area based on Masson's trichrome staining. $p^{ns} \geq 0.05$, $p^{*} < 0.05$, $p^{**} < 0.01$, $p^{***} < 0.001$, $p^{****} < 0.0001$. ● represents an individual sample data point. HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; HF, Heart failure; DHODH, Dihydroorotate Dehydrogenase; GAPDH, Glyceraldehyde 3-Phosphate Dehydrogenase; TAC, Transverse Aortic Constriction; L, Low Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; H, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; CoQ10H2, Reduced Coenzyme Q10; GPX4, Glutathione Peroxidase 4; FSP1, Ferroptosis Suppressor Protein 1; B, Brequinar; i, Inhibitor of FSP1; E, Erastin; TEM, Transmission Electron Microscopy; MDA, Malondialdehyde; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; HM, Heart Mass; TL, Tibia Length; LVEF, Left Ventricular Ejection Fraction.

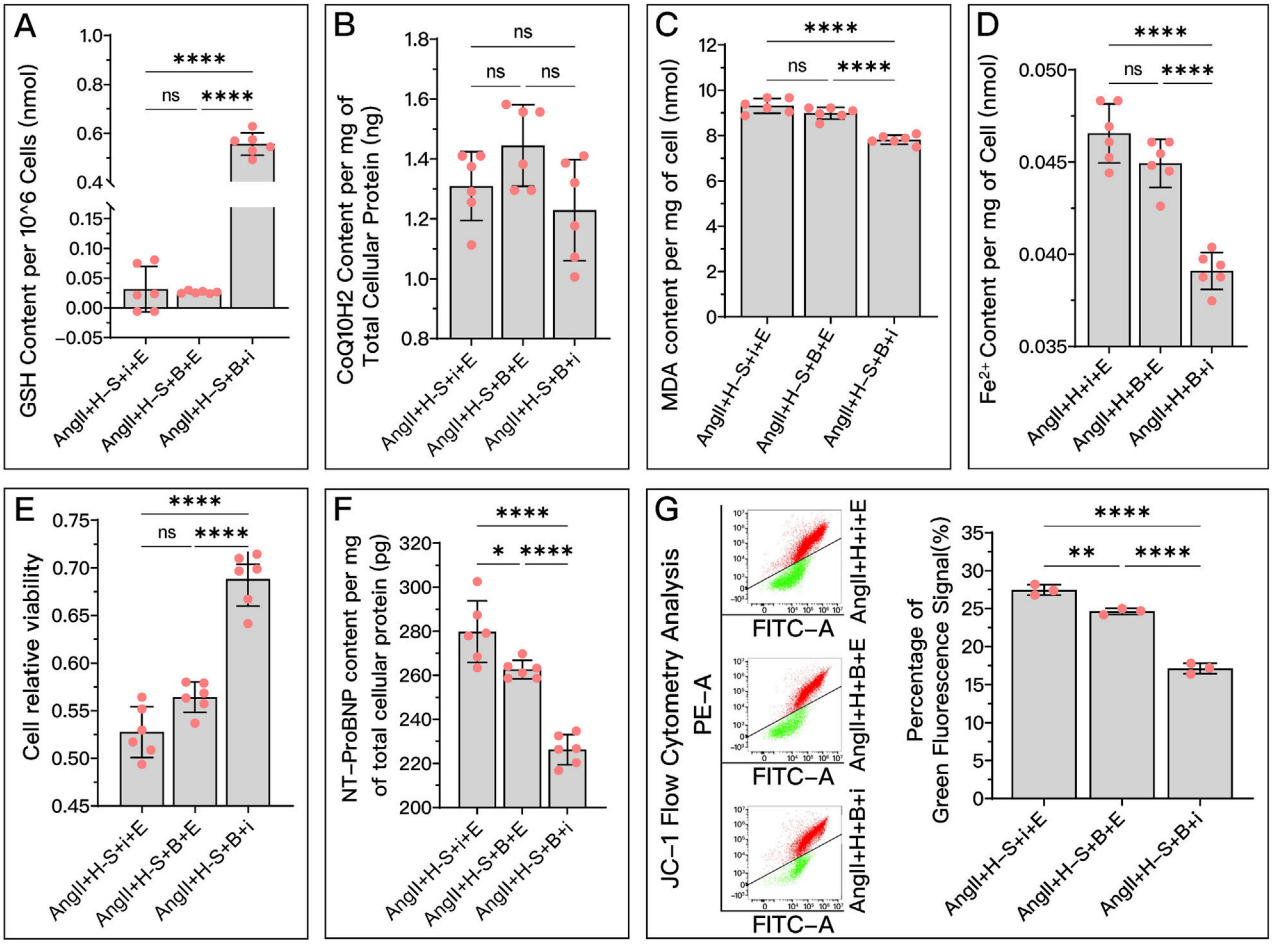


FIGURE 10
Comparative analysis of the effectiveness of GPX4, FSP1, and DHODH in mediating HDC's improvement of H9c2 cell dysfunction. In this figure, H9c2 cells are divided into three groups: the AngII + H-S + i + E group, primarily mediated by DHODH for HDC's protective effect; the AngII + H-S + B + E group, primarily mediated by FSP1 for HDC's protective effect; and the AngII + H-S + B + i group, primarily mediated by GPX4 for HDC's protective effect. **(A–F)** Measurements in these three groups of H9c2 cells include GSH levels, CoQ10H2 levels, MDA levels, Fe^{2+} content, cell viability, and NT-proBNP levels. **(G)** Flow cytometry images post JC-1 staining of the H9c2 cells and the quantitative analysis of the proportion of green fluorescence signal. $p^{ns} \geq 0.05$, $p^{*} < 0.05$, $p^{**} < 0.01$, $p^{****} < 0.0001$. ● represents an individual sample data point. GPX4, Glutathione Peroxidase 4; FSP1, Ferroptosis Suppressor Protein 1; DHODH, Dihydroorotate Dehydrogenase; HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; AngII, Angiotensin II; H-S, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Medication-Containing Serum; i (iFSP1), Inhibitor of FSP1; E, Erastin; B, Brequinar; GSH, Reduced Glutathione; CoQ10H2, Reduced Coenzyme Q10; MDA, Malondialdehyde; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; PE-A, Phycoerythrin Area; FITC-A, Fluorescein Isothiocyanate Area.

et al., 2022). Therefore, despite continuous innovation and progress in treatment methods, HF remains an unresolved medical challenge. Even with ongoing treatment, patients with HF often experience recurrent episodes and worsening of the condition (Greene et al., 2023). This underscores the importance of early prevention and treatment. TCM offers many approaches that have been proven effective in treating HF. Combining Western medicine with TCM in the prevention of HF shows great promise. TCM can complement and enhance Western treatment modalities, potentially increasing efficacy and reducing side effects. AM and SM, traditional Chinese botanical drugs frequently used in cardiovascular diseases, are often employed together in complex formulas as primary and auxiliary agents in the treatment of HF (Project Group of Traditional Chinese Medicine Guideline for Diagnosis and Treatment of Chronic Heart

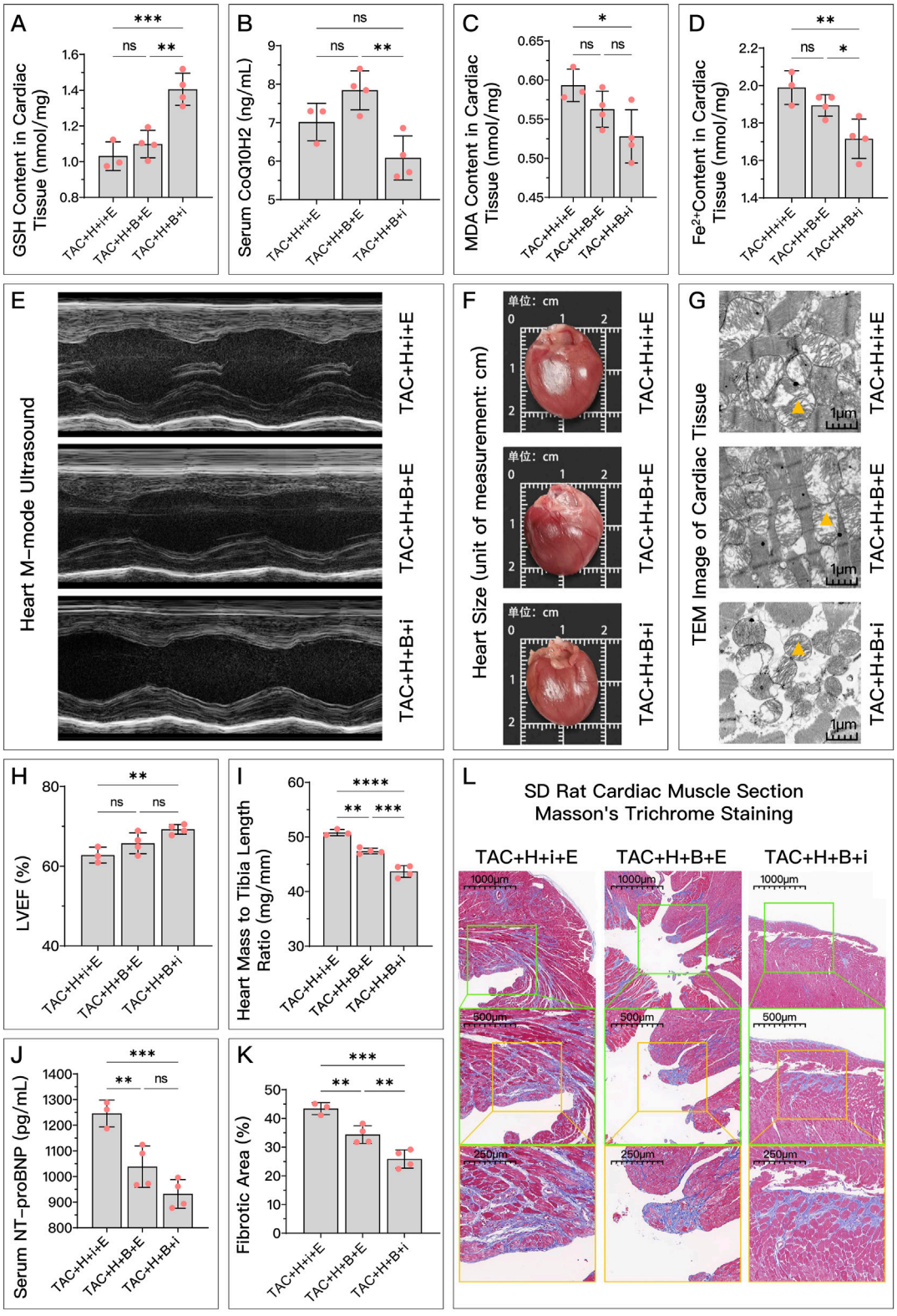


FIGURE 11
Comparative analysis of the effectiveness of GPX4, FSP1, and DHODH in mediating HDC's amelioration of HF in SD rats. In this study, SD rats with HF were divided into three groups: TAC + H + i + E group, primarily mediated by DHODH for HDC's protective effect; TAC + H + B + E group, primarily mediated by FSP1 for HDC's protective effect; and TAC + H + B + I group, primarily mediated by GPX4 for HDC's protective effect. **(A–D)** Measurements in these groups include myocardial GSH levels, MDA levels, Fe^{2+} content, and serum CoQ10H2 levels in SD rats. **(E)** Parasternal long-axis echocardiography images of the left ventricle in these groups of SD rats. **(H)** Quantitative calculation of LVEF based on echocardiography images. **(F)** Gross cardiac images of the rats in these groups. **(I)** Heart mass to tibia length ratio in these groups of SD rats. **(G)** TEM images of myocardial tissue, ▲ indicates one of the mitochondria. **(J)** Serum NT-proBNP levels in these groups of SD rats. (L) Masson's trichrome staining of myocardial tissue

(*Continued*)

FIGURE 11 (Continued)
(×50, ×100, ×200 magnifications), where blue staining indicates collagen deposition, suggestive of myocardial fibrosis. **(K)** Quantitative analysis of the fibrotic area ratio based on Masson's trichrome staining images. $p^{ns} \geq 0.05$, $p^{*} < 0.05$, $p^{**} < 0.01$, $p^{****} < 0.0001$. ● represents an individual sample data point. GPX4, Glutathione Peroxidase 4; FSP1, Ferroptosis Suppressor Protein 1; DHODH, Dihydroorotate Dehydrogenase; HDC, Astragalus mongholicus and Salvia miltiorrhiza Combination; HF, Heart failure; TAC, Transverse Aortic Constriction; H, High Dosage Astragalus mongholicus and Salvia miltiorrhiza Decoction; i, Inhibitor of FSP1; E, Erastin; B, Brequinar; GSH, Reduced Glutathione; CoQ10H2, Reduced Coenzyme Q10; MDA, Malondialdehyde; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-terminal pro B-type Natriuretic Peptide; PE-A, Phycoerythrin Area; FITC-A, Fluorescein Isothiocyanate Area.

Failure and China Association of Chinese Medicine, 2023). Ferroptosis, a mode of programmed cell death discovered over a decade ago, characterized by iron-dependent lipid peroxidation and structural changes like mitochondrial membrane thickeningexp, volume reduction, and typical cristae fusion and loss (Dixon et al., 2012), has been established as a significant contributor to the progression of HF. Research indicates that inhibiting ferroptosis can halt the advancement of HF (Zhang et al., 2022; Sahebkar et al., 2023). The effectiveness of simplifying complex traditional formulas to just HDC in preventing and treating HF, and the underlying mechanisms of such an approach, however, remain to be elucidated.

In our study, we further explored the impact of HDC on HF, particularly in the context of heart function decline caused by overload stress. Through *in vitro* and *in vivo* experiments, we found that HDC significantly ameliorates heart function decline induced by overload stress. This includes improving cell viability, reducing NT-proBNP, alleviating myocardial remodeling, and maintaining ejection fraction. By comparing with ferroptosis inducers and inhibitors, we further clarified the key role of ferroptosis in the process of overload-induced HF and confirmed for the first time the important role of inhibiting ferroptosis in HDC's improvement of HF. Specifically, HDC, like Fer-1, can increase the levels of GSH and CoQ10H2, thereby enhancing antioxidant capacity, inhibiting lipid peroxidation (reducing MDA), restoring mitochondrial membrane potential, and improving mitochondrial morphology and function, ultimately inhibiting ferroptosis. The improvement of these ferroptosis markers is synchronous with the alleviation of HF. When ferroptosis was induced using Era, an exacerbation of HF was observed. Previous studies (Sui et al., 2020; Lin et al., 2021; Li et al., 2023) support our findings, as they found that AM and SM, particularly their active metabolites such as Astragaloside and Tanshinone IIA, improve myocardial hypertrophy, myocardial fibrosis, and ejection fraction through multiple pathways. Additionally, pharmacological interventions that reduce ferroptosis have been shown to inhibit the progression of HF (Chen et al., 2023).

The Nrf2/cGPX4/GSH pathway, FSP1/CoQ10/NADPH pathway, mitochondrial DHODH/CoQ10 pathway, and mGPX4/GSH pathway are the primary regulatory pathways of ferroptosis (Mao et al., 2021), highlighting GPX4, FSP1, and DHODH as key proteins in regulating ferroptosis. These proteins primarily inhibit ferroptosis by suppressing lipid peroxidation (Mao et al., 2021). Our study uncovers for the first time that HDC can inhibit ferroptosis and improve HF by simultaneously regulating the GPX4/GSH, FSP1/CoQ10, and DHODH/CoQ10 pathways. In both *in vitro* and *in vivo* experiments, HDC increased the levels of these key proteins and downstream antioxidants (GSH, CoQ10H2). When we inhibited these key regulatory proteins, the inhibitory effects of HDC on ferroptosis and the improvement in HF were reduced to varying degrees. This further confirms that these pathways are important targets for HDC in inhibiting ferroptosis. However, in *in vivo* experiments, the effect of HDC on reducing NT-proBNP levels through the regulation of DHODH was not observed, which is inconsistent with our cellular experiment results. This discrepancy may be due to several factors: firstly, DHODH's role in regulating ferroptosis is relatively minor, as evidenced by our findings in result 3.8; secondly, HDC has numerous targets for improving HF (Wang et al., 2018; Nandi et al., 2020), not limited to ferroptosis regulated by GPX4, FSP1, and DHODH; and lastly, the systemic metabolic regulation in animals is more complex. These three factors combined lead to the insufficient inhibition of DHODH-mediated ferroptosis to significantly improve NT-proBNP levels post-HF, or the effects may be too weak to observed.

While exploring the key targets of HDC in inhibiting ferroptosis and improving HF, we found that inhibiting DHODH alone in certain situations did not weaken the protective effects of HDC. However, this does not necessarily mean that DHODH does not mediate the protective effects of HDC; it is possible that the effects of GPX4 and FSP1 are stronger, overshadowing the role of DHODH. Therefore, we used a combination of inhibitors for the three key proteins to assess their interactions during HDC treatment of HF. We found that during HDC treatment of HF, the pathways involving GPX4 and the pathways involving FSP1 were not affected by the other pathways. However, the role of DHODH in mediating the effects of HDC on inhibiting ferroptosis and improving HF was somewhat influenced by GPX4 and FSP1, or its effects were overshadowed by those of GPX4 and FSP1, particularly in inhibiting iron accumulation, improving mitochondrial membrane potential, reducing myocardial fibrosis, and improving LVEF. Once FSP1 and GPX4 were inhibited, the mediating effect of DHODH on the protective effects of HDC became apparent. Therefore, conclusions drawn from studies focusing solely on DHODH should be approached with caution. Studies (Mishima et al., 2023) have shown that DHODH plays a minor role in tumor cell ferroptosis, which questions its role as a ferroptosis-regulating protein and supports our findings.

We retained the function of one pathway by inhibiting two of the pathways involving GPX4, FSP1, and DHODH. This innovative approach allowed us to compare the relative strengths of these three key proteins in the process of HDC treatment for HF. Overall, GPX4 was found to mediate the protective effects of HDC most strongly, followed by FSP1, with DHODH having the weakest mediating effect. Previous research has generally considered

GPX4 to be the most crucial regulatory protein in ferroptosis (Liu M. et al., 2022). However, in terms of increasing CoQ10H2 levels (Figures 10B, 11B), the effect of FSP1 was more significant than that of GPX4, while the effect of DHODH was comparable to both GPX4 and FSP1. This is because FSP1 and DHODH are the primary upstream proteins regulating CoQ10H2, rather than GPX4 (Liu et al., 2023). These findings provide valuable insights for personalized clinical treatments.

HF patients are often elderly and have multiple coexisting conditions. Currently or in the future, many drugs used to treat cancer, rheumatoid diseases, or other conditions work by promoting ferroptosis. For HF patients who also suffer from these conditions, it is crucial to choose treatments that minimize adverse impacts on HF. For example, if these ferroptosis-promoting drugs have comparable therapeutic effects, it would be prudent to consider using drugs that inhibit DHODH to achieve the desired outcomes. From our research, inhibiting DHODH has the least impact on HF treatment compared to inhibiting GPX4 or FSP1. Therefore, using DHODH inhibitors could potentially offer a dual benefit: treating cancer or rheumatoid diseases while minimally compromising HF management. This strategic approach underscores the importance of understanding the interplay between ferroptosis pathways and disease states, allowing for more nuanced and effective individualized treatment plans.

Due to budget constraints, conditional knockout models were not feasible, and specific inhibitors were used to block the pathways. While this approach may result in incomplete pathway inhibition, it does not affect the validity of the final conclusions. We strictly controlled variables during the study and ensured that there was only a single variable difference between the comparison groups. This ensured the high accuracy of the comparison results and conclusions. Additionally, in our experiments comparing the strengths of regulatory proteins, we used HDC treatment of HF as a unified background. This limits our results and conclusions to this specific context and cannot be extrapolated to other cells, diseases, or drug treatments. Moreover, since the decoction used in this study was prepared manually, we were only able to ensure the specific component content for this particular experiment. As the quality of botanical drugs is influenced by factors such as environment and processing methods, we cannot completely guarantee the consistency of the decoction. However, this more closely simulates the real-world situation of human consumption of herbal decoctions and does not affect the results and conclusions of this study. In future research, industrially processed decoctions could be used to ensure greater consistency and reproducibility. We also hope to conduct more direct comparisons of the relative strengths of ferroptosis regulatory proteins in future experiments, not limited to specific diseases or drug interventions, to better generalize the results.

5 Conclusion

This study unveils a novel mechanism where the combined use of the traditional Chinese botanical drugs AM and SM inhibits ferroptosis, thereby exerting cardioprotective effects. We demonstrate that this combination of botanical drugs mitigates lipid peroxidation, iron accumulation, and mitochondrial dysfunction by simultaneously modulating three key regulatory pathways: GPX4/GSH, FSP1/CoQ10, and DHODH/CoQ10, thereby inhibiting ferroptosis. Concomitantly, HF markers such as myocardial hypertrophy, fibrosis, reduced ejection fraction, and elevated NT-proBNP levels are also improved. Comparative analysis indicates that HDC primarily inhibit iron dysregulation through GPX4, followed by FSP1, while the role of DHODH is comparatively minor. The effectiveness of DHODH is contingent upon the functional status of the other pathways. Overall, these findings emphasize ferroptosis inhibition as a key mechanism underlying the therapeutic efficacy of HDC in treating HF, providing new molecular evidence for the benefits of this combination of traditional botanical drugs. Additionally, this study suggests future research directions, recommending that DHODH may not be a suitable primary target in studies aimed at inhibiting ferroptosis to improve HF.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://zenodo.org/records/14418483.

Ethics statement

The animal study was approved by the Ethics Committee of the Jiangsu Province Academy of Traditional Chinese Medicine. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

QX: Conceptualization, Investigation, Methodology, Visualization, Writing–original draft. XL: Formal Analysis, Investigation, Visualization, Writing–original draft. ZC: Formal Analysis, Investigation, Visualization, Writing–original draft. CG: Investigation, Methodology, Writing–review and editing. PL: Methodology, Writing–review and editing. SZ: Writing–review and editing. XW: Writing–review and editing, Conceptualization, Methodology, Supervision. JS: Conceptualization, Methodology, Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Natural Science Foundation of China (Nos 82374203, 81973766, 82274469, and 82204995) and the National Administration of Traditional Chinese Medicine by Construction Project of Inheritance Studio of National Famous Traditional Chinese Medicine Experts [(2022) No. 75].

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1447546/full#supplementary-material

References

Carley, A. N., Maurya, S. K., Fasano, M., Wang, Y., Selzman, C. H., Drakos, S. G., et al. (2021). Short-chain fatty acids outpace ketone oxidation in the failing heart. *Circulation* 143, 1797–1808. doi:10.1161/CIRCULATIONAHA.120.052671

Chen, X., Xu, S., Zhao, C., and Liu, B. (2019). Role of TLR4/NADPH oxidase 4 pathway in promoting cell death through autophagy and ferroptosis during heart failure. *Biochem. Biophys. Res. Commun.* 516, 37–43. doi:10.1016/j.bbrc.2019.06.015

Chen, Y., Guo, X., Zeng, Y., Mo, X., Hong, S., He, H., et al. (2023). Ferroptosis contributes to catecholamine-induced cardiotoxicity and pathological remodeling. *Free Radic. Biol. Med.* 207, 227–238. doi:10.1016/j.freeradbiomed.2023.07.025

Chen, Y. J., Chung, T. Y., Chen, W. Y., Chen, C. Y., Lee, M. R., Jinn, T. R., et al. (2014). Detecting metabolites of different transition metal-lithospermate B complexes after intravenous injection in rats. *Acta Pharmacol. Sin.* 35, 937–944. doi:10.1038/aps.2014.37

Cheon, Y. I., Kim, J. M., Shin, S. C., Kim, H. S., Lee, J. C., Park, G. C., et al. (2023). Effect of deferoxamine and ferrostatin-1 on salivary gland dysfunction in ovariectomized rats. *Aging* 15, 2418–2432. doi:10.18632/aging.204641

Cheu, J. W., Lee, D., Li, Q., Goh, C. C., Bao, M. H., Yuen, V. W., et al. (2023). Ferroptosis suppressor protein 1 inhibition promotes tumor ferroptosis and anti-tumor immune responses in liver cancer. *Cell Mol. Gastroenterol. Hepatol.* 16, 133–159. doi:10.1016/j.jcmgh.2023.03.001

Chinese Pharmacopeia Commission (2020). *Pharmacopoeia of the People's Republic of China (2020 edition Part One)*. Beijing: China Medical Science Press.

Chung, T. Y., Lin, N. H., Li, Y. C., Chen, T. Y., Kuo, P. C., Chen, W. Y., et al. (2018). Detection of lithospermate B in rat plasma at the nanogram level by LC/MS in multi reaction monitoring mode. *J. Food Drug Anal.* 26, 353–361. doi:10.1016/j.jfda.2017.06.003

Ding, F., Wang, Y., and Zhang, Y. (2021). Research advances in pharmacological effect and clinical application of active ingredients of Danshen. *China J. Traditional Chin. Med. Pharm.* 36, 659–662.

Dixon, S. J., Lemberg, K. M., Lamprecht, M. R., Skouta, R., Zaitsev, E. M., Gleason, C. E., et al. (2012). Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell* 149, 1060–1072. doi:10.1016/j.cell.2012.03.042

Foroutan, F., Rayner, D. G., Ross, H. J., Ehler, T., Srivastava, A., Shin, S., et al. (2023). Global comparison of readmission rates for patients with heart failure. *J. Am. Coll. Cardiol.* 82, 430–444. doi:10.1016/j.jacc.2023.05.040

Garrott, K., Dyavanapalli, J., Cauley, E., Dwyer, M. K., Kuzmiak-Glancy, S., Wang, X., et al. (2017). Chronic activation of hypothalamic oxytocin neurons improves cardiac function during left ventricular hypertrophy-induced heart failure. *Cardiovasc. Res.* 113, 1318–1328. doi:10.1093/cvr/cvx084

Greene, S. J., Bauersachs, J., Brugts, J. J., Ezekowitz, J. A., Lam, C., Lund, L. H., et al. (2023). Worsening heart failure: nomenclature, epidemiology, and future directions: JACC review topic of the week. *J. Am. Coll. Cardiol.* 81, 413–424. doi:10.1016/j.jacc.2022.11.023

Guo, H. X., Wang, J. R., Peng, G. C., Li, P., and Zhu, M. J. (2022). A data mining-based study on medication rules of Chinese herbs to treat heart failure with preserved ejection fraction. *Chin. J. Integr. Med.* 28, 847–854. doi:10.1007/s11655-022-2892-5

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverria, J., Kulić, Ž., McGaw, L. J., et al. (2022). Best Practice in the chemical characterisation of extracts used in pharmacological and toxicological research-The ConPhyMP-Guidelines. *Front. Pharmacol.* 13, 953205. doi:10.3389/fphar.2022.953205

Horwath, M. C., Bell-Horwath, T. R., Lescano, V., Krishnan, K., Merino, E. J., and Deepe, G. S., Jr. (2017). Antifungal activity of the lipophilic antioxidant ferrostatin-1. *Chembiochem* 18, 2069–2078. doi:10.1002/cbic.201700105

Hou, K., Shen, J., Yan, J., Zhai, C., Zhang, J., Pan, J. A., et al. (2021). Loss of TRIM21 alleviates cardiotoxicity by suppressing ferroptosis induced by the chemotherapeutic agent doxorubicin. *EBioMedicine* 69, 103456. doi:10.1016/j.ebiom.2021.103456

Li, S., Lei, Z., Yang, X., Zhao, M., Hou, Y., Wang, D., et al. (2022). Propofol protects myocardium from ischemia/reperfusion injury by inhibiting ferroptosis through the AKT/p53 signaling pathway. *Front. Pharmacol.* 13, 841410. doi:10.3389/fphar.2022.841410

Li, Y., Sun, X. L., Qiu, H., Qin, J., Li, C. S., Yu, X. Z., et al. (2021). Long-term outcomes and independent predictors of mortality in patients presenting to emergency departments with acute heart failure in Beijing: a multicenter cohort study with a 5-year follow-up. *Chin. Med. J.* 134, 1803–1811. doi:10.1097/CM9.0000000000001617

Li, Z., Liu, M., Chen, M., Luo, G., Wu, J., Mazhar, M., et al. (2023). Clinical effect of Danshen decoction in patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* 18, e0284877. doi:10.1371/journal.pone.0284877

Liang, Y., Xia, L., Lu, S., Yang, S., Guo, S., Shan, X., et al. (2023). A new mechanism of therapeutic effect of stachydrine on heart failure by inhibiting myocardial ferroptosis. *Eur. J. Pharmacol.* 954, 175881. doi:10.1016/j.ejphar.2023.175881

Lin, S., Shi, Q., Ge, Z., Liu, Y., Cao, Y., Yang, Y., et al. (2021). Efficacy and safety of traditional Chinese medicine injections for heart failure with reduced ejection fraction: a bayesian network meta-analysis of randomized controlled trials. *Front. Pharmacol.* 12, 659707. doi:10.3389/fphar.2021.659707

Liu, B., Zhao, C., Li, H., Chen, X., Ding, Y., and Xu, S. (2018). Puerarin protects against heart failure induced by pressure overload through mitigation of ferroptosis. *Biochem. Biophys. Res. Commun.* 497, 233–240. doi:10.1016/j.bbrc.2018.02.061

Liu, J., Lane, S., Lall, R., Russo, M., Farrell, L., Debreli Coskun, M., et al. (2022). Circulating hemopexin modulates anthracycline cardiac toxicity in patients and in mice. *Sci. Adv.* 8, eadc9245. doi:10.1126/sciadv.adc9245

Liu, M., Kong, X. Y., Yao, Y., Wang, X. A., Yang, W., Wu, H., et al. (2022). The critical role and molecular mechanisms of ferroptosis in antioxidant systems: a narrative review. *Ann. Transl. Med.* 10, 368. doi:10.21037/atm-21-6942

Liu, Y., Lu, S., Wu, L. L., Yang, L., Yang, L., and Wang, J. (2023). The diversified role of mitochondria in ferroptosis in cancer. *Cell Death Dis.* 14, 519. doi:10.1038/s41419-023-06045-y

Liu, Z. H., Liu, H. B., and Wang, J. (2018). Astragaloside IV protects against the pathological cardiac hypertrophy in mice. *Biomed. Pharmacother.* 97, 1468–1478. doi:10.1016/j.biopha.2017.09.092

Ma, X., Yang, J., Ma, G., Zeng, W., Guo, J., and Ma, Y. (2022). Modernization of Chinese medicine Salviae Miltiorrhizae Radix et Rhizoma:a review. *China J. Chin. Materia Medica* 47, 5131–5139. doi:10.19540/j.cnki.cjcmm.20220808.101

Mao, C., Liu, X., Zhang, Y., Lei, G., Yan, Y., Lee, H., et al. (2021). DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. *Nature* 593, 586–590. doi:10.1038/s41586-021-03539-7

Mishima, E., Nakamura, T., Zheng, J., Zhang, W., Mourão, A., Sennhenn, P., et al. (2023). DHODH inhibitors sensitize to ferroptosis by FSP1 inhibition. *Nature* 619, E9–E18. doi:10.1038/s41586-023-06269-0

Nakamura, T., Hipp, C., Santos Dias Mourão, A., Borggräfe, J., Aldrovandi, M., Henkelmann, B., et al. (2023). Phase separation of FSP1 promotes ferroptosis. *Nature* 619, 371–377. doi:10.1038/s41586-023-06255-6

Nandi, S. S., Katsurada, K., Sharma, N. M., Anderson, D. R., Mahata, S. K., and Patel, K. P. (2020). MMP9 inhibition increases autophagic flux in chronic heart failure. *Am. J. Physiol. Heart Circ. Physiol.* 319, H1414–H1437. doi:10.1152/ajpheart.00032.2020

Owen, R. K., Lyons, J., Akbari, A., Guthrie, B., Agrawal, U., Alexander, D. C., et al. (2023). Effect on life expectancy of temporal sequence in a multimorbidity cluster of psychosis, diabetes, and congestive heart failure among 1·7 million individuals in Wales with 20-year follow-up: a retrospective cohort study using linked data. *Lancet Public Health* 8, e535–e545. doi:10.1016/S2468-2667(23)00098-1

Project Group of Traditional Chinese Medicine Guideline for Diagnosis and Treatment of Chronic Heart Failure and China Association of Chinese Medicine

(2023). Traditional Chinese medicine Diagnosis and treatment guidelines for chronic heart failure. *J. TCM* 64 (07), 743–756. doi:10.13288/j.11-2166/r.2023.07.016

Sahebkar, A., Foroutan, Z., Katsiki, N., Jamialahmadi, T., and Mantzoros, C. S. (2023). Ferroptosis, a new pathogenetic mechanism in cardiometabolic diseases and cancer: is there a role for statin therapy. *Metab. Clin. Exp.* 146, 155659. doi:10.1016/j.metabol.2023.155659

Sui, Y. B., Zhang, K. K., Ren, Y. K., Liu, L., and Liu, Y. (2020). The role of Nrf2 in astragaloside IV-mediated antioxidative protection on heart failure. *Pharm. Biol.* 58, 1192–1198. doi:10.1080/13880209.2020.1849319

Sykes, D. B., Kfoury, Y. S., Mercier, F. E., Wawer, M. J., Law, J. M., Haynes, M. K., et al. (2016). Inhibition of dihydroorotate dehydrogenase overcomes differentiation blockade in acute myeloid leukemia. *Cell* 167, 171–186. doi:10.1016/j.cell.2016.08.057

Wang, J., Deng, B., Liu, Q., Huang, Y., Chen, W., Li, J., et al. (2020). Pyroptosis and ferroptosis induced by mixed lineage kinase 3 (MLK3) signaling in cardiomyocytes are essential for myocardial fibrosis in response to pressure overload. *Cell Death Dis.* 11, 574. doi:10.1038/s41419-020-02777-3

Wang, J., Wu, M. L., Cao, S. P., Cai, H., Zhao, Z. M., and Song, Y. H. (2018). Cycloastragenol ameliorates experimental heart damage in rats by promoting myocardial autophagy via inhibition of AKT1-RPS6KB1 signaling. *Biomed. Pharmacother.* 107, 1074–1081. doi:10.1016/j.biopha.2018.08.016

Wei, J. J., Zhu, Z. W., Peng, G. C., Yu, R., Zhang, Q., Hao, P. L., et al. (2022). Medication rule of traditional Chinese medicine for heart failure after myocardial infarction: based on data mining. *China J. Chin. materia medica* 47, 5654–5661. doi:10.19540/j.cnki.cjcmm.20220609.501

Wei, W., Wu, X., and Li, Y. (2020). *Experimental methodology of Pharmacology*. Beijing: People's Medical Publishing House.

Yuan, S. N., Wang, M. X., Han, J. L., Feng, C. Y., Wang, M., Wang, M., et al. (2023). Improved colonic inflammation by nervonic acid via inhibition of NF-κB signaling pathway of DSS-induced colitis mice. *Phytomedicine* 112, 154702. doi:10.1016/j.phymed.2023.154702

Zhang, L. L., Chen, G. H., Tang, R. J., Xiong, Y. Y., Pan, Q., Jiang, W. Y., et al. (2023). Levosimendan reverses cardiac malfunction and cardiomyocyte ferroptosis during heart failure with preserved ejection fraction via connexin 43 signaling activation. *Cardiovasc Drugs Ther.* 38, 705–718. doi:10.1007/s10557-023-07441-4

Zhang, R. H., Zhang, J. W., and Liu, L. (2021). The pharmacological effects and current situation of clinical application of Astragalus and its effective components. *Shaanxi J. Traditional Chin. Med.* 42 (08), 1138–1141+1146. doi:10.3969/j.issn.1000-7369.2021.08.037

Zhang, Z., Tang, J., Song, J., Xie, M., Liu, Y., Dong, Z., et al. (2022). Elabela alleviates ferroptosis, myocardial remodeling, fibrosis and heart dysfunction in hypertensive mice by modulating the IL-6/STAT3/GPX4 signaling. *Free Radic. Biol. Med.* 181, 130–142. doi:10.1016/j.freeradbiomed.2022.01.020

Zhou, Y., Chen, K., Lin, W. K., Liu, J., Kang, W., Zhang, Y., et al. (2023). Photo-enhanced synergistic induction of ferroptosis for anti-cancer immunotherapy. *Adv. Healthc. Mater* 12, e2300994. doi:10.1002/adhm.202300994

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 17 December 2024
DOI 10.3389/fphar.2024.1478558

OPEN ACCESS

EDITED BY
Kuo Gao,
Beijing University of Chinese Medicine, China

REVIEWED BY
Jiahong Wang,
Shenyang Pharmaceutical University, China
Mingjun Zhu,
First Affiliated Hospital of Henan University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Dazhuo Shi,
shidazhuo@126.com
Jie Zhang,
zhangjie_by@163.com

†These authors have contributed equally to this work

RECEIVED 10 August 2024
ACCEPTED 27 November 2024
PUBLISHED 17 December 2024

CITATION
Chen P, Zhang H, Gao Z, Shi D and Zhang J (2024) Efficacy and safety of salvianolate injection in treating acute myocardial infarction: a meta-analysis and systematic literature review.
Front. Pharmacol. 15:1478558.
doi: 10.3389/fphar.2024.1478558

Efficacy and safety of salvianolate injection in treating acute myocardial infarction: a meta-analysis and systematic literature review

Pengfei Chen[1,2†], He Zhang[1,2†], Zhuye Gao[1,2†], Dazhuo Shi[1,2*] and Jie Zhang[1,2*]

[1]Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Cardiovascular Diseases Center, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China

Purpose: Salvianolate for injection (SFI) is a widely used treatment for acute myocardial infarction (AMI). This study aims to assess the efficacy and safety of SFI in treating AMI by synthesizing evidence from published randomized controlled trials (RCTs).

Methods: Seven databases were searched for relevant RCTs published up to 1 July 2024. Two investigators independently conducted the literature searches, data extraction, and quality assessment. Subgroup and sensitivity analyses were performed to address potential heterogeneity. Data analyses were conducted using RevMan 5.4 software.

Result: Thirty RCTs with a total of 3,931 participants were included in the study and analyzed. The results revealed that SFI significantly reduced major adverse cardiac events (MACEs) (RR = 0.34, 95% CI: 0.24 to 0.49, $p < 0.05$). In addition, SFI lowered creatine kinase-MB (CK-MB) (MD = −5.65, 95% CI: −9.55 to −1.76, $p < 0.05$) and improved left ventricular ejection fraction (LVEF) (MD = 6.2, 95% CI: 4.82 to 7.57, $p < 0.05$). Further reductions were observed in C-reactive protein (CRP) (MD = −6.17, 95% CI: −8.11 to −4.23, $p < 0.05$), malondialdehyde (MDA) (MD = −1.95, 95% CI: −2.08 to −1.83, $p < 0.05$), and endothelin-1 (ET-1) (MD = −12.27, 95% CI: −17.13 to −7.40, $p < 0.05$). The incidence of adverse events did not significantly differ between the EG and CG [RR = 0.74, 95% CI: 0.42 to 1.33, $p = 0.32$].

Conclusion: This study suggests that SFI may be a promising alternative therapy for treating AMI without increasing the risk of adverse events. However, our findings may be limited by the quality of the existing studies. High-quality RCTs are needed to provide more robust evidence.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42024567279.

KEYWORDS

salvianolic acids, salvianolic acid B, acute myocardial infarction, randomized controlled trials, systematic review

Introduction

Acute myocardial infarction (AMI) is a critical cardiovascular condition characterized by the sudden obstruction of coronary arteries, typically resulting from atherosclerotic plaque rupture or thrombus formation, leading to myocardial cell necrosis (Reed et al., 2017). Globally, AMI is responsible for 9.14 million fatalities, constituting 49.2% of all cardiovascular disease (CVD)-related deaths (Nichols et al., 2014; Yeh et al., 2010). The immediate management of AMI prioritizes the rapid restoration of blood flow to the occluded coronary artery to achieve myocardial reperfusion, with percutaneous coronary intervention (PCI) being the preferred therapeutic approach (Gunnar et al., 1990; De Luca et al., 2008). Concurrently, a combination of antiplatelet agents, anticoagulants, vasodilators, and other supportive medications is administered to maintain myocardial function and mitigate further damage (Windecker et al., 2013; Levine et al., 2016; Puymirat et al., 2017; Valgimigli and Gragnano, 2020). Although these interventions effectively reduce myocardial injury in the acute phase, reperfusion injury may occur, potentially causing additional damage to cardiomyocytes during the restoration of blood flow (Puymirat et al., 2017). Moreover, current treatment strategies predominantly focus on acute management, inadequately addressing the long-term structural and functional recovery of the heart. Consequently, AMI patients continue to face elevated morbidity and mortality rates in the long term.

Danshen, scientifically known as Salvia miltiorrhiza Bunge, is a traditional Chinese medicinal botanical drug utilized in the treatment of various conditions, including myocardial infarction, ischemic stroke, and hepatitis (Ho and Hong, 2011; Xu et al., 2018). Salvianolate for injection (SFI), a metabolite derived from Danshen, received approval from the Chinese Food and Drug Administration in 2005 for the treatment of CVD (Cao et al., 2021; Zhang et al., 2016). This formulation primarily comprises salvianolic acid B (Sal-B) and its homologous metabolites (Li W. et al., 2018; Hu et al., 2024). SFI has been reported to confer cardiovascular benefits through multiple mechanisms, including anti-inflammatory, anti-apoptotic, anti-ischemia reperfusion injury, and anti-fibrotic effects (Liang et al., 2021; Xu et al., 2023; Qiu et al., 2018; Jiang et al., 2023; Ma et al., 2019). In China, SFI has been employed in clinical settings as an adjunctive therapy for AMI. However, a comprehensive literature review evaluating its efficacy and safety has not been conducted. Therefore, this study aims to elucidate the cardioprotective effects of SFI in patients with AMI through a systematic review of existing research.

Methods

The protocol were registered in the PROSPERO, with registration number CRD42024567279. This study was carried out following the protocol and in compliance with the PRISMA 2020 guidelines.

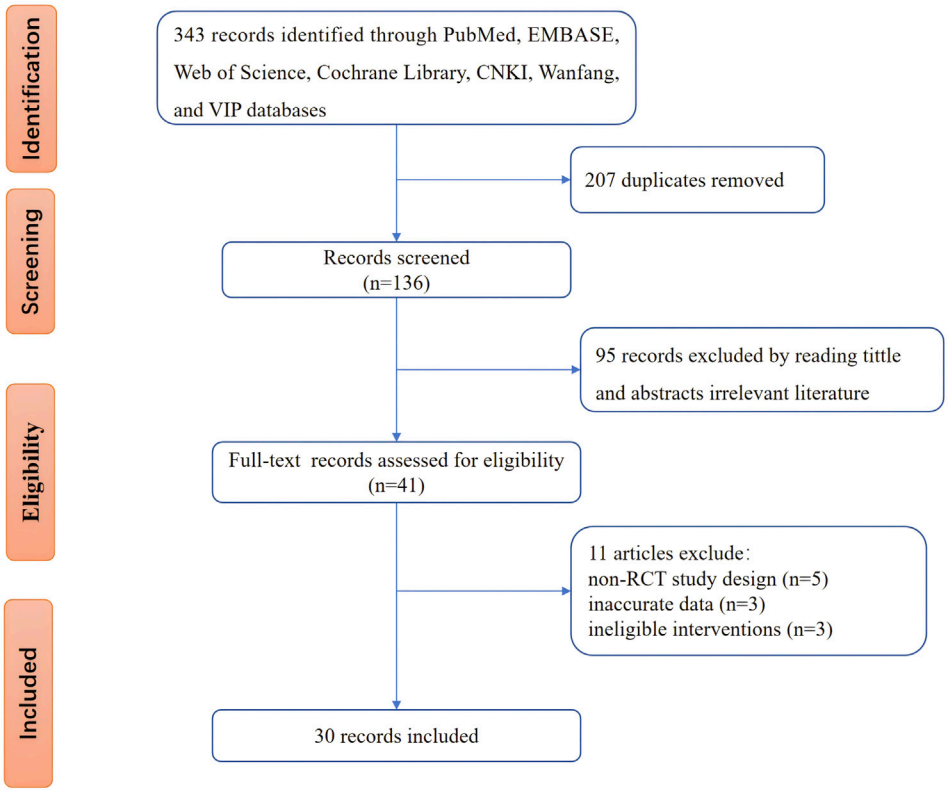


FIGURE 1
Flow chart of study selection and identification.

TABLE 1 Characteristics of included studies.

Author (publication year)	Sample size (T/C)	Male/female		Age (year)	Intervention		Courses/day	Outcomes
		T	C	T/C	T	C		
Dong Yuren (2019)	52/52	32/20	30/22	58.50 ± 3.80/ 58.60 ± 4.50	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	④⑯⑰⑱⑲㉓
Duan Xinyun (2016)	30/30	17/13	19/11	59.76 ± 7.23/ 60.00 ± 7.35	Salvianolate 200 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	—	⑤⑥⑩⑪⑫⑯⑰
Fu Xiaolong (2024)	40/40	22/18	26/14	62.76 ± 3.02/ 64.02 ± 3.17	Salvianolate 150 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	14 day	①②④⑥⑦
Guo Xiufang (2017)	58/58	40/18	38/20	63.80 ± 6.40/ 64.00 ± 6.20	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	7 day	②⑩⑭⑮⑯㉑㉒㉓
He Tao (2014)	37/35	—	—	—	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	10 day	③⑤⑥⑩⑱⑲⑳㉓
Hou Lifang (2018)	47/46	30/17	27/19	63.64 ± 5.28/ 62.83 ± 4.92	Salvianolate 150 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	14 day	①⑥⑦⑧⑨⑭
Hu Xiaochun (2023)	51/51	30/21	28 / 23	51.24 ± 5.42/ 50.38 ± 5.01	Salvianolate 150 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	14 day	②④⑤⑥⑧⑨⑭⑮
Li Hongmei (2017)	40/40	26/14	25/15	66.52 ± 4.75/ 66.75 ± 5.12	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	⑤⑯⑰
Li Jizhong (2020)	49/49	26/23	27/22	62.28 ± 7.63/ 61.26 ± 7.45	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	①②⑥⑦⑩
Li Sai (2020)	57/57	32/25	33/24	54.14 ± 7.85/ 53.92 ± 7.92	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	②③⑫
Lin Weibin (2023)	45/45	24/21	25/20	59.12 ± 6.38/ 58.43 ± 6.56	Salvianolate 200 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	14 day	②③⑥⑧⑨⑩⑲⑳
Liu Tiezhen (2020)	75/75	45/30	42/33	59.60 ± 3.20/ 60.30 ± 3.90	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	①⑥⑮⑯㉓
Liu Zhen (2022)	41/41	27/14	25/16	68.61 ± 3.28/ 68.55 ± 3.05	Salvianolate 200 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	14 day	⑥⑧⑨
Ni Lan (2011)	80/80	45/35	44/36	71.55 ± 8.35/ 71.56 ± 8.37	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	10 day	③⑤⑩㉓
Qiu Jun (2019)	41/41	28/13	30/11	61.40 ± 6.42/ 61.33 ± 5.78	Salvianolate 200 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	—	⑥⑩⑪⑫⑭⑮⑯⑰㉑㉒
Tang Changlin (2023)	45/44	23/21	25/20	52.16 ± 5.39/ 52.10 ± 5.48	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	⑥⑦⑪
Wang Xifu (2014)	165/155	109/56	113 /42	58.60 ± 11.30/ 57.30 ± 9.30	Salvianolate 400 mg + 5% G.S. 250 mL, qd, ivgtt	CT	7 day	⑬
Wang Xifu (2017)	150/150	110/40	107/ 43	60.90 ± 10.30/ 59.80 ± 10.10	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	5 day	⑬
Wang Zerong (2018)	45/45	24/21	25/20	60.80 ± 5.50/ 60.50 ± 5.30	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	7 day	⑤⑥⑩⑬
Wu Dexun (2016)	44/44	29/15	27/17	54.08 ± 3.97/ 55.97 ± 4.28	Salvianolate 200 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	7 day	①⑥⑭⑮⑯⑰㉓
Ye Ming (2014)	165/155	109/56	113/ 42	58.60 ± 11.30/ 57.30 ± 9.30	Salvianolate 400 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	7 day	⑭⑮⑯㉑㉒㉓
Yu Zushan (2016)	50/50	26/24	27/23	60.00 ± 4.80/ 59.00 ± 4.90	Salvianolate 200 mg + 0.9% N.S. 250 mL, qd, ivgtt	CT	7 day	⑩⑮⑰
Zhang Xaiojie (2017)	28/28	16/12	17/11	56.18 ± 9.66/ 55.72 ± 9.52	Salvianolate 100 mg + 0.9% N.S. 100 mL, bid, ivgtt	CT	14 day	⑥⑦
Zhang Yan (2022)	64/64	36/28	35/29	69.50 ± 5.99/ 68.94 ± 6.49	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	①⑪⑫⑭⑮

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of included studies.

Author (publication year)	Sample size (T/C)	Male/female		Age (year)	Intervention		Courses/day	Outcomes
		T	C	T/C	T	C		
Zhao Jian (2021)	43/43	25/18	23/20	69.04 ± 4.12/ 69.45 ± 4.20	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	21 day	⑥⑦⑨⑩⑪
Zheng Yi (2017)	30/30	17/13	16/14	60.35 ± 8.84/ 62.23 ± 9.65	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	1 day	②③
Zhu Ganlin (2018)	40/40	28/12	25/15	57.05 ± 6.68/ 56.05 ± 6.50	Salvianolate 200 mg + 0.9% N.S. 100 mL, qd, ivgtt	CT	14 day	⑰
Zhu Ganlin (2021)	38/38	23/15	22/16	68.06 ± 8.86/ 69.11 ± 9.05	Salvianolate 200 mg + 5% G.S. 250 mL, qd, ivgtt	CT	14 day	①②③⑪⑯⑰
Shen Li (2020)	262/265	219/43	217/ 48	61.10 ± 12.70/ 62.40 ± 11.30	Salvianolate 200 mg + 0.9% N.S. 100 mL, qd, ivgtt	CT	7 day	①㉓
Ou Yang (2020)	60/68	54/6	55/13	64.80 ± 11.00/ 65.20 ± 10.70	Salvianolate 200 mg + 0.9% N.S. 100 mL, qd, ivgtt	CT	3 day	①㉓

T/C, treatment group/control group; CT, conventional treatment; qd, once a day; ivgtt, intravenous guttae; ①MACEs, ②CK-MB, ③cTnI, ④LDH, ⑤NT-proBNP, ⑥LVEF, ⑦LVEDD, ⑧LVEDV, ⑨LVESV, ⑩CRP, ⑪TNF-α, ⑫IL-6, ⑬TLR-4, ⑭ET-1, ⑮NO, ⑯MDA, ⑰SOD, ⑱WBSV, ⑲PSV, ⑳fibrinogen, ㉑CD62p, ㉒CD63, ㉓adverse response.

Inclusion criteria

Studies were included according to the four criteria:

(1) Study type: randomized controlled trials (RCTs) assessing the efficacy and safety of SFI for AMI, with no status, language, or data restrictions;
(2) Participants: patients diagnosed with AMI according to the diagnostic criteria outlined in the 2023 European Society of Cardiology (ESC) guidelines (Byrne et al., 2023), the Fourth Universal Definition of Myocardial Infarction (2018) (Thygesen et al., 2018), or the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (O'Gara et al., 2013). These criteria include typical ischemic symptoms, electrocardiographic changes indicative of ischemia (such as ST-segment elevation or new left bundle branch block), and elevated cardiac troponin levels with a rise and/or fall indicative of myocardial injury;
(3) Interventions: the experimental groups (EG) received both SFI and conventional therapy (CT), while control groups (CG) received only CT. The courses and dosages of SFI were not restricted;
(4) Outcomes: the primary efficacy outcome was evaluated by major adverse cardiac events (MACEs). The secondary outcomes included myocardial injury markers, such as creatine kinase-MB (CK-MB), cardiac troponin I (cTnI), and lactate dehydrogenase (LDH); cardiac function indices, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV). Inflammatory markers included C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and toll-like receptor-4 (TLR-4). Oxidative stress markers were malondialdehyde (MDA) and superoxide dismutase (SOD). Vascular endothelial function was assessed using endothelin-1 (ET-1) and nitric oxide (NO). Hemorheological indicators included whole blood specific viscosity (WBSV), plasma specific viscosity (PSV), and fibrinogen. Platelet function was evaluated by measuring P-selectin (CD62p) and CD63. Safety was assessed by adverse events.

Exclusion criteria

Studies were excluded according to the four criteria:

(1) Unclear reporting of interventions;
(2) Insufficient data for statistical analysis;
(3) Duplicate publications or data;
(4) Conference abstracts, reviews, and technical reports.

Search strategy

The keywords used were "salvianolate," "salvianolic acids," "danshen polyphenolate salts," "acute myocardial infarction," and "randomized controlled trial" in both English and Chinese. Literature search was carried out independently by two investigators (PFC and HZ) in seven databases, including PubMed, Web of Science, EMBASE, Cochrane Library, CNKI, VIP, and Wanfang. The search period spanned from each database's inception to 1 July 2024. Additionally, references from similar systematic reviews were manually checked to ensure all relevant studies were included. Detailed search strategies and screening processes are provided in Supplementary Table S1.

Study selection and data extraction

Two investigators (PFC and HZ) independently screened studies by examining titles, abstracts, and full texts according to the eligibility criteria. Any disputes were settled by the senior reviewer (DZS).

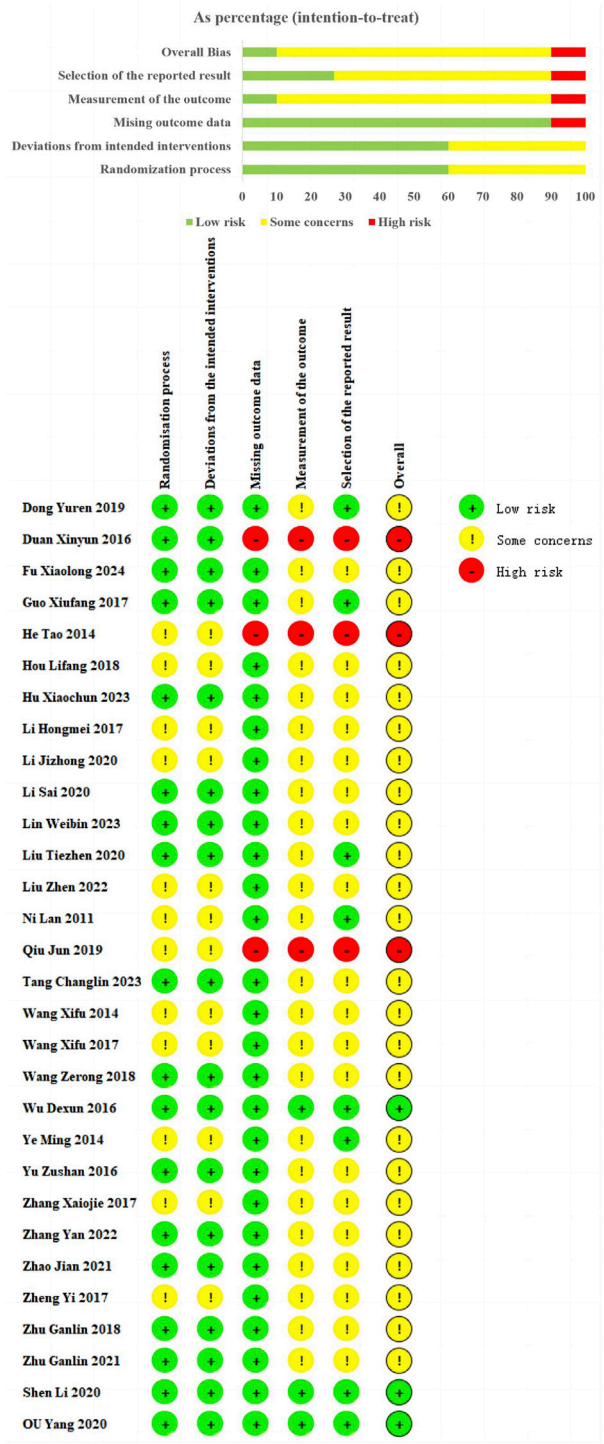


FIGURE 2
Risk of bias of included studies.

The following information was extracted, including trial characteristics (first author, publication year, country, follow-up period); patient characteristics (sample size, gender, age); SFI treatments (start time, administration frequency, dosage, duration); and treatment outcomes.

Bias risk

Two investigators (PFC and HZ) independently assessed the quality and risk of bias using the RoB 2 tool proposed by Cochrane (Sterne et al., 2019). The tool used algorithms to assign responses to signaling questions and generate a risk-of-bias judgment. We assessed five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Each was categorized as either "low risk," "some concerns," or "high risk."

Statistical analysis

In this study, data analysis was performed using the RevMan 5.4. Continuous variables were expressed as weighted mean differences (WMD) and 95% confidence intervals (CIs), while dichotomous variables were presented as pooled risk ratios (RR) and 95% CIs. Heterogeneity among the RCTs was evaluated using the Cochrane's Q test and I^2 statistic. Significant statistical heterogeneity was indicated by $p < 0.05$ or $I^2 > 50\%$, in which case a random-effects model was employed to assess outcomes; otherwise, a fixed-effects model was applied. For analyses involving only two trials, a random-effects model was chosen regardless of heterogeneity significance to ensure result accuracy. A p-value of less than 0.05 denoted a statistically significant difference.

Subgroup and sensitivity analysis

Subgroup and sensitivity analyses were performed to identify the sources of heterogeneity when I^2 was ≥50%. Subgroup analysis focused on treatment duration and follow-up time. Sensitivity analysis involved omitting one study at a time to identify sources of heterogeneity related to sample, gender, age, and interventions.

Publication bias

For datasets with 10 or more trials, a funnel plot was used to assess publication bias. While we planned to use Egger's or Begg's test, these tests were deemed unreliable for datasets with fewer than 10 trials, and thus were not performed.

Results

Study selection

Figure 1 illustrates the database search process and study identification. Initially, 343 potentially relevant articles were identified (PubMed: 35, Embase: 42, Web of Science: 38, Cochrane Library: 9, CNKI: 85, Wanfang: 76, VIP: 40, other sources: 18). After excluding 207 duplicate records and 95 ineligible records through title and abstract screening, 41 articles underwent full-text review. Of these, 11 were excluded

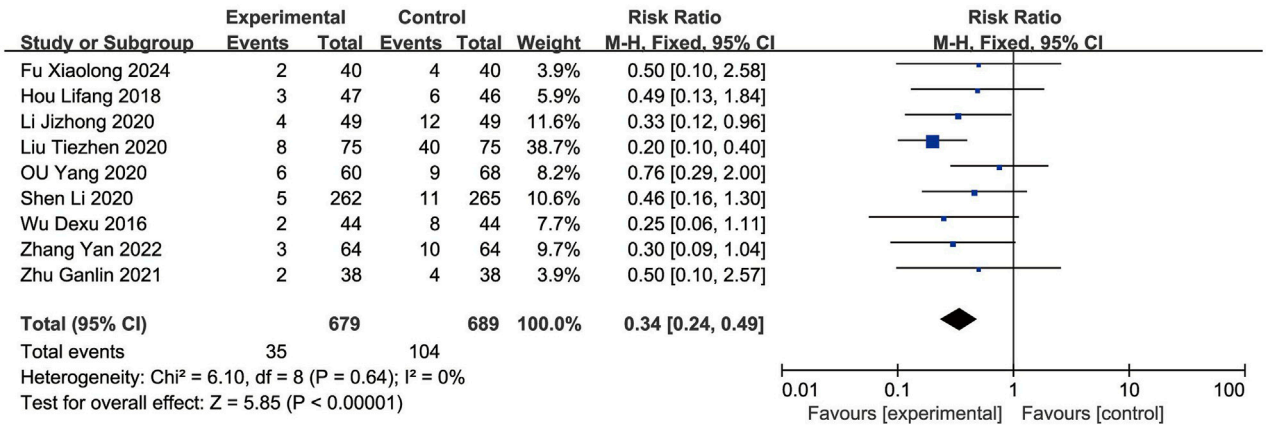


FIGURE 3
Forest plot of MACEs.

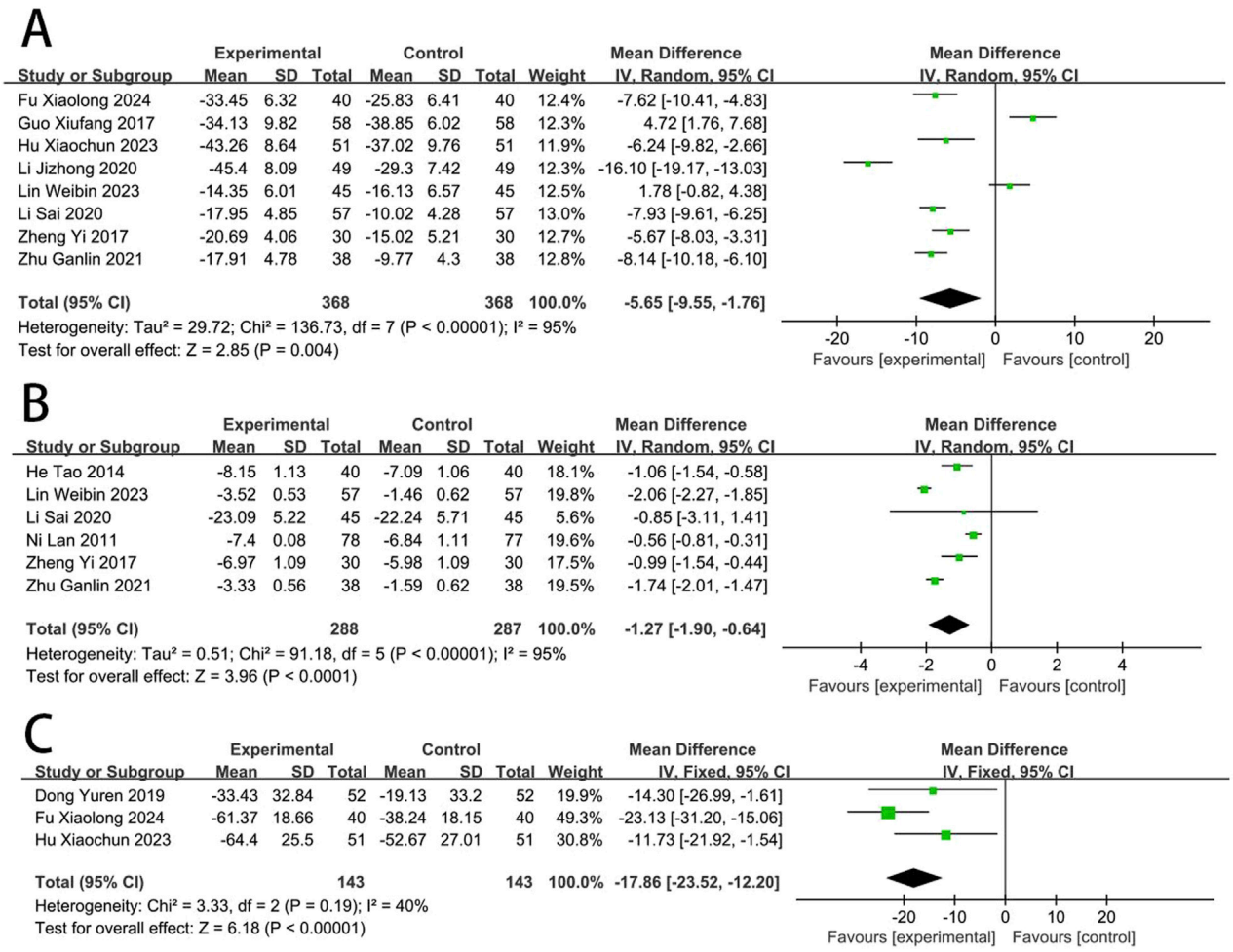


FIGURE 4
Forest plot of myocardial injury [**(A)** CK-MB; **(B)** cTnI; **(C)** LDH].

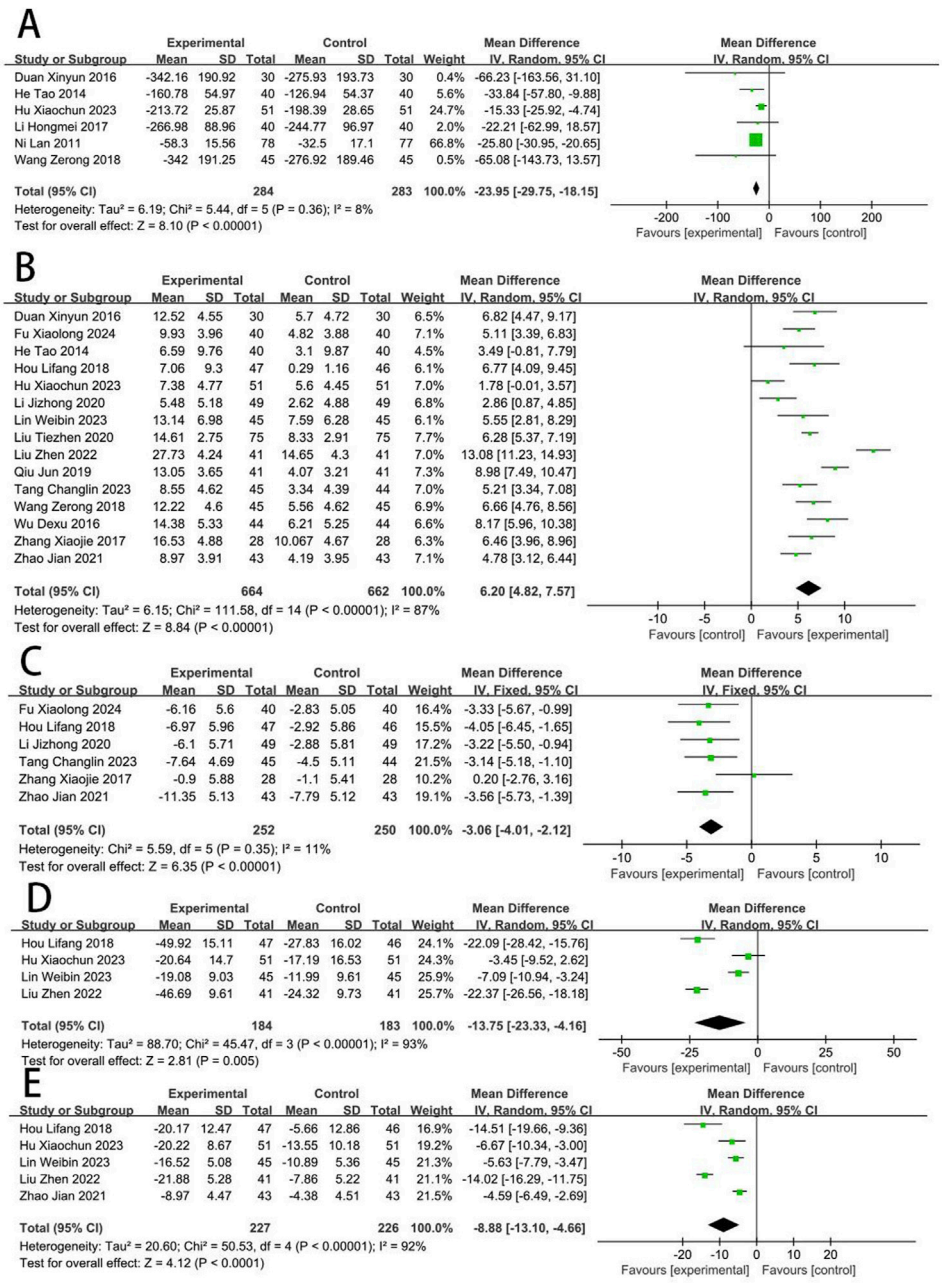


FIGURE 5
Forest plot of cardiac function [**(A)** BNP; **(B)** LVEF; **(C)** LVEDD; **(D)** LVEDV; **(E)** LVESV].

due to non-RCT study design, inaccurate data, or ineligible interventions. The excluded studies and reasons are detailed in Supplementary Table S2. Ultimately, 30 studies (Shen L. et al., 2020; Ou et al., 2020; Wang, 2018; Wang et al., 2017; Yi et al., 2017; Zu-shan et al., 2016; Wu et al., 2016; Wang et al., 2013; Ye et al., 2014; Qiu, 2019; Zhu and Wang, 2018; Tang, 2023; Liu et al., 2020; Liu et al., 2022; Zhang et al., 2022; Zhang et al., 2017; Hu Xiaochun et al., 2023; Hongmei et al., 2017; Jizheng and Lu, 2020; Guo, 2017; Duan and Jian-Hong, 2016; Dong et al., 2019; He et al., 2014; Hou and Yunfeng, 2018; Li et al., 2020; Zhu and Wang, 2022; Fu, 2024; Zhao, 2021; Lan et al., 2011; Lin et al., 2023) were included in our study.

Characteristics of studies

Table 1 summarizes the characteristics of the 30 RCTs included, involving a total of 3,931 participants (1,972 in the EG and 1,959 in the CG). There were no statistically significant differences in baseline information between the EG and CG. The patients' ages ranged from 50.38 ± 5.01 to 71.56 ± 8.37 years. The treatment duration with SFI varied from 1 to 21 days. Following the ConPhyMP guidelines (Heinrich et al., 2022), all the included RCTs focused on "type A" extracts, which are listed in the national pharmacopeia and have licensed applications. Detailed information on the source, composition, and chemical

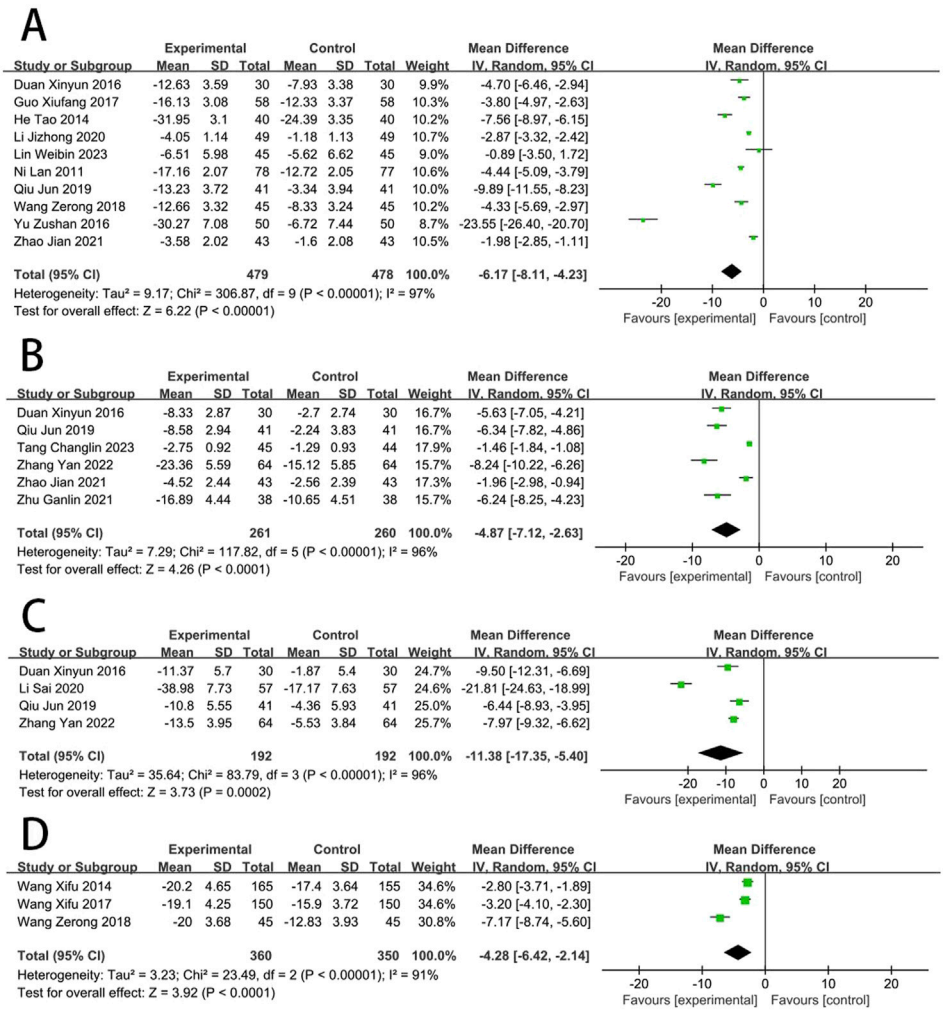


FIGURE 6
Forest plot of inflammatory response [**(A)** CRP; **(B)** TNF-α; **(C)** IL-6; **(D)** TLR-4].

properties of SFI used in these trials is provided in Supplementary Table S3.

Literature quality evaluation of included studies

Among the 30 studies included, all used random sequence generation. However, 12 studies (Wang et al., 2017; Yi et al., 2017; Wang et al., 2013; Ye et al., 2014; Qiu, 2019; Liu et al., 2022; Zhang et al., 2017; Hongmei et al., 2017; Jizheng and Lu, 2020; He et al., 2014; Hou and Yunfeng, 2018; Lan et al., 2011) did not detail the randomization method, resulting in an "some concerns." These missing details introduce potential risks of selection bias, which could affect the reliability of the reported outcomes. Eighteen studies provided clear descriptions of their randomization methods, including 15 studies (Shen L. et al., 2020; Ou et al., 2020; Wang, 2018; Zu-shan et al., 2016; Wu et al., 2016; Tang, 2023; Zhang et al., 2022; Hu Xiaochun et al., 2023; Guo, 2017; Duan and Jian-Hong, 2016; Dong et al., 2019; Li et al., 2020; Zhu and Wang, 2022; Fu, 2024; Lin et al., 2023) using random number tables, 2 study (Zhu and Wang, 2018; Zhao, 2021) using coin-toss method, 1 study (Liu et al., 2020) using drew lots method, and were evaluated as "low risk." Regarding measurement of the outcome and mising outcome data. Three study (Shen L. et al., 2020; Ou et al., 2020; Wu et al., 2016) reported some details regarding the methods of allocation concealment, and rated as "low risk." Three RCTs (Qiu, 2019; Duan and Jian-Hong, 2016; He et al., 2014) were rated as "high risk" due to incomplete data, which could introduce bias into the analysis. The remaining studies were classified as "some concerns" due to insufficient information on these aspects, raising concerns about the potential for unrecognized biases. Regarding the selection of reported results, we rated nine trials (Shen L. et al., 2020; Ou et al., 2020; Wu et al., 2016; Ye et al., 2014; Liu et al., 2020; Guo, 2017; Dong et al., 2019; He et al., 2014; Lan et al., 2011) as "low risk" because the adverse events or adverse reactions were mentioned in the results. However, for the remaining studies, the absence of reported safety events raises the possibility of selective reporting bias (Figure 2).

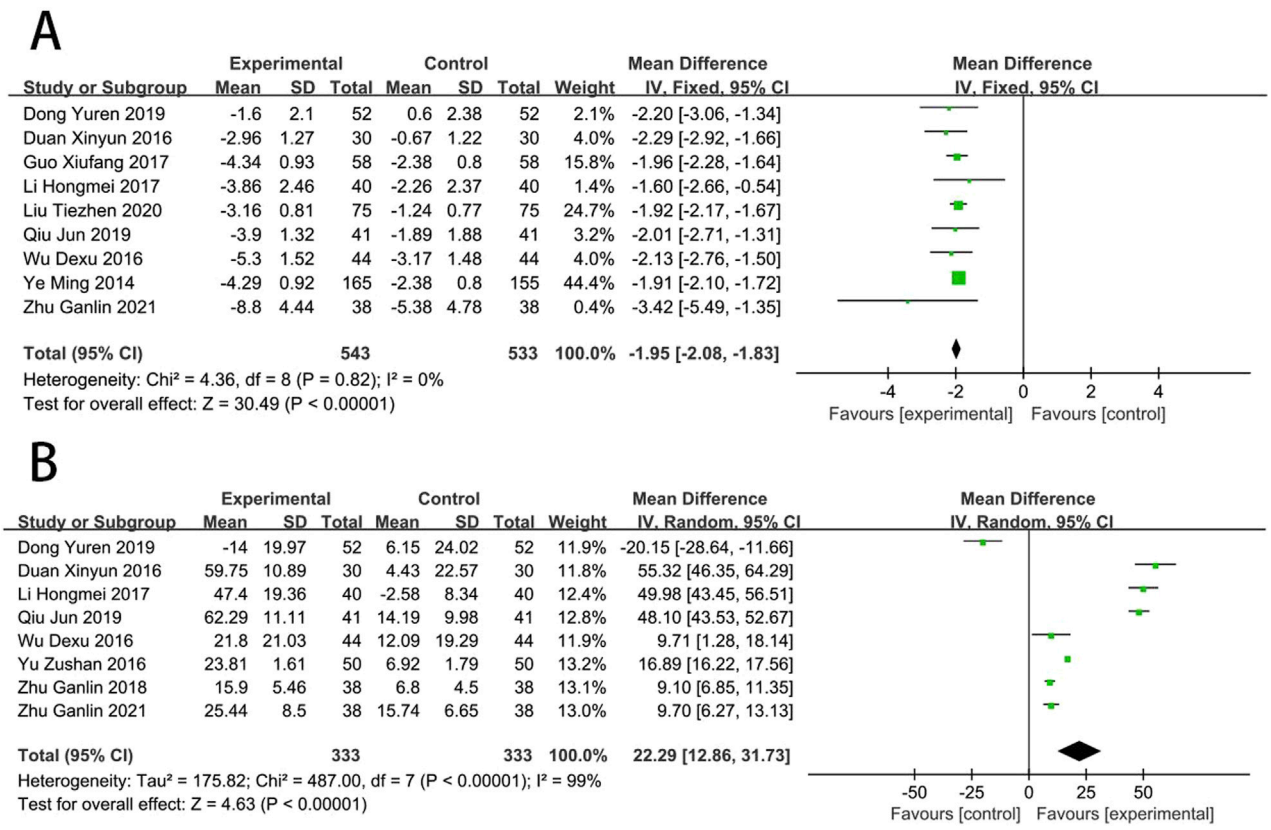


FIGURE 7
Forest plot of oxidative stress [**(A)** MDA; **(B)** SOD].

Main efficacy outcomes

MACEs

Nine RCTs (Shen L. et al., 2020; Ou et al., 2020; Wu et al., 2016; Liu et al., 2020; Zhang et al., 2022; Jizheng and Lu, 2020; Hou and Yunfeng, 2018; Zhu and Wang, 2022; Fu, 2024) reported the MACEs. As the heterogeneity was not significant (p = 0.64, I^2 = 0%), a fixed-effects model was used to analysis. The result showed that the occurrence of MACEs in the EG was significantly lower than in the CG, with the difference being statistically significant [RR = 0.34, (0.24–0.49), $p < 0.05$] (Figure 3).

Secondary efficacy outcomes

Myocardial injury

Eight RCTs (Yi et al., 2017; Zhu and Wang, 2018; Hu Xiaochun et al., 2023; Jizheng and Lu, 2020; Guo, 2017; Li et al., 2020; Fu, 2024; Lin et al., 2023) reported the CK-MB. The meta-analysis revealed a significant reduction in CK-MB concentrations in the EG compared to the CG [MD = −5.65, (−9.55 to −1.76), $p < 0.05$; I^2 = 95%, random-effects model]. Six RCTs (Yi et al., 2017; He et al., 2014; Li et al., 2020; Zhu and Wang, 2022; Lan et al., 2011; Lin et al., 2023) reported the cTnI. Meta-analysis showed that cTnI was significantly reduced in EG compared to CG [MD = −1.27, (−1.90 to −0.64), $p < 0.05$; I^2 = 95%]. Three RCTs (Hu Xiaochun et al., 2023; Dong et al., 2019; Fu, 2024) reported the LDH, and meta-analysis showed that the LDH was significantly reduced in EG compared to CG [MD = −17.86, (−23.52 to −12.20), $p < 0.05$; I^2 = 40%] (Figure 4).

Cardiac function

Six RCTs (Wang, 2018; Qiu, 2019; Hu Xiaochun et al., 2023; Hongmei et al., 2017; Duan and Jian-Hong, 2016; He et al., 2014; Lan et al., 2011) reported the NT-proBNP. The meta-analysis revealed that the NT-proBNP in the EG was significantly lower compared to the CG [MD = −24.36, (−28.87 to −19.86), $p < 0.05$; I^2 = 8%]. Fifteen RCTs (Shen L. et al., 2020; Wang, 2018; Wu et al., 2016; Qiu, 2019; Tang, 2023; Liu et al., 2020; Liu et al., 2022; Zhang et al., 2017; Hu Xiaochun et al., 2023; Jizheng and Lu, 2020; Duan and Jian-Hong, 2016; He et al., 2014; Hou and Yunfeng, 2018; Fu, 2024; Zhao, 2021; Lin et al., 2023) reported the LVEF, and meta-analysis revealed that the LVEF in EG was significantly higher compared to the CG [MD = 6.2, (4.82–7.57), $p < 0.05$; I^2 = 87%]. Six RCTs (Tang, 2023; Zhang et al., 2017; Jizheng and Lu, 2020; Hou and Yunfeng, 2018; Fu, 2024; Zhao, 2021) reported the LVEDD, and revealed that the LVEDD in EG is significantly lower compared to the CG [MD = −3.06, (−4.01 to −2.12), $p < 0.05$; I^2 = 11%]. Four RCTs (Liu et al., 2022; Hu Xiaochun et al., 2023; Hou and Yunfeng, 2018; Lin et al., 2023) reported the LVEDV, and showed that the LVEDV

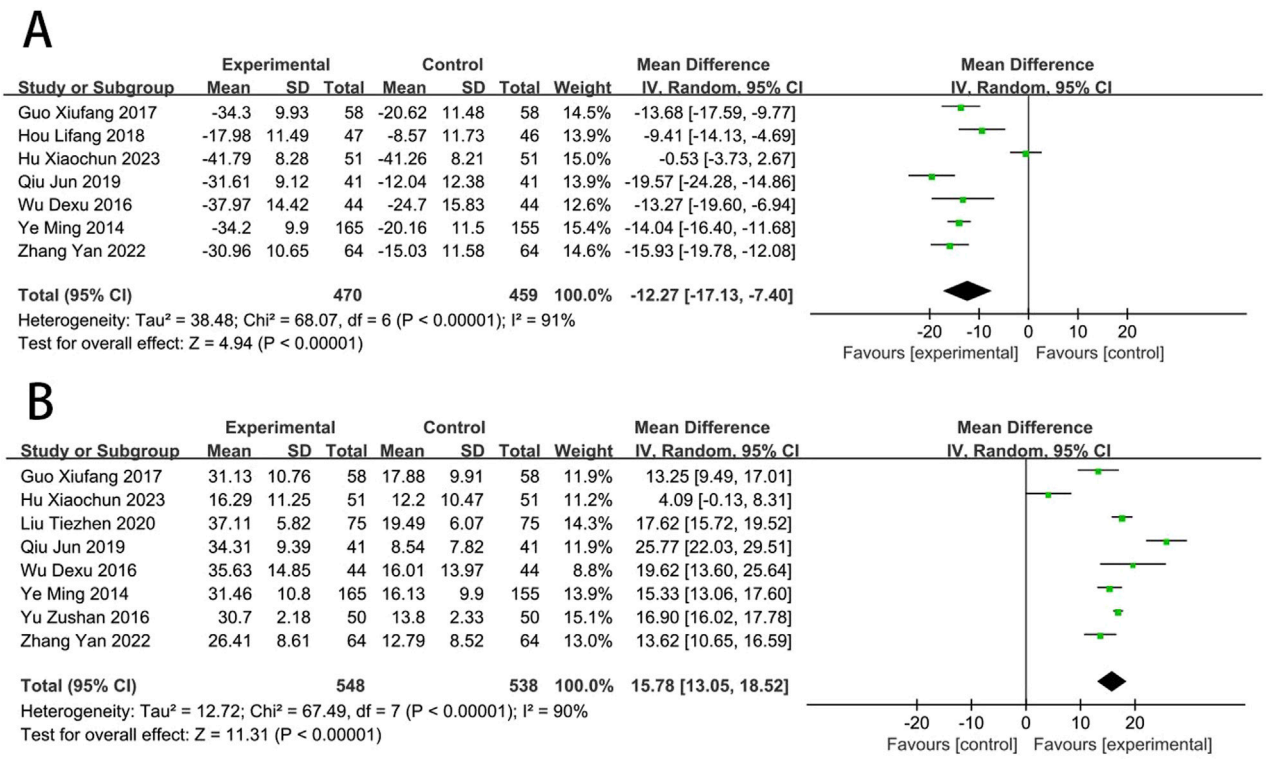


FIGURE 8
Forest plot of vascular endothelial function [**(A)** ET-1; **(B)** NO].

in EG is significantly lower compared to the CG [MD = −13.75, (−23.33 to −4.16), $p < 0.05$; $I^2 = 93\%$]. Five RCTs (Liu et al., 2022; Hu Xiaochun et al., 2023; Hou and Yunfeng, 2018; Zhao, 2021; Lin et al., 2023) reported the LVESV, and revealed that the LVESV in EG is significantly lower compared to the CG [MD = −8.88, (−13.10 to −4.66), $p < 0.05$; $I^2 = 92\%$] (Figure 5).

Inflammatory response

Ten RCTs (Wang, 2018; Zu-shan et al., 2016; Qiu, 2019; Jizheng and Lu, 2020; Guo, 2017; Duan and Jian-Hong, 2016; He et al., 2014; Zhao, 2021; Lan et al., 2011; Lin et al., 2023) reported the CRP. The meta results suggested that SFI significantly improved CRP [MD = −6.17, (−8.11 to −4.23), $p < 0.05$; $I^2 = 97\%$]. Six RCTs (Qiu, 2019; Tang, 2023; Zhang et al., 2022; Duan and Jian-Hong, 2016; Zhu and Wang, 2022; Zhao, 2021) reported the TNF-α amd meta results suggested that SFI significantly improved TNF-α [MD = −4.87, (−7.12 to −2.63), $p < 0.05$; $I^2 = 96\%$]. Four RCTs (Qiu, 2019; Zhang et al., 2022; Duan and Jian-Hong, 2016; Li et al., 2020) reported the IL-6, and suggested that SFI significantly improved IL-6 [MD = −11.38, (−17.35 to −5.40), $p < 0.05$; $I^2 = 96\%$]. Three RCTs (Wang, 2018; Wang et al., 2017; Wang et al., 2013) reported the TLR-4, and suggested that SFI significantly improved TLR-4 [MD = −4.28, (−6.42 to −2.14), $p < 0.05$; $I^2 = 91\%$] (Figure 6).

Oxidative stress

Nine RCTs (Wu et al., 2016; Ye et al., 2014; Qiu, 2019; Liu et al., 2020; Hongmei et al., 2017; Guo, 2017; Duan and Jian-Hong, 2016; Dong et al., 2019; Zhu and Wang, 2022) reported the MDA. Compared with CT, results suggested that SFI can significantly reduce the MDA [MD = −1.95, (−2.08 to −1.83), $p < 0.05$; $I^2 = 0\%$]. Eight RCTs (Zu-shan et al., 2016; Wu et al., 2016; Qiu, 2019; Zhu and Wang, 2018; Hongmei et al., 2017; Duan and Jian-Hong, 2016; Dong et al., 2019; Zhu and Wang, 2022) reported the SOD. Compared with CT, results suggested that SFI can significantly increase the SOD [MD = 22.29, (12.86–31.73), $p < 0.05$; $I^2 = 99\%$] (Figure 7).

Vascular endothelial function

Seven RCTs (Wu et al., 2016; Ye et al., 2014; Qiu, 2019; Zhang et al., 2022; Hu Xiaochun et al., 2023; Guo, 2017; Hou and Yunfeng, 2018) reported the ET-1. The meta-analysis indicated that EG was more effective than CG on reducing the level of ET-1 [MD = −12.27, (−17.13 to −7.40), $p < 0.05$; $I^2 = 91\%$]. Eight RCTs (Zu-shan et al., 2016; Wu et al., 2016; Ye et al., 2014; Qiu, 2019; Liu et al., 2020; Zhang et al., 2022; Hu Xiaochun et al., 2023; Guo, 2017) reported the NO, and meta-analysis indicated that EG was more effective than CG on increasing the NO [MD = 15.78, (13.05–18.52), $p < 0.05$; $I^2 = 90\%$] (Figure 8).

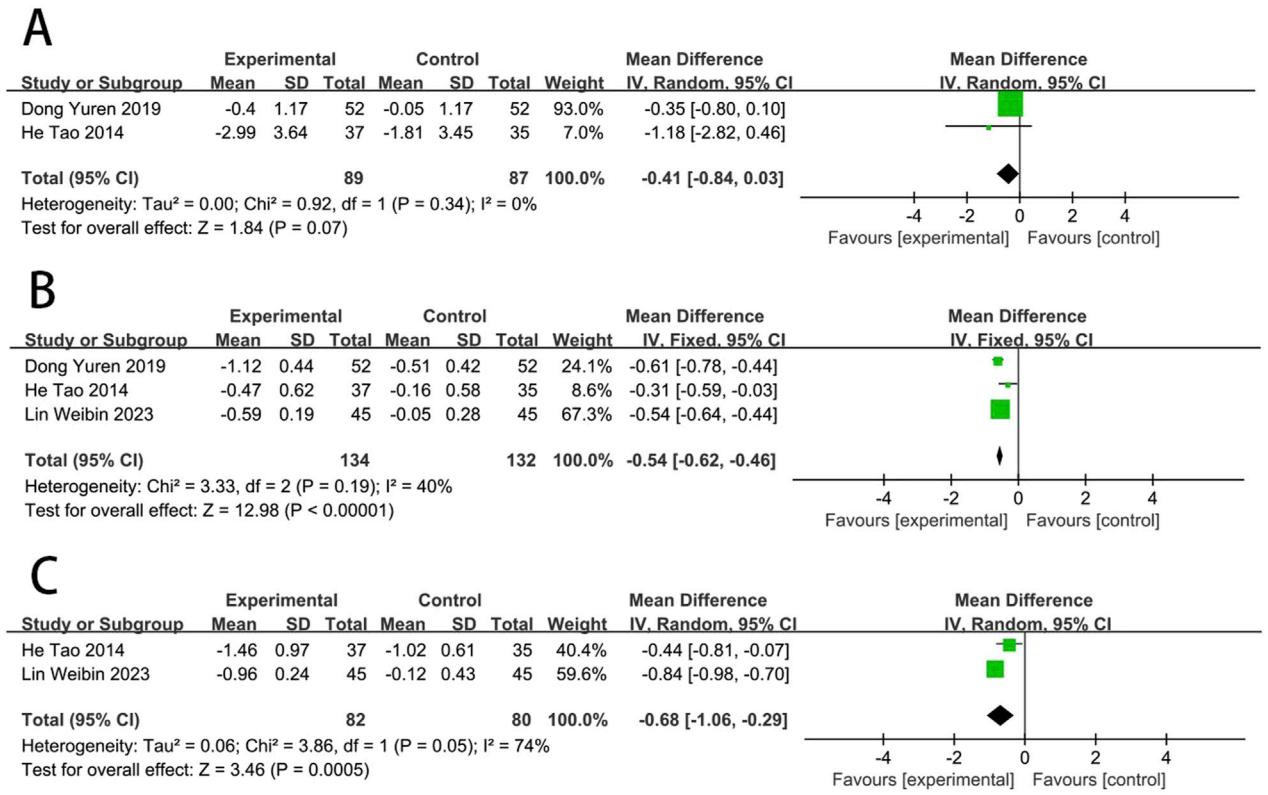


FIGURE 9
Forest plot of hemorheological function [**(A)** WBSV; **(B)** PSV; **(C)** fibrinogen].

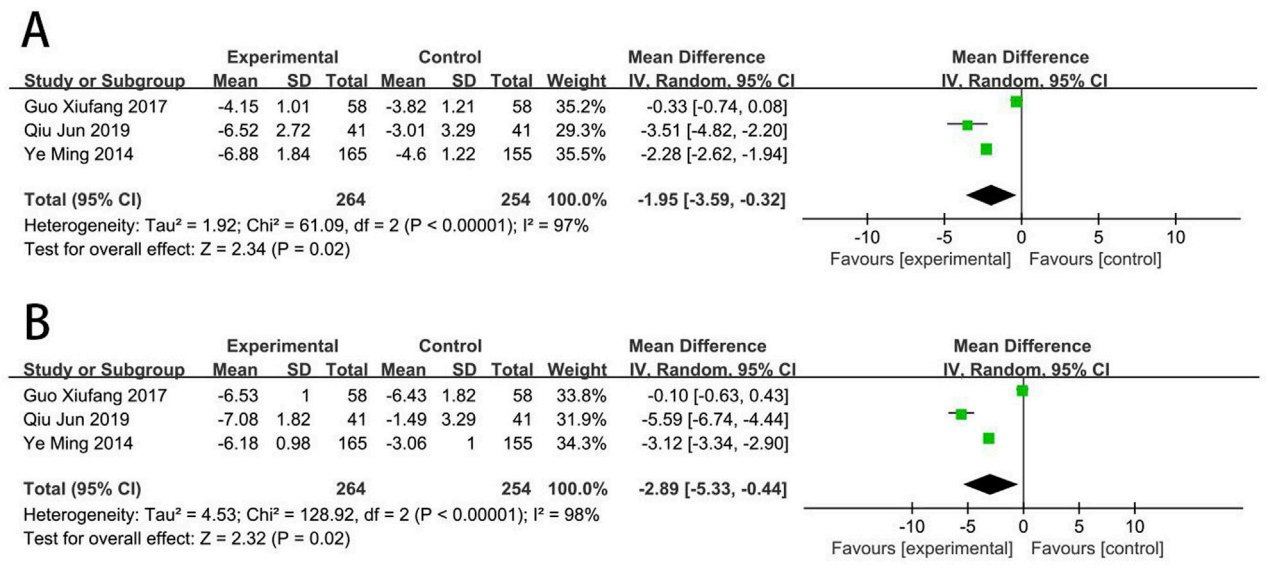


FIGURE 10
Forest plot of platelet function [**(A)** CD62p; **(B)** CD63].

Hemorheological indicators

Two RCTs (Dong et al., 2019; He et al., 2014) reported the WBSV. The results showed no statistically significant difference in WBSV between EG and CG [MD = −0.41, (−0.84 to 0.03), $p > 0.05$; $I^2 = 0\%$]. Three RCTs (Dong et al., 2019; He et al., 2014; Lin et al., 2023) reported the PSV. The results showed that PSV levels improved better in EG than in CG [MD = −0.54,

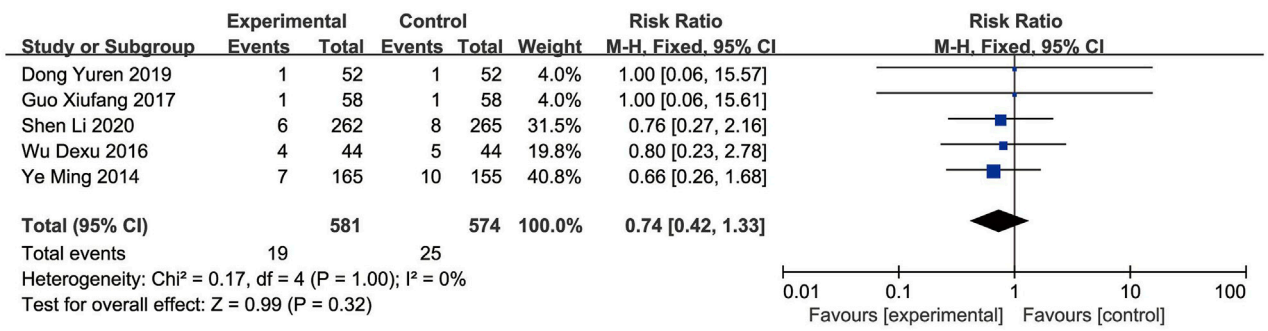


FIGURE 11
Forest plot of adverse events.

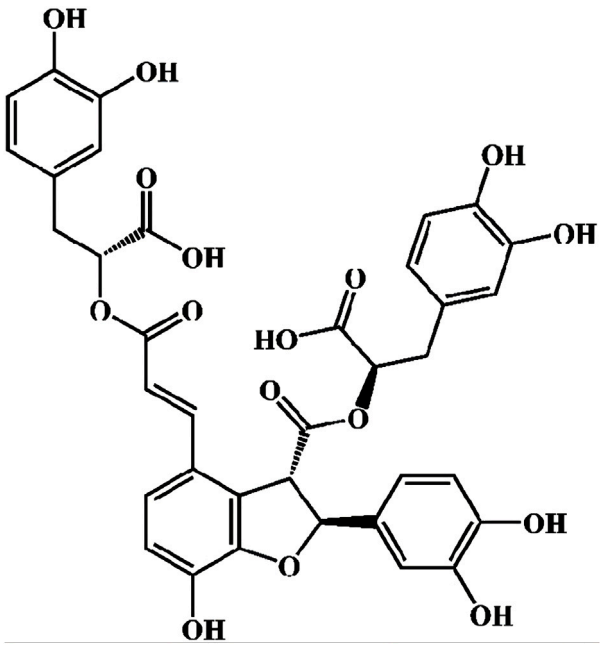


FIGURE 12
The molecular structural of Sal B.

(−0.62 to −0.46), $p < 0.05$; $I^2 = 40\%$]. Two RCTs (He et al., 2014; Lin et al., 2023) reported the fibrinogen. The results showed that fibrinogen levels improved better in EG than in CG [MD = −0.68, (−1.06 to −0.29), $p < 0.05$; $I^2 = 74\%$] (Figure 9).

Platelet function

Three RCTs (Ye et al., 2014; Qiu, 2019; Guo, 2017) reported the CD62p. Meta-analysis showed that EG was more effective than CG on reducing the level of CD62p [MD = −1.95, (−3.59 to −0.32), $p < 0.05$; $I^2 = 97\%$]. Three RCTs (Ye et al., 2014; Qiu, 2019; Guo, 2017) reported the CD63. Meta-analysis showed that EG was more effective than CG on reducing the level of CD63 [MD = −2.89, (−5.33 to −0.44), $p < 0.05$; $I^2 = 98\%$] (Figure 10).

Safety outcomes

Nine RCTs (Shen L. et al., 2020; Ou et al., 2020; Wu et al., 2016; Ye et al., 2014; Liu et al., 2020; Guo, 2017; Dong et al., 2019; He et al., 2014; Lan et al., 2011) reported the adverse events. The Meta-analysis showed that the incidence of adverse events did not significantly differ between the EG and CG [RR = 0.74, 95% CI: 0.42 to 1.33, $p = 0.32$]. Given the non-significant heterogeneity ($p = 1.00$, $I^2 = 0\%$), a fixed-effects model was employed for the analysis (Figure 11). Across the included studies, four studies (Ou et al., 2020; Liu et al., 2020; He et al., 2014; Lan et al., 2011) found no adverse events in both the EG and CG. Other studies documented adverse events related to the AMI, including dizziness, rash, thrombocytopenia, hypotension, hemorrhage, and arrhythmia, with similar frequencies observed between the EG and CG. Overall, the reported adverse events were infrequent and comparable, indicating no major safety concerns related to SFI.

Subgroup analysis

One subgroup analysis stratified by the follow-up duration (1-month, 3-month, and 6-month) indicated that SFI could decrease MACEs at 3-month checkpoint [RR = 0.38, (0.15–0.91), $p < 0.05$] and 6-month [RR = 0.25, (0.15–0.41), $p < 0.05$]. Nonetheless, there was no notable difference was observed at the 1-month [RR = 0.52, (0.25–1.09), $p > 0.05$] (Supplementary Figure 1).

Another subgroup analysis by the treatment duration of SFI (7-days or 14-days), indicated that SFI could decrease MACEs at 7-days checkpoint [RR = 0.49, (0.26–0.92), $p < 0.05$] and 14-days [RR = 0.29, (0.19–0.45), $p < 0.05$]. In addition, SFI could decrease CK-MB at 14-days checkpoint [MD = −7.35, (−11.39 to −3.32), $p < 0.05$]. However, there was no notable difference observed at the 7-days checkpoint of CK-MB [MD = 2.05, (−3.17–7.28), $p > 0.05$] (Supplementary Figure 2).

Sensitivity analysis

When significant heterogeneity was observed ($I^2 \geq 50\%$) in outcomes such as CK-MB, cTnI, LVEF, LVEDV, LVESV, CRP, TNF-α, IL-6, ET-1, and NO, we conducted a sensitivity analysis.

This analysis suggested that the variability could be attributed to differences in participant sample size, age, gender, and SFI intervention durations across trials. Excluding these studies substantially reduced the heterogeneity, with minimal impact on the overall results (Supplementary Table S4).

Publication bias

Publication bias for LVEF and CRP was assessed using a funnel plot, as there were ten or more trials available. The results showed a symmetrical inverted funnel shape, indicating a low likelihood of publication bias for both LVEF and CRP (Supplementary Figure 3).

Discussion

Findings overview

To the best of our knowledge, this is the first study to systematically evaluate the efficacy and safety of SFI for AMI treatment. The findings reveal a substantial decrease in MACEs among AMI patients receiving SFI treatment. Additionally, SFI was found to mitigate myocardial injury, enhance cardiac function, reduce inflammatory responses and oxidative stress, and improve vascular endothelial, hemorheological, and platelet function. These effects likely contribute to the cardioprotective mechanism of action of SFI in AMI. Safety evaluations indicate that SFI does not increase the risk of adverse events, particularly bleeding. These findings highlight the efficacy and safety of SFI, demonstrating enhanced structural and functional outcomes in AMI patients and suggesting SFI as a promising treatment option for AMI.

The mechanism of SFI for treating AMI

The chemical metabolites of Danshen extract are primarily categorized into two groups: water-soluble metabolites and lipophilic phenanthraquinones. The principal lipophilic phenanthraquinones include Tanshinone I, Tanshinone IIA, and Tanshinone IIB. The major water-soluble metabolites comprise Danshensu, Rosmarinic Acid, Lithospermic Acid, Salvianolic Acid A, and Sal-B (Ho and Hong, 2011; Wang et al., 2019; Li ZM. et al., 2018). Sal-B, also referred to as lithospermic acid B, is a key bioactive metabolite found in the hydrophilic extracts of Salvia miltiorrhiza, with a molecular formula of C36H30O16 and a molecular weight of 718 (Figure 12). The SFI formula is predominantly composed of Sal-B, which has been recognized for its cardiovascular protective effects, particularly in mitigating oxidative stress, inflammation, and myocardial injury. Sal-B's magnesium salt derivative, magnesium tanshinoate B (MTB), may offer enhanced therapeutic potential in treating AMI due to the physiological benefits of magnesium ions on cardiac muscle function (Xiao et al., 2020). Given that Sal-B constitutes 80% of the active metabolites in SFI and has been more extensively studied than other metabolites, this investigation primarily focuses on the pharmacological effects of Sal-B in AMI treatment.

Oxidative stress-induced injury plays a crucial role in causing severe and irreversible damage to cardiomyocytes in AMI. Sal-B exhibits potent antioxidant activity, effectively neutralizing free radicals and attenuating myocardial cell damage caused by oxidative stress (Xiao et al., 2020; Wu et al., 2009). The cardioprotective effects of Sal-B are mediated through the enhancement of SOD activity and the reduction of MDA production. Furthermore, Sal-B significantly protects bone marrow-derived endothelial progenitor cells from oxidative stress-induced injury by inhibiting the MKK3/6-p38, MAPK-ATF2, and ERK1/2 signaling pathways, thereby reducing intracellular reactive oxygen species (ROS) levels (Tang et al., 2014). Research conducted by Gao et al. demonstrated that Sal-B protects human umbilical vein endothelial cells (HUVECs) from oxidative stress, partially through the enhancement of autophagy via activation of the AMPK pathway and suppression of the mTOR pathway (Gao S. et al., 2019). Additionally, Lu et al. (2022) reported that Sal-B shields cardiomyocytes from ischemia/reperfusion (I/R)-induced oxidative stress both *in vitro* and *in vivo*, a process partially mediated by the TRIM8/GPX1 axis.

The inflammatory response plays a pivotal role in myocardial injury and remodeling following AMI. Sal-B has been demonstrated to inhibit the release of various inflammatory mediators, including CRP, TNF-α, IL-16, and TLR-4, primarily through the modulation of the TNF-α/NF-κB and TLR pathways. Researches conducted by Hu Y. et al. (2019) and Hu et al. (2020) revealed that Sal-B significantly attenuated AMI injury induced by subcutaneous isoproterenol (ISO) injection in a rat model. Sal-B treatment was observed to markedly reduce intracellular ROS production, inhibit NLRP3 inflammasome activation, and decrease apoptosis in H9C2 cardiomyocytes. Furthermore, Sal-B has been shown to promote the formation of anti-inflammatory M2 macrophages by regulating macrophage polarization, thereby mitigating myocardial damage caused by the inflammatory response (Li et al., 2021; Zou et al., 2022).

Cardiomyocyte apoptosis represents a key mechanism of myocardial injury following AMI. Sal-B has been found to reduce markers of myocardial damage, including CK-MB, cTnI, and LDH. The anti-apoptotic effects of Sal-B are mediated through the regulation of the Bcl-2/Bax expression ratio and the suppression of caspase activation (Wang et al., 2022; Chen HM. et al., 2017). Additionally, Sal-B exerts cardioprotective effects by activating the PI3K/Akt signaling pathway, thereby enhancing cell survival signals (Liu et al., 2007). Research conducted by Liu et al. (Liu et al., 2020) demonstrated that Sal-B significantly ameliorated myocardial I/R injury in a dose-dependent manner. This protective effect was characterized by a reduction in myocardial infarction size, decreased expression of myocardial injury markers, attenuated cell apoptosis, enhanced PI3K/Akt expression, and inhibition of high mobility group box 1 (HMGB1) expression.

Sal-B has been shown to exhibit antiplatelet and anticoagulant properties through multiple mechanisms. The metabolite reduces the expression of CD62p on the platelet surface and inhibits platelet activation induced by adenosine diphosphate (ADP), collagen, and thrombin (Chen et al., 2023). Moreover, Sal-B demonstrates anticoagulant effects by decreasing thrombin production and fibrin formation, thereby preventing blood clot formation. A study conducted by Liu et al. (Liu et al., 2014) elucidated two primary mechanisms underlying the antiplatelet effects of Sal-B: firstly, as a P2Y12 receptor antagonist, Sal-B significantly inhibits the interaction between ADP and the P2Y12 receptor; secondly, it inhibits phosphodiesterase (PDE) activity in platelets, preventing cyclic adenosine monophosphate (cAMP) degradation and thus suppressing platelet activation.

Furthermore, Sal-B has been observed to reduce Ca^{2+} mobilization within platelets, further contributing to its antiplatelet aggregation effects (Song et al., 2017; Chen RC. et al., 2017).

Endothelial dysfunction has been identified as a crucial factor in the pathophysiology of AMI. Sal-B has been demonstrated to improve endothelial function through the promotion of endothelial cell survival and repair mechanisms. Extensive research has elucidated that Sal-B enhances the synthesis and release of NO, thereby improving vasodilation and reducing endothelial cell apoptosis (Ling et al., 2017). Furthermore, Sal-B exerts protective effects on endothelial cells by attenuating oxidative stress and inflammatory responses (Ren et al., 2016; Ko et al., 2020). A study conducted by Chen et al. (Chen et al., 2001) revealed that Sal-B primarily safeguards vascular endothelial cells through the concentration-dependent reduction of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) activity.

Pharmacological investigations have confirmed that hemodynamic alterations represent a primary etiological factor in thrombosis formation. Fibrinogen plays a pivotal role in platelet aggregation, a reduction in fibrinogen levels can lead to decreased thrombus formation. Sal-B has been shown to significantly lower fibrinogen and lipid peroxide levels, while concomitantly increasing high-density lipoprotein (HDL) concentrations. These effects contribute to improved blood viscosity and a reduction in the nitric oxide/endothelin (NO/ET) ratio (Dong et al., 2019; He et al., 2014; Lin et al., 2023). Moreover, Sal-B enhances vascular dilation and improves hemodynamics through the modulation of vascular smooth muscle cell function (He H. et al., 2008). Clinical studies have demonstrated that Sal-B administration significantly reduces blood viscosity, increases red blood cell deformability, and improves microcirculation in patients with AMI (He HB. et al., 2008).

Sal-B has been demonstrated to mitigate fibrosis and cardiac remodeling while promoting angiogenesis. In AMI rat models, Sal-B selectively inhibits MMP-9 activity, effectively augments left ventricular wall thickness, enhances cardiac contractility, and attenuates myocardial fibrosis (Ma et al., 2015; Sun et al., 2021; Luo et al., 2023). The metabolite inhibits type I collagen production in the LX-2 cell line under non-TGF-β2 stimulation and exerts anti-fibrotic effects through the inhibition of p38 and ERK signaling pathways (Luo et al., 2023; Gao H. et al., 2019; Li et al., 2020). Clinical studies have revealed that Sal-B significantly elevates serum VEGF levels in AMI patients, thereby promoting vascular endothelial cell proliferation and migration and facilitating new blood vessel formation (He HB. et al., 2008; Chen et al., 2022; Dhapare and Sakagami, 2018). Furthermore, Sal-B enhances hypoxia-induced angiogenesis and promotes myocardial repair through the activation of the HIF-1α signaling pathway (Yang et al., 2016; Wei et al., 2018).

Clinical application suggestions

The findings of this study suggest that SFI may play a therapeutic role in the AMI population. Subgroup analysis further revealed that SFI significantly reduced MACEs at 3 and 6 months follow-up, while no significant reduction was observed at 1 month. These results indicate that SFI can potentially reduce mortality and the incidence of recurrent myocardial infarction, thereby improving the long-term prognosis of AMI patients. Additional subgroup analysis demonstrated SFI's efficacy in reducing MACE at 7 and 14 days of treatment. However, SFI reduced CK-MB at 14 days, with no significant difference observed at 7 days. Based on these findings, a treatment duration of 2 weeks is recommended.

Comparison with existing literature

Our findings contribute to the growing body of evidence on the clinical applications of SFI. Yang et al. (Yang et al., 2020) conducted a retrospective analysis using national health insurance data in China to assess the economic impact of SFI in coronary heart disease (CHD). The study demonstrated that SFI was associated with lower hospitalization costs and shorter hospital stays compared to other treatments, such as Danhong and alprostadil injections, highlighting its potential to reduce the financial burden on patients and healthcare systems. However, their focus on economic outcomes left a gap in clinical efficacy assessment. By integrating our RCT-based clinical findings with Yang et al.'s economic insights, we emphasize the dual value of SFI—not only as a clinically effective treatment for AMI but also as a cost-efficient therapy for broader cardiovascular care.

Similarly, Shen Y. et al. (2020) explored SFI's therapeutic potential in a different clinical setting—diabetic nephropathy. Their meta-analysis revealed that SFI improved renal function, reduced oxidative stress, and lowered inflammatory markers, demonstrating its potential beyond cardiovascular conditions. These therapeutic effects align with the cardioprotective benefits observed in our study. However, both studies, including ours, face limitations such as variability in methodological quality, differences in treatment regimens, and a lack of long-term follow-up. These limitations underscore the need for larger, high-quality RCTs to validate salvianolate's long-term efficacy and safety across different clinical populations and to explore optimal dosing strategies for both cardiovascular and non-cardiovascular applications.

Implications for future research

This study highlights SFI as a promising alternative treatment option for AMI. Despite these encouraging results, several key areas warrant further investigation. While SFI has demonstrated notable effectiveness in reducing MACEs, determining the optimal dosage to ensure maximum efficacy and minimal side effects remains crucial. Future research should prioritize dosage optimization and conduct long-term follow-ups to evaluate the sustained efficacy and safety of SFI across diverse patient populations. The study also reveals SFI's significant improvement of myocardial injury markers, cardiac function, and inflammatory responses. However, its precise mechanisms of action remain elucidated. Future studies should delve into the molecular and cellular mechanisms of SFI to enhance understanding of its role in AMI management and to identify potential biological pathways and targets.

Advantages and limitations

This study presents several notable strengths. Firstly, a comprehensive search was conducted across multiple databases

without language or time restrictions. Secondly, the involvement of two independent investigators in study selection, data extraction, and bias assessment minimized the potential for errors. Thirdly, the application of rigorous standards in assessing and reviewing eligible trials ensured methodological robustness and aimed to draw unbiased conclusions. Lastly, an in-depth discussion of the mechanism of Sal-B in AMI treatment was provided.

Nevertheless, certain limitations must be acknowledged. Our findings should be interpreted with caution due to the risk of bias identified in some included studies. In particular, the absence of clear randomization methods and incomplete outcome reporting in some studies raise serious concerns about selection and reporting biases. These limitations suggest that some of the included studies may not be sufficiently reliable for assessing the efficacy and safety of SFI. To address these concerns, we conducted sensitivity analyses by excluding high-risk studies and found that the main results remained consistent, indicating a certain degree of robustness. In addition, subgroup analyses based on study characteristics showed no significant differences, further supporting the stability of our findings. However, the quality of safety reporting across the studies remains a concern. Some studies reported no adverse events, which could reflect either genuine safety or incomplete monitoring, increasing the possibility of selective reporting bias. Moreover, we acknowledge that the overall quality of the evidence remains a concern, and the limitations of some included studies restrict the strength of our conclusions. Therefore, while our findings provide preliminary evidence for the therapeutic potential of SFI, future studies should employ rigorous RCT designs with clear randomization methods, transparent reporting, and comprehensive outcome documentation to ensure more reliable and conclusive assessments.

Conclusion

This study suggests that SFI may be a promising alternative therapy for treating AMI without increasing the risk of adverse events. However, our findings may be limited by the quality of the existing studies. High-quality RCTs are needed to provide more robust evidence.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

PC: Data curation, Writing–original draft, Writing–review and editing. HZ: Software, Writing–original draft. ZG: Conceptualization, Data curation, Writing–review and editing. DS: Conceptualization, Writing–review and editing. JZ: Data curation, Formal Analysis, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the project of Hospital capability enhancement project of Xiyuan Hospital, CACMS. (NO. XYZX0404-15, NO. XYZX0204-02, and NO. XYZX0201-03).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1478558/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Subgroup analysis stratified by follow-up time of MACEs.

SUPPLEMENTARY FIGURE S2
Subgroup analysis stratified by treatment time of SAI [**(A)** MACEs; **(B)** CK-MB].

SUPPLEMENTARY FIGURE S3
The publication bias [**(A)** LVEF; **(B)** CRP].

References

Byrne, R. A., Rossello, X., Coughlan, J. J., Barbato, E., Berry, C., Chieffo, A., et al. (2023). 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur. Heart J.* 44 (38), 3720–3826. doi:10.1093/eurheartj/ehad191

Cao, W., Yang, Q., Zhang, W., Xu, Y., Wang, S., Wu, Y., et al. (2021). Drug-drug interactions between salvianolate injection and aspirin based on their metabolic enzymes. *Biomed. Pharmacother.* 135, 111203. doi:10.1016/j.biopha.2020.111203

Chen, H. M., Luo, H., Zeng, W. B., Liu, B., Huang, J. C., Liu, M., et al. (2017a). Salvianolic acid B attenuates oxidized low-density lipoprotein-induced endothelial cell apoptosis through inhibition of oxidative stress, p53, and caspase-3 pathways. *Chin. J. Integr. Med.* doi:10.1007/s11655-016-2645-4

Chen, J., Wang, Y., Wang, S., Zhao, X., and Zhao, L. (2022). Salvianolic acid B and ferulic acid synergistically promote angiogenesis in HUVECs and zebrafish via regulating VEGF signaling. *J. Ethnopharmacol.* 283, 114667. doi:10.1016/j.jep.2021.114667

Chen, Q., Xu, Q., Zhu, H., Wang, J., Sun, N., Bian, H., et al. (2023). Salvianolic acid B promotes angiogenesis and inhibits cardiomyocyte apoptosis by regulating autophagy in myocardial ischemia. *Chin. Med.* 18 (1), 155. doi:10.1186/s13020-023-00859-w

Chen, R. C., Sun, G. B., Ye, J. X., Wang, J., Zhang, M. D., and Sun, X. B. (2017b). Salvianolic acid B attenuates doxorubicin-induced ER stress by inhibiting TRPC3 and TRPC6 mediated Ca(2+) overload in rat cardiomyocytes. *Toxicol. Lett.* 276, 21–30. doi:10.1016/j.toxlet.2017.04.010

Chen, Y. H., Lin, S. J., Ku, H. H., Shiao, M. S., Lin, F. Y., Chen, J. W., et al. (2001). Salvianolic acid B attenuates VCAM-1 and ICAM-1 expression in TNF-alpha-treated human aortic endothelial cells. *J. Cell Biochem.* 82 (3), 512–521. doi:10.1002/jcb.1176

De Luca, G., Suryapranata, H., and Marino, P. (2008). Reperfusion strategies in acute ST-elevation myocardial infarction: an overview of current status. *Prog. Cardiovasc Dis.* 50 (5), 352–382. doi:10.1016/j.pcad.2007.11.004

Dhapare, S., and Sakagami, M. (2018). Salvianolic acid B as an anti-emphysema agent I: *in vitro* stimulation of lung cell proliferation and migration, and protection against lung cell death, and *in vivo* lung STAT3 activation and VEGF elevation. *Pulm. Pharmacol. Ther.* 53, 107–115. doi:10.1016/j.pupt.2018.10.001

Dong, Y., Li, Y., Luo, S., and Duan, B. (2019). Application of salvianolate in the treatment of ischemic myocardial injury in emergency patients. *Shaanxi Chin. Med.* 40 (07), 871–874. doi:10.3969/j.issn.1000-7369.2019.07.016

Duan, X., and Jian-Hong, L. (2016). Effect of salvianolate in the treatment of acute myocardial infarction with hypertension after PCI. *J. Qiqihar Med. Coll.* 37 (31), 3911–3912.

Fu, X. (2024). Effect of coronary intervention combined with salvianolate in the treatment of hypertension and acute myocardial infarction. *Knowl. Prev. Treat. Cardiovasc. Dis.* 14 (02), 34–37.

Gao, H., Bo, Z., Wang, Q., Luo, L., Zhu, H., and Ren, Y. (2019b). Salvanic acid B inhibits myocardial fibrosis through regulating TGF-β1/Smad signaling pathway. *Biomed. Pharmacother.* 110, 685–691. doi:10.1016/j.biopha.2018.11.098

Gao, S., Li, S., Li, Q., Zhang, F., Sun, M., Wan, Z., et al. (2019a). Protective effects of salvianolic acid B against hydrogen peroxide-induced apoptosis of human umbilical vein endothelial cells and underlying mechanisms. *Int. J. Mol. Med.* 44 (2), 457–468. doi:10.3892/ijmm.2019.4227

Gunnar, R. M., Bourdillon, P. D., Dixon, D. W., Fuster, V., Karp, R. B., Kennedy, J. W., et al. (1990). ACC/AHA guidelines for the early management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (subcommittee to develop guidelines for the early management of patients with acute myocardial infarction). *Circulation* 82 (2), 664–707. doi:10.1161/01.cir.82.2.664

Guo, X. (2017). Effect of salvianolate in the treatment of acute myocardial infarction with hypertension after PCI. *J. Med. Forum* 38 (04), 13–16.

He, H., Shi, M., Yang, X., Zeng, X., Wu, L., and Li, L. (2008a). Comparison of cardioprotective effects using salvianolic acid B and benazepril for the treatment of chronic myocardial infarction in rats. *Naunyn Schmiedeb. Arch. Pharmacol.* 378 (3), 311–322. doi:10.1007/s00210-008-0287-6

He, H. B., Yang, X. Z., Shi, M. Q., Zeng, X. W., Wu, L. M., and Li, L. D. (2008b). Comparison of cardioprotective effects of salvianolic acid B and benazepril on large myocardial infarction in rats. *Pharmacol. Rep.* 60 (3), 369–381.

He, T., He, Q., Zhu, Y., Wu, J., and Xu, S. (2014). Clinical study of salvianolate in treatment of non-ST segment elevation myocardial infarction. *Chin. J. General Med.* 12 (05), 735–736. doi:10.16766/j.cnki.issn.1674-4152.2014.05.030

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverria, J., Kulić, Ž., McGaw, L. J., et al. (2022). Best Practice in the chemical characterisation of extracts used in pharmacological and toxicological research-The ConPhyMP-Guidelines. *Front. Pharmacol.* 13, 953205. doi:10.3389/fphar.2022.953205

Ho, J. H., and Hong, C. Y. (2011). Salvianolic acids: small compounds with multiple mechanisms for cardiovascular protection. *J. Biomed. Sci.* 18 (1), 30. doi:10.1186/1423-0127-18-30

Hongmei, L., Pin, F., and Zhang, W. (2017). Effects of salvianolate combined with atorvastatin on oxidative stress injury and inflammatory factors in elderly patients with acute myocardial infarction. *Hebei Med.* 39 (12), 1842–1844. doi:10.3969/j.issn.1002-7386.2017.12.024

Hou, L., and Yunfeng, F. (2018). Effects of salvianolate injection on myocardial injury, neuroendocrine hormone, vascular endothelial function and cardiac function associated with PCI. *J. Mod. Integr. Chin. West. Med.* 27 (23), 2573–2576. doi:10.3969/j.issn.1008-8849.2018.23.019

Hu, S., Wen, J., Fan, X. D., and Li, P. (2024). Study on therapeutic mechanism of total salvianolic acids against myocardial ischemia-reperfusion injury based on network pharmacology, molecular docking, and experimental study. *J. Ethnopharmacol.* 326, 117902. doi:10.1016/j.jep.2024.117902

Hu, X., Cong, Y., Ma, R., Zhou, Y., and Li, H. (2023). Perioperative clinical observation of salvianolate assisted percutaneous coronary intervention for acute myocardial infarction. *Chin. Pharm. Ind.* 32 (18), 93–97. doi:10.3969/j.issn.1006-4931.2023.18.020

Hu, Y., Li, Q., Pan, Y., and Xu, L. (2019). Sal-B alleviates myocardial ischemic injury by inhibiting TLR4 and the priming phase of NLRP3 inflammasome. *Molecules* 24 (23), 4416. doi:10.3390/molecules24234416

Hu, Y., Wang, X., Li, Q., Pan, Y., and Xu, L. (2020). Salvianolic acid B alleviates myocardial ischemic injury by promoting mitophagy and inhibiting activation of the NLRP3 inflammasome. *Mol. Med. Rep.* 22 (6), 5199–5208. doi:10.3892/mmr.2020.11589

Jiang, Y., Cai, Y., Han, R., Xu, Y., Xia, Z., and Xia, W. (2023). Salvianolic acids and its potential for cardio-protection against myocardial ischemic reperfusion injury in diabetes. *Front. Endocrinol. (Lausanne)* 14, 1322474. doi:10.3389/fendo.2023.1322474

Jizheng, L., and Lu, Y. (2020). Effect of salvianolate combined with ticagrelor in the treatment of ST-segment elevation myocardial infarction and its influence on cardiac function indexes and serological indexes. *J. Qiqihar Med. Coll.* 41 (10), 1255–1257. doi:10.3969/j.issn.1002-1256.2020.10.028

Ko, Y. S., Jin, H., Park, S. W., and Kim, H. J. (2020). Salvianolic acid B protects against oxLDL-induced endothelial dysfunction under high-glucose conditions by downregulating ROCK1-mediated mitophagy and apoptosis. *Biochem. Pharmacol.* 174, 113815. doi:10.1016/j.bcp.2020.113815

Lan, N., Peng, X., and Wu, X. (2011). Clinical observation of salvianolate injection combined with percutaneous coronary intervention in the treatment of non-ST segment elevation myocardial infarction. *Shanghai J. Chin. Med.* 45 (01), 41–43. doi:10.16305/j.1007-1334.2011.01.027

Levine, G. N., Bates, E. R., Bittl, J. A., Brindis, R. G., Fihn, S. D., Fleisher, L. A., et al. (2016). 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation* 134 (10), e123–e155. doi:10.1161/CIR.0000000000000404

Li, C. L., Liu, B., Wang, Z. Y., Xie, F., Qiao, W., Cheng, J., et al. (2020). Salvianolic acid B improves myocardial function in diabetic cardiomyopathy by suppressing IGFBP3. *J. Mol. Cell Cardiol.* 139, 98–112. doi:10.1016/j.yjmcc.2020.01.009

Li, J., Chen, Y. H., Li, L. Z., Wang, F., Song, W., Alolga, R. N., et al. (2021). Omics and transgenic analyses reveal that salvianolic acid B exhibits its anti-inflammatory effects through inhibiting the mincle-syk-related pathway in macrophages. *J. Proteome Res.* 20 (7), 3734–3748. doi:10.1021/acs.jproteome.1c00325

Li, W., Polachi, N., Wang, X., Chu, Y., Wang, Y., Tian, M., et al. (2018a). A quality marker study on salvianolic acids for injection. *Phytomedicine* 44, 138–147. doi:10.1016/j.phymed.2018.02.003

Li, Z. M., Xu, S. W., and Liu, P. Q. (2018b). Salvia miltiorrhizaBurge (Danshen): a golden herbal medicine in cardiovascular therapeutics. *Acta Pharmacol. Sin.* 39 (5), 802–824. doi:10.1038/aps.2017.193

Li, S., Wu, Z., Chang, Y., and Ding, H. (2020). Effect of salvianolate injection combined with Rosuvastatin in the treatment of acute myocardial infarction and its effect on inflammatory response. *Chin. J. Med.* 22 (01), 24–27.

Liang, Y., Liu, H., Fang, Y., Lin, P., Lu, Z., Zhang, P., et al. (2021). Salvianolate ameliorates oxidative stress and podocyte injury through modulation of NOX4 activity in db/db mice. *J. Cell Mol. Med.* 25 (2), 1012–1023. doi:10.1111/jcmm.16165

Lin, W., Liu, Z., and Bo, L. (2023). Effect of recombinant human TNK tissue type plasminogen activator combined with salvianolic acid on quality of life and prognosis of patients with acute myocardial infarction after PCI. *Jilin Med. Sci.* 44 (08), 2276–2279.

Ling, W. C., Liu, J., Lau, C. W., Murugan, D. D., Mustafa, M. R., and Huang, Y. (2017). Treatment with salvianolic acid B restores endothelial function in angiotensin II-induced hypertensive mice. *Biochem. Pharmacol.* 136, 76–85. doi:10.1016/j.bcp.2017.04.007

Liu, C. L., Xie, L. X., Li, M., Durairajan, S. S. K., Goto, S., and Huang, J. D. (2007). Salvianolic acid B inhibits hydrogen peroxide-induced endothelial cell apoptosis through regulating PI3K/Akt signaling. *PLoS One* 2 (12), e1321. doi:10.1371/journal.pone.0001321

Liu, H., Liu, W., Qiu, H., Zou, D., Cai, H., Chen, Q., et al. (2020). Salvianolic acid B protects against myocardial ischaemia-reperfusion injury in rats via inhibiting high mobility group box 1 protein expression through the PI3K/Akt signalling pathway. *Naunyn Schmiedeb. Arch. Pharmacol.* 393 (8), 1527–1539. doi:10.1007/s00210-019-01755-7

Liu, L., Li, J., Zhang, Y., Zhang, S., Ye, J., Wen, Z., et al. (2014). Salvianolic acid B inhibits platelets as a P2Y12 antagonist and PDE inhibitor: evidence from clinic to laboratory. *Thromb. Res.* 134 (4), 866–876. doi:10.1016/j.thromres.2014.07.019

Liu, T., Cao, G., Wang, W., Wang, L., Liu, Y., and Li, N. (2020). Effects of salvianolate on oxidative stress, cardiac function and vascular endothelial function in patients with emergency PCI. *J. Mod. Chin. West. Integr. Med.* 29 (10), 1089–1092. doi:10.3969/j.issn.1008-8849.2020.10.016

Liu, Z., Yuan, Y., and Chen, Y. (2022). Effects of salvianolate on cardiac function and coagulation function in elderly patients with acute myocardial infarction after PCI. *Guizhou Med.* 46 (10), 1623–1625.

Lu, B., Li, J., Gui, M., Yao, L., Fan, M., Zhou, X., et al. (2022). Salvianolic acid B inhibits myocardial I/R-induced ROS generation and cell apoptosis by regulating the TRIM8/GPX1 pathway. *Pharm. Biol.* 60 (1), 1458–1468. doi:10.1080/13880209.2022.2096644

Luo, H., Fu, L., Wang, X., Yini, X., Ling, T., and Shen, X. (2023). Salvianolic acid B ameliorates myocardial fibrosis in diabetic cardiomyopathy by deubiquitinating Smad7. *Chin. Med.* 18 (1), 161. doi:10.1186/s13020-023-00868-9

Ma, L., Guan, Y. Q., and Du, Z. D. (2015). Salvianolic acid B down-regulates matrix metalloproteinase-9 activity and expression in tumor necrosis factor-α-induced human

coronary artery endothelial cells. *Chin. Med. J. Engl.* 128 (19), 2658–2663. doi:10.4103/0366-6999.166037

Ma, L., Tang, L., and Yi, Q. (2019). Salvianolic acids: potential source of natural drugs for the treatment of fibrosis disease and cancer. *Front. Pharmacol.* 10, 97. doi:10.3389/fphar.2019.00097

Nichols, M., Townsend, N., Scarborough, P., and Rayner, M. (2014). Cardiovascular disease in Europe 2014: epidemiological update. *Eur. Heart J.* 35 (42), 2929. doi:10.1093/eurheartj/ehu378

O'Gara, P. T., Kushner, F. G., Ascheim, D. D., Casey, D. E., Jr, Chung, M. K., de Lemos, J. A., et al. (2013). 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology foundation/American heart association task force on practice guidelines. *Circulation* 127 (4), e362–e425. doi:10.1161/CIR.0b013e3182742cf6

Ou, Y., Sun, S. J., Shi, H. M., Luo, J. F., Luo, X. P., Shen, Y. Z., et al. (2020). Protective effects of salvianolate on myocardial injury or myocardial infarction after elective percutaneous coronary intervention in NSTE-ACS patients: a randomized placebo-controlled trial. *Chin. J. Integr. Med.* 26 (9), 656–662. doi:10.1007/s11655-020-2728-0

Puymirat, E., Simon, T., Cayla, G., Cottin, Y., Elbaz, M., Coste, P., et al. (2017). Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 Years in the FAST-MI program (French registry of acute ST-elevation or non-ST-elevation myocardial infarction) 1995 to 2015. *Circulation* 136 (20), 1908–1919. doi:10.1161/CIRCULATIONAHA.117.030798

Qiu, H., Liu, W., Lan, T., Pan, W., Chen, X., Wu, H., et al. (2018). Salvianolate reduces atrial fibrillation through suppressing atrial interstitial fibrosis by inhibiting TGF-β1/Smad2/3 and TXNIP/NLRP3 inflammasome signaling pathways in post-MI rats. *Phytomedicine* 51, 255–265. doi:10.1016/j.phymed.2018.09.238

Qiu, J. (2019). Protective effect of salvianolate on myocardium in patients with acute myocardial infarction after PCI. *J. Cardio-Cerebrovascular Dis. Integr. Chin. West. Med.* 17 (02), 256–259. doi:10.12102/j.issn.1672-1349.2019.02.026

Reed, G. W., Rossi, J. E., and Cannon, C. P. (2017). Acute myocardial infarction. *Lancet* 389 (10065), 197–210. doi:10.1016/S0140-6736(16)30677-8

Ren, Y., Tao, S., Zheng, S., Zhao, M., Zhu, Y., Yang, J., et al. (2016). Salvianolic acid B improves vascular endothelial function in diabetic rats with blood glucose fluctuations via suppression of endothelial cell apoptosis. *Eur. J. Pharmacol.* 791, 308–315. doi:10.1016/j.ejphar.2016.09.014

Shen, L., Xu, R., Yin, J., Lu, H., Zhang, S., Huang, Z., et al. (2020a). Effects of salvianolate on myocardial perfusion after primary percutaneous catheter intervention in patients with ST-segment elevation myocardial infarction: a multicenter, randomized, double-blind, placebo-controlled study. *Ann. Transl. Med.* 8 (18), 1185. doi:10.21037/atm-20-6081

Shen, Y., Wang, S., Liu, Y., Ge, L., Xia, L., Zhang, X., et al. (2020b). The effects of salvianolate combined with western medicine on diabetic nephropathy: a systematic review and meta-analysis. *Front. Pharmacol.* 11, 851. doi:10.3389/fphar.2020.00851

Song, Q., Han, X., Xue, Y., Song, T., Chu, X., Zhang, X., et al. (2017). Effects of salvianolic acid B on L-type calcium channels and myocardial contractility in isolated rat ventricular myocytes and hERG K(+) channels expressed in HEK293 cells. *Naunyn Schmiedeb. Arch. Pharmacol.* 390 (8), 791–799. doi:10.1007/s00210-017-1381-4

Sterne, J., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 366, l4898. doi:10.1136/bmj.l4898

Sun, Z., Luo, D., Wang, S., Huang, R., and Dong, P. (2021). Salvianolic acid B inhibits myofibroblast differentiation and extracellular matrix accumulation in nasal polyp fibroblasts via the TGF-β1 signaling pathway. *Mol. Med. Rep.* 23 (6), 478. doi:10.3892/mmr.2021.12117

Tang, C. (2023). Effects of salvianolate on cardiac function and microinflammatory indexes in patients with acute myocardial infarction. *Halbin Med.* 43 (06), 6–8. doi:10.3969/j.issn.1001-8131.2023.06.003

Tang, Y., Jacobi, A., Vater, C., Zou, X., and Stiehler, M. (2014). Salvianolic acid B protects human endothelial progenitor cells against oxidative stress-mediated dysfunction by modulating Akt/mTOR/4EBP1, p38 MAPK/ATF2, and ERK1/2 signaling pathways. *Biochem. Pharmacol.* 90 (1), 34–49. doi:10.1016/j.bcp.2014.04.008

Thygesen, K., Alpert, J. S., Jaffe, A. S., Chaitman, B. R., Bax, J. J., Morrow, D. A., et al. (2018). Fourth universal definition of myocardial infarction (2018). *J. Am. Coll. Cardiol.* 72 (18), 2231–2264. doi:10.1016/j.jacc.2018.08.1038

Valgimigli, M., and Gragnano, F. (2020). The benefit and harm of treating STEMI: between ischemia, bleeding, and reperfusion injury. *Eur. Heart J. Acute Cardiovasc Care* 9 (4), 259–261. doi:10.1177/2048872620934298

Wang, J., Xu, J., Gong, X., Yang, M., Zhang, C., and Li, M. (2019). Biosynthesis, chemistry, and pharmacology of polyphenols from Chinese Salvia species: a review. *Molecules* 24 (1), 155. doi:10.3390/molecules24010155

Wang, Q. Q., Wang, M., Li, Y., Liu, Y. H., and Sun, L. Q. (2022). Attenuation of oxidative stress-induced cell apoptosis and pyroptosis in RSC96 cells by salvianolic acid B. *Chin. J. Integr. Med.* 28 (3), 243–248. doi:10.1007/s11655-021-3507-2

Wang, X., Ye, M., Wang, J., Wang, X., Wang, Y., and Zhu, X. (2013). Effects of salvianolate on reactive oxygen species and toll-like receptors in CD14~+ monocytes after PCI in acute myocardial infarction. *J. Cardiopulm. Vasc. Dis.* 32 (03), 243–246. doi:10.3969/j.issn.1007-5062.2013.03.002

Wang, X., Zhang, X., Ye, M., and Mi, Y. (2017). Effects of salvianolate on the adhesion of CD14~+ monocytes and toll-like receptors in patients with acute ST-segment elevation myocardial infarction after interventional therapy. *J. Cardiopulm. Vasc. Dis.* 36 (02), 82–85. doi:10.3969/j.issn.1007-5062.2017.02.002

Wang, Z. R. (2018). Effect of salvianolate on myocardial remodeling indexes in patients with acute ST-segment elevation myocardial infarction after coronary intervention. *J. Community Med.* 16 (09), 51–52.

Wei, J., Wu, J., Xu, W., Nie, H., Zhou, R., Wang, R., et al. (2018). Salvianolic acid B inhibits glycolysis in oral squamous cell carcinoma via targeting PI3K/AKT/HIF-1α signaling pathway. *Cell Death Dis.* 9 (6), 599. doi:10.1038/s41419-018-0623-9

Windecker, S., Bax, J. J., Myat, A., Stone, G. W., and Marber, M. S. (2013). Future treatment strategies in ST-segment elevation myocardial infarction. *Lancet* 382 (9892), 644–657. doi:10.1016/S0140-6736(13)61452-X

Wu, D., Zhu, J., Cai, W., Wang, G., and Teng, M. (2016). Effects of salvianolate on oxidative stress and vascular endothelial function in patients with acute myocardial infarction after PCI. *J. Pract. Clin. Med.* 20 (19), 16–19. doi:10.7619/jcmp.201619005

Wu, H. L., Li, Y. H., Lin, Y. H., Wang, R., Li, Y. B., and Tie, L. (2009). Salvianolic acid B protects human endothelial cells from oxidative stress damage: a possible protective role of glucose-regulated protein 78 induction. *Cardiovasc Res.* 81 (1), 148–158. doi:10.1093/cvr/cvn262

Xiao, Z., Liu, W., Mu, Y. P., Zhang, H., Wang, X. N., Zhao, C. Q., et al. (2020). Pharmacological effects of salvianolic acid B against oxidative damage. *Front. Pharmacol.* 11, 572373. doi:10.3389/fphar.2020.572373

Xu, J., Wei, K., Zhang, G., Lei, L., Yang, D., Wang, W., et al. (2018). Ethnopharmacology, phytochemistry, and pharmacology of Chinese Salvia species: a review. *J. Ethnopharmacol.* 225, 18–30. doi:10.1016/j.jep.2018.06.029

Xu, Q., Shen, Y., Zhao, J., and Shen, J. (2023). Salvianolate injection for hypertensive nephropathy patients who were using valsartan: a systematic review and meta-analysis. *Front. Pharmacol.* 14, 1119150. doi:10.3389/fphar.2023.1119150

Yang, L., Chen, X., Oi Lam Ung, C., Zhu, H., Hu, H., and Han, S. (2020). Clinical and economic evaluation of salvianolate injection for coronary heart disease: a retrospective study based on national health insurance data in China. *Front. Pharmacol.* 11, 887. doi:10.3389/fphar.2020.00887

Yang, M. C., You, F. L., Wang, Z., Liu, X. N., and Wang, Y. F. (2016). Salvianolic acid B improves the disruption of high glucose-mediated brain microvascular endothelial cells via the ROS/HIF-1α/VEGF and miR-200b/VEGF signaling pathways. *Neurosci. Lett.* 630, 233–240. doi:10.1016/j.neulet.2016.08.005

Ye, M., Hui, A., and Zeng, Y. (2014). Effect of salvianolic acid on vascular endothelium and platelet activation in patients with acute myocardial infarction after PCI. *J. Anhui Med.* 18 (11), 2178–2181. doi:10.3969/j.issn.1009-6469.2014.11.056

Yeh, R. W., Sidney, S., Chandra, M., Sorel, M., Selby, J. V., and Go, A. S. (2010). Population trends in the incidence and outcomes of acute myocardial infarction. *N. Engl. J. Med.* 362 (23), 2155–2165. doi:10.1056/NEJMoa0908610

Yi, Z., Shi, X., and Pan, R. (2017). Effect of salvianolate on blood flow in patients with acute ST-segment elevation myocardial infarction after percutaneous coronary intervention. *Prev. Treat. cardio-cerebrovascular Dis.* 17 (01), 32–34. doi:10.3969/j.issn.1009-816x.2017.11

Zhang, Y., Chen, N., Zhang, M., and Wei, X. (2022). Effects of salvianolate on inflammation and vascular endothelial function in elderly patients with acute myocardial infarction after percutaneous coronary intervention. *Henan Med. Res.* 31 (22), 4098–4101. doi:10.3969/j.issn.1004-437X.2022.22.015

Zhang, D., Wu, J., Liu, S., Zhang, X., and Zhang, B. (2016). Salvianolate injection in the treatment of unstable angina pectoris: a systematic review and meta-analysis. *Med. Baltim.* 95 (51), e5692. doi:10.1097/MD.0000000000005692

Zhang, X., Chen, Z., Huang, S., Zhang, Q., Jin, L., and Deng, M. (2017). Effect of salvianolate on myocardial microcirculation after PCI in diabetic patients with acute myocardial infarction. *Zhejiang J. Integr. Chin. West. Med.* 27 (01), 27–29.

Zhao, J. (2021). To investigate the effects of salvianolate combined with rosuvastatin on cardiac function and inflammatory indexes in elderly patients with acute myocardial infarction. *Curr. Med.* 27 (33), 181–182. doi:10.3969/j.issn.1009-4393.2021.33.078

Zhu, G., and Wang, D. (2018). Effects of salvianolate on cardiac function and hypersensitive C-reactive protein in patients with acute myocardial infarction. *Mod. Hosp.* 18 (05), 713–714. doi:10.3969/j.issn.1671-332X.2018.05.027

Zhu, G., and Wang, D. (2022). Effect of salvianolic acid injection combined with Rosuvastatin on the inflammatory pathway of NF-κB in elderly patients with acute myocardial infarction. *Chin. J. Gerontology* 41 (16), 3400–3404. doi:10.3969/j.issn.1005-9202.2021.16.003

Zou, T., Gao, S., Yu, Z., Zhang, F., Yao, L., Xu, M., et al. (2022). Salvianolic acid B inhibits RAW264.7 cell polarization towards the M1 phenotype by inhibiting NF-κB and Akt/mTOR pathway activation. *Sci. Rep.* 12 (1), 13857. doi:10.1038/s41598-022-18246-0

Zu-shan, Y., Dan-Lei, X., and Yi, H. (2016). Effects of salvianolate on myocardial microcirculation and cardiac function in patients with acute coronary syndrome after percutaneous coronary intervention. *Chin. Pharm.* 19 (01), 109–111.

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 19 December 2024
DOI 10.3389/fphar.2024.1454348

OPEN ACCESS

EDITED BY
Chen Huei Leo,
National University of Singapore, Singapore

REVIEWED BY
Cheng Xue Helena Qin,
Monash University, Australia
Xiaoyong Yu,
Shaanxi Provincial Hospital of Traditional Chinese Medicine, China

*CORRESPONDENCE
Yanxin Wang,
wyanxin2000@126.com
Hongfeng Wang,
ccwhf@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 25 June 2024
ACCEPTED 03 December 2024
PUBLISHED 19 December 2024

CITATION
Li M, He M, Sun M, Li Y, Li M, Jiang X, Wang Y and Wang H (2024) Oxylipins as therapeutic indicators of herbal medicines in cardiovascular diseases: a review.
Front. Pharmacol. 15:1454348.
doi: 10.3389/fphar.2024.1454348

Oxylipins as therapeutic indicators of herbal medicines in cardiovascular diseases: a review

Mengqi Li[1†], Min He[2†], Mengmeng Sun[2], Yongping Li[3], Mengyuan Li[2], Xiaobo Jiang[1], Yanxin Wang[4*] and Hongfeng Wang[2*]

[1]College of Acupuncture and Tuina, Changchun University of Chinese Medicine, Changchun, Jilin, China, [2]Northeast Asia Institute of Traditional Chinese Medicine, Changchun University of Chinese Medicine, Changchun, Jilin, China, [3]Changchun Sino-Russian Science and Technology Park Co., Ltd., Changchun, Jilin, China, [4]Department of Cardiovascular Rehabilitation, The Third Clinical Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, Jilin, China

Globally, cardiovascular diseases (CVDs) remain the leading cause of death, and their prevention and treatment continue to face major challenges. Oxylipins, as novel circulating markers of cardiovascular disease, are crucial mediators linking cardiovascular risk factors such as inflammation and platelet activation, and they play an important role in unraveling cardiovascular pathogenesis and therapeutic mechanisms. Chinese herbal medicine plays an important role in the adjuvant treatment of cardiovascular diseases, which has predominantly focused on the key pathways of classic lipids, inflammation, and oxidative stress to elucidate the therapeutic mechanisms of cardiovascular diseases. However,The regulatory effect of traditional Chinese medicine on oxylipins in cardiovascular diseases remains largely unknown. With the increasing number of recent reports on the regulation of oxylipins by Chinese herbal medicine in cardiovascular diseases, it is necessary to comprehensively elucidate the regulatory role of Chinese herbal medicine in cardiovascular diseases from the perspective of oxylipins. This approach not only benefits further research on the therapeutic targets of Chinese herbal medicine, but also brings new perspectives to the treatment of cardiovascular diseases.

KEYWORDS

herbal medicine, cardiovascular disease, polyunsaturated fatty acids, oxylipins, review

1 Introduction

The incidence of cardiovascular diseases is increasing worldwide. In 2021, cardiovascular diseases (CVDs) were responsible for the deaths of 20.5 million people globally, accounting for one-third of all global deaths, and standing as the leading cause of human mortality (World Heart Federation, 2023). CVDs remain a major public health issue worldwide, imposing a significant socioeconomic burden. This group of disorders encompasses a variety of heart diseases related to blood flow, circulation, and cardiac function, such as coronary artery disease, heart failure. (Roth et al., 2020). The pathogenesis of CVD involves a complex interplay of genetic, environmental, and lifestyle factors that contribute to the development of key pathological features such as inflammation (Henein et al., 2022), endothelial dysfunction (Xu et al., 2021), and thrombosis (Khodadi, 2020). These pathophysiological processes are mediated by a variety of biochemical and molecular mechanisms, including the dysregulation of lipid mediators (Manke et al., 2022), cytokines

(Henein et al., 2022), and cellular adhesion molecules (Troncoso et al., 2021), making them critical targets for therapeutic intervention. As research deepens, researchers have found that cytokines and cellular adhesion molecules are both closely related to lipid mediators, making lipid mediators a key focus in the study of cardiovascular disease mechanisms.

Lipid mediators are important chemical substances in living organisms that can be converted into highly active substances through processes such as fatty acid oxidation. Among them, the oxidation products produced by lipid molecules through endogenous peroxidase and reactive oxygen species pathways are called oxylipins (Nayeem, 2018). These oxylipins play critical roles in modulating various biological processes, including inflammation, vascular endothelial dysfunction, and platelet aggregation (Caligiuri et al., 2017b; Nayeem, 2018). Oxylipins are integral to the regulation of cardiovascular function and pathology, influencing processes such as atherosclerosis (Gleim et al., 2012), hypertension (Gleim et al., 2012), heart failure (Lau et al., 2023) As such, oxylipins represent promising diagnostic tools and target for novel therapeutic approaches aimed at modulating these pathways to improve cardiovascular health (Shearer and Walker, 2018).

Traditional Chinese herbal medicine, which has been utilized for thousands of years in East Asia, is increasingly being integrated into standard biomedical treatments as a complementary or alternative treatment option for CVDs. Interestingly, it has been found that certain herbal medicines, including herbal monomers, extracts, and compound preparations, significantly regulate oxylipin products, their substrates, and the enzymes involved in their pathways (Fu et al., 2018; Zhi et al., 2021). These herbal medicines have also been shown to play an important role in cardioprotection and in slowing the progression of cardiovascular and cerebrovascular diseases in pharmacological studies. This suggests the great potential of Chinese medicines in treating cardiovascular diseases. Therefore, fully elucidating the mechanisms by which Chinese medicines exert cardioprotective effects from the perspective of oxylipins is essential. Such elucidation would facilitate further in-depth studies on the therapeutic mechanisms of Chinese medicines and promote the development of novel therapeutic strategies based on oxylipins, bringing new hope for the treatment of cardiovascular diseases. In this review, we will summarize relevant cellular, animal, and clinical trials, providing a comprehensive overview of the mechanism by which Chinese herbal medicine regulates oxylipins in cardiovascular disease.

2 The biosynthesis pathways of oxylipins and their bioactivities relating to vascular and inflammatory regulations

Oxylipins are bioactive substances formed by the decomposition of polyunsaturated fatty acids (PUFAs) through spontaneous oxidation or enzymatic processes (Nayeem, 2018). Typically, free PUFAs are oxidized into oxylipins either via auto-oxidation, or through three main enzymatic pathways including lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome P450 (CYP450) pathways. Free PUFAs like arachidonic acid (AA) can be converted into epoxyeicosatrienoic acids (EETs) by the CYP pathway, into hydroxyeicosatetraenoic acids (HETEs) by the CYP or LOX pathway, into leukotrienes (LTs) by the LOX pathway, or into prostanoids by the COX pathway; free PUFAs like linoleic acid (LA) can be metabolized into hydroxyoctadecadienoic acids (HODEs) by the LOX pathway, or into epoxymetabolites (EpoMEs) through the CYP epoxygenase pathway (Nayeem, 2018). (Detailed pathways of oxylipins formation are provided in Figure 1). Oxylipin disorder is commonly present in cardiovascular diseases (see Table 1). Oxylipins play diverse regulatory roles (For select examples of oxylipins with cardiovascular bioactive functions, see Table 2), exerting cardioprotective effects and maintaining vascular homeostasis through direct or indirect actions, such as interactions with oxylipin receptors and modulation of inflammation (Hernandez-Saavedra and Stanford, 2022).

2.1 Epoxyeicosatrienoic acids (EETs) in cardiovascular systems

EETs are synthesized in cardiomyocytes and endothelial cells (Campbell et al., 2017) through the metabolism of AA. Cytochrome P450 enzymes, such as CYP2J2, convert AA into four regioisomeric EETs: 5, 6-, 8, 9-, 11, 12-, and 14,15-EET, which are then rapidly hydrolyzed to the less active dihydroxyeicosatrienoic acids (DHETs) in the presence of soluble epoxide hydrolase (sEH) (Lai and Chen, 2021). EETs have a wide range of cardioprotective effects, including inhibiting cardiomyocyte hypertrophy, ameliorating apoptosis, inhibiting platelet adhesion to endothelial cells, and possessing anti-inflammatory properties (Krötz et al., 2004; Spector, 2009; Tacconelli and Patrignani, 2014). DHETs, as stable metabolites of EETs, reflect the concentration of EETs in circulation. These metabolites contribute to improved vascular endothelial function by increasing the expression of nitric oxide, which has been identified as the main chemical compound of endothelial-derived relaxation factors (Zuo et al., 2021).

In CYP2J knockout (KO) rats, plasma EET levels were significantly reduced, exacerbating myocardial inflammation, hypertrophy, and fibrosis. Additionally, myocardial injury became more severe with age in KO rats, corresponding with significant reductions in 11,12-EET and 14,15-EET levels in the plasma (Zhang Y. et al., 2023). Changes in EET or DHET were also observed in animal models of hyperlipidemia and acute myocardial infarction (AMI). Specifically, levels of 14, 15-DHET decreased in hyperlipidemic mice (Chen et al., 2022); and 5, 6-EET, 8, 9-EET, 14, 15-EET, 5, 6-DHET, 11, 12-EET, 14, 15-DHET showed a clear downward trend in post-myocardial infarction rats (Zhi et al., 2021). In large-scale clinical studies, coronary artery disease (CAD) patients exhibit elevated levels of plasma EETs (Theken et al., 2012) and 5, 6-EET is closely associated with blood pressure status (Palmu et al., 2020).

2.2 Hydroxyeicosatetraenoic acids (HETEs) in cardiovascular systems

AA produces medium-chain HETEs, including 5-, 8-, 9-, 11-, 12-, and 15-HETEs, through allylic oxidation in the presence of LOX (Nayeem, 2018). In addition, AA is also metabolized by

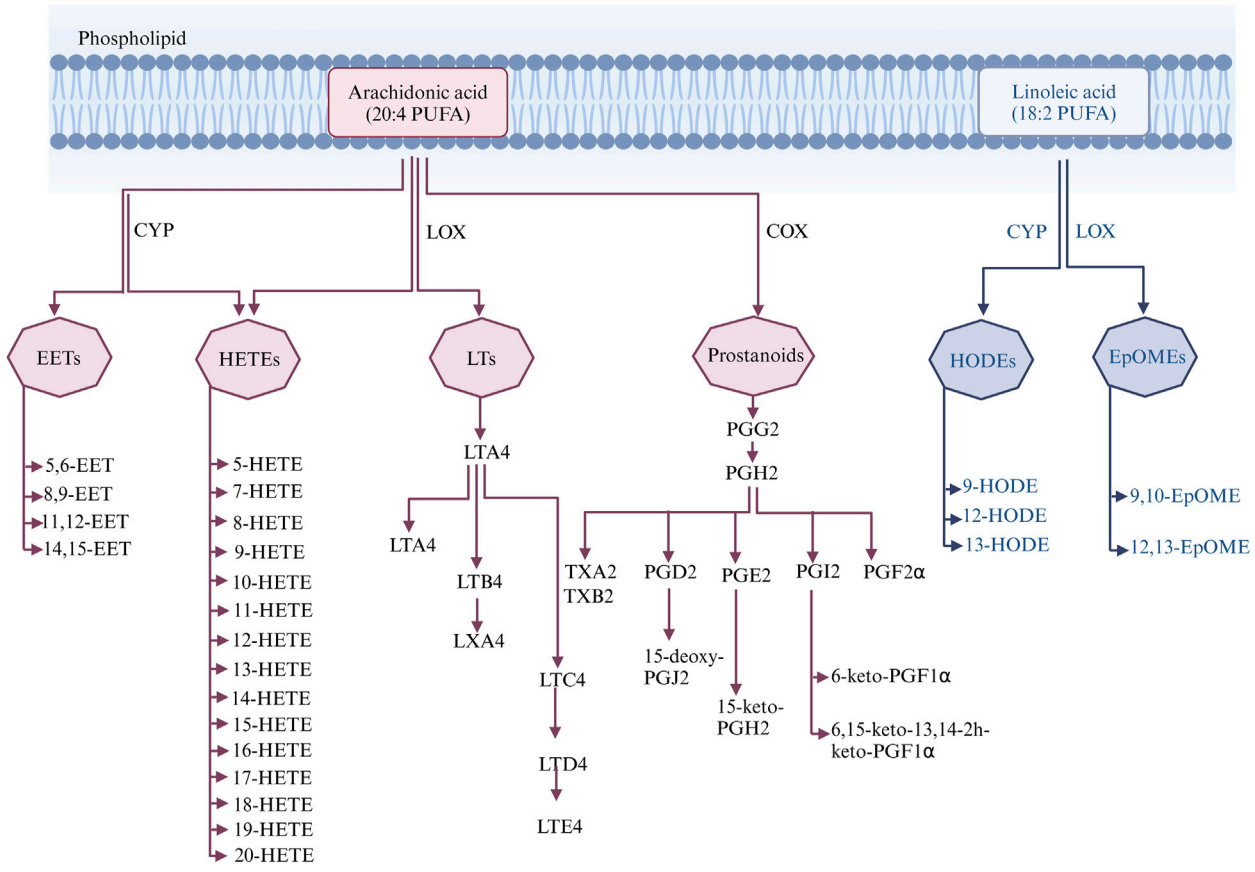


FIGURE 1
Enzymatic pathways of oxylipins generation.

CYP450 enzymes, such as CYP4A and CYP4F, through allylic oxidation to produce terminal HETEs, including 16-, 17-, 18-, 20-HETE, etc. (Shoieb et al., 2019). Multiple cell types in the heart, including cardiomyocytes and fibroblasts, synthesize and respond to HETEs (Escoubet et al., 1986).

Unlike the effects of EETs, most medium-chain HETEs have pro-inflammatory and vasoconstrictive properties, and their formation can increase cardiovascular dysfunction (Nayeem, 2018; ElKhatib et al., 2023). HETEs also block the synthesis of EETs by RL-14 cells and increase the conversion of EETs to DHETs, affecting EET levels (Maayah et al., 2015). Among the medium-chain HETEs, 12- and 15-HETE are closely associated with the cardiovascular system (Breitbart et al., 1996; Huang et al., 2020). Both are produced through CYP in addition to the LOX pathway. 12-HETE has chemotactic properties, can alter vascular tone, and induce VEGF growth (Buchanan et al., 1998). Levels of 12-HETE were also significantly elevated in patients 24–40 h after acute myocardial infarction (Freeman et al., 2015). 15-HETE has been reported to have anti-inflammatory effects and can be converted to LXs, which play a role in reducing inflammation (Buckley et al., 2014). In large-scale clinical studies, patients with coronary artery disease who experienced an acute myocardial ischemic event within 2 years had elevated levels of 8-, 9-, 11-, 12-, and 15-HETE compared to those without a cardiovascular event (Huang et al., 2020). In hypertensive patients, elevated levels of 5-, 8-, 11-, 12-, and 15-HETE have also been observed (Xie et al., 2019; Feugray et al., 2022).

Among the terminal HETEs, 16-HETE, 18-HETE, and 19-HETE and metabolites of 20-HETE can promote vasodilation (Carroll et al., 1996; Caligiuri et al., 2017b). The main functions of 16-HETE include promoting vasodilation and inhibiting inflammation mediated by neutrophil adhesion (Reddy et al., 2003; Shoieb et al., 2019). The precise role of 20-HETE in the cardiovascular system is complex. Studies have shown that 20-HETE produced by CYP4A is an effective vasoconstrictor in mouse aortas and coronary arteries (Hoopes et al., 2015), but there is also research evidence suggesting that 20-HETE can promote the proliferation of endothelial cells through activation of the vascular endothelial growth factor (VEGF) pathway. In clinical trials, among acute coronary syndrome (ACS) patients, the main abnormalities in oxylipins concentrate in terminal HETEs, with higher levels of 19-HETE associated with better ACS prognosis (Solati and Ravandi, 2019). In AMI rats, levels of oxylipins such as 20-HETE increased, while 16-HETE and 18-HETE showed a decreased tendency post-myocardial infarction (Zhi et al., 2021).

However, it is worth noting that HETEs have a relatively short existence time and can be converted into oxoETE under the action of

TABLE 1 Oxylipin changes in cardiovascular diseases.

Diseases	Lipid (↑ Rise; ↓ decline)	Reference
Hyperlipidemia	CYP: ↑ 20-HETE ↓ 14,15-DHET LOX: ↑ LTB4	Caligiuri et al. (2017a)
Hypertension	CYP/LOX: ↑ 5-, 8-, 11-, 12-, 15-, 19-, 20-, HETE LOX: ↑LTD4, TXA2 ↓ PGs Significantly associated with hypertension:11-dehydro-2,3-dinor-TXB2, 12-HHTrE, 295.2279/4.89 (putative eicosanoid), 5,6-EET, Tetranor-12(R)-HETE	Jiang et al. (2015), Xie et al. (2019), Palmu et al. (2020), Feugray et al. (2022)
Thrombosis	COX: ↑ TXA2, TXB2, 6-keto-PGF1α Ratio: ↑ TXB2/6-keto-PGF1α	Dang et al. (2015), Zhang et al. (2020)
Atherosclerosis	COX: ↑ TXB2 ↓ 6-keto-PGF1α Ratio: ↑ TXB2/6-keto-PGF1α	Zhang et al. (2013), Tong et al. (2022)
Coronary artery disease	CYP: ↑ EETs, 9,10-EpOME, 8-HETE, 12,13-EpOME, 8,9-DiHETrE LOX/CYP: ↑ (±)5-HETE, PGE2 ↓ LXA4 Correlation with CAD: PGD2, PGE2, 15d-PGJ2 and 5-HETE negatively correlated with CAD; 13-oxo-ODE positively correlated	Li et al. (2016)
Acute coronary syndrome	COX: ↑ TXB2, 6-keto-PGF1α, TXB2/6-keto-PGF1α, PGE2 CYP/LOX: ↑ 8,9-DiHETrE, 11,12-DiHETrE, 8-HETE, 9-HETE, 11-HETE, 20-HETE, 20-COOH-AA LOX/CYP: ↑ LTB4, 5-HETE, 12-HETE, 15-HETE, 12-HEPE ↓ 9-HODE Associated with ACS: Higher levels of 19-HETE are associated with a better prognosis for ACS Plasma concentrations of 18-HEPE were positively correlated with ACS	Solati and Ravandi (2019)
Myocardial infarction	CYP: ↑ 20-COOH- AA,19,20-EpDPE, 8-HETE, 9-HETE, 11-HETE ↓ 5,6-EET, 8,9-EET, 14,15-EET, 5,6-DHET, 11,12-EET, 14,15-DHET, 16-HETE, 17-HETE, 12,13-EpODE, 12,13-EpOME, 9,10-EpOME COX: ↑ TXB2, TXA2, PGE2, PGF2, 15-Deoxy-PGJ2 ↓ 6-keto-PGF1α, PGI2 ↑↓ PGD2 LOX: ↑ 7-HDoHE, 8-HDoHE, 17-Keto DHA, 5-HEPE, LTB4, 6-trans LTB4, 20-COOH-LTB4, 15-HETE, 12-OxoETE, 15-HPETE ↓tetranor 12-oxoETE, 9-oxoOTrE, 11-HDoHE, 9-HODE, 13-HODE, 9-OxoODE, 13-OxoODE, LXA4 ↑↓ 5-HETE, 12-HETE, 5-oxoETE, 15-oxoETE, 20-HETE Ratio: ↑ TXB2/6-keto-PGF1α	Freeman et al. (2015), Cao et al. (2016), Li et al. (2016), Rocic and Schwartzman (2018), Roman and Fan (2018), Huang et al. (2020), Jiang et al. (2021), Zhi et al. (2021), 2021; Solati et al. (2023)
Myocardial infarction reperfusion injury	CYP: ↑ 20-COOH-AA LOX: ↓ 9-HODE, 13-HODE	Solati et al. (2023)
Heart failure	CYP: ↑ 9,10-EpOME, 12,13-EpOME, 9,10-DiHOME,9,10,13-TriHOME, PGE2, 19,20-DiHDPA, 5,6-DiHETrE,14,15-EpETE, 14,15-DiHETE, 17,18-DiHETE LOX: ↑ 9-oxoODE, 13-oxoODE, 9,10,13-DiHODE, 12,13-DiHODE, 16,17-EpDPE, 15HETE, 15-hPETE, 20-carboxy-LTB4, 9-HOTrE ↓ 8-HOTE, 8-HETrE COX: ↑ 13,14-dihydro-PGF2α, TXB2, PGE2 ↓6-keto-PGF1α Ratio: ↑ TXB2/6-keto-PGF1α RNS: ↑ NO2-LA Automatic oxidation: ↓ 20-HDoHE	Wang et al. (2015b), 2015a; Lau et al. (2023)

dehydrogenase. Among various oxoETEs, 5-oxoETE has been shown to have the effect of inducing myocardial injury (Lai et al., 2021); And 15-oxoETE has a hypotensive effect (Yu et al., 2023). In cell cultures, 15-oxoETE activates NRF2-regulated antioxidant responses and inhibits NF-κB-mediated pro-inflammatory responses (Snyder et al., 2015).

2.3 Leukotrienes (LTs) in cardiovascular systems

Leukotrienes (LTs) are formed from AA through the 5-LOX pathway, producing unstable epoxide metabolites LTA4, which are then metabolized by leukotriene A4 hydrolase (LTA4H) and

TABLE 2 Cardiovascular bioactive functions of oxylipins.

Substrate	Lipid	Bioactive functions	Reference
LA	9-HODE	Harms: regulation of stress and inflammation	Kwon et al. (2020)
	13-HODE	Benefits: inhibits platelet adhesion and aggregation	Buchanan et al. (1991), Marmol et al. (1999), Belvisi and Mitchell (2009)
	9, 10-EpOME	Harms: cardiac inhibition, cardiotoxicity, cytotoxicity	Sugiyama et al. (1987), Hildreth et al. (2020)
	12, 13-EpOME	Dual action: Harms: cardiotoxicity, cytotoxicity, induction of heart failure Benefits: improvement of cardiac structure and function	Bannehr et al. (2019), Hildreth et al. (2020), Pinckard et al. (2021), Lau et al. (2023)
AA	5, 6-EET	Benefits: anti-inflammatory; relaxes vascular smooth muscle; affects migration and proliferation of endothelial and vascular smooth muscle cells	Spector (2009), Sudhahar et al. (2010), Tacconelli and Patrignani (2014), Zuo et al. (2021)
	8, 9-EET	Benefits: anti-inflammatory, improves fibrosis and apoptosis, vasodilator	Sudhahar et al. (2010)
	11, 12-EET	Benefits: anti-inflammatory; vasodilator, prevents IR-induced mitochondrial dysfunction, reduces ROS levels	Sudhahar et al. (2010)
	14, 15-EET	Benefits: restoration of IR, cardioprotective effect, vasodilator	Sudhahar et al. (2010)
	5-HETE	Harms: induces inflammation and cardiomyocyte hypertrophy	Nayeem (2018)
	11-HETE	Benefits: inhibits proliferation of human vascular smooth muscle cells	Brinkman et al. (1990)
	12-HETE	Harms: alter vascular tone, induce vascular endothelial growth factor growth, Induction of myocardial fibrosis and hypertension	Buchanan et al. (1998), Stanke-Labesque et al. (2002)
	15-HETE	Dual action: Benefits: inhibits atherosclerosis, inhibits leukocyte adhesion and aggregation, and vasodilates blood vessels Harms: induces myocardial fibrosis, heart failure, and inflammation	Wittwer and Hersberger (2007), Buckley et al. (2014), Hernandez-Saavedra and Stanford (2022)
	16-HETE	Benefits: vasodilatation, inhibition of adhesion and inflammatory response	Reddy et al. (2003), Shoieb et al. (2019)
	17-(R/S)-HETE	Harms: Induced cardiac hypertrophy	Isse et al. (2023)
	19-HETE	Benefits: vasodilator, anti-inflammatory, regulates blood pressure, prevents cardiac hypertrophy	Alonso-Galicia et al. (1999), Zhang et al. (2005), El-Sherbeni and El-Kadi (2014), Shoieb et al. (2019)
	20-HETE	Dual action: Harms: vasoconstriction, pro-inflammatory Benefits: promotes endothelial cell proliferation	Chen et al. (2012), Hoopes et al. (2015)
	5-oxoETE	Harms: trigger myocardial injury	Lai et al. (2021)
	15-oxoETE	Benefits: antihypertensive effect, antioxidant responses, and inhibits pro-inflammatory responses	Snyder et al. (2015), Yu et al. (2023)
	5, 6-DiHETrE	Related to heart failure	Zhang et al. (2016)
	PGD2	Benefits: anti-inflammatory, inhibits platelet aggregation, vasodilator	Cipollone (2008), Yousefnia et al. (2018)
	15-deoxy-PGJ2	15-Deoxy-PGJ2 is a PGD2 metabolite that activates plasminogen activator inhibitor type-1 via PPAR-activation in endothelial cells	Caligiuri et al. (2017b)
	PGE2	Dual action: Harms: increased vascular permeability, immunosuppression, pro-inflammatory, reduction of infarct size, alleviation of neutrophil accumulation in reperfused myocardium Benefits: anti-inflammatory	Nayeem (2018), Hernandez-Saavedra and Stanford (2022)
	PGF2α	Harms: constricts coronary vessels, promotes cardiac dysfunction and hypertrophy, pro-inflammatory, associated with tachycardia, cardiac dysfunction, and cardiac hypertrophy	Hernandez-Saavedra and Stanford (2022)
	PGI2	Benefits: reduces atherosclerosis, prevents thrombosis and atherosclerosis, lowers hypertension, prevents cardiac hypertrophy, vascular remodeling	Yuhki et al. (2011), Hernandez-Saavedra and Stanford (2022)
	TXA2	Harms: promote platelet aggregation, adhesion, vasoconstriction, pro-inflammatory	Hernandez-Saavedra and Stanford (2022)

(Continued on following page)

TABLE 2 (*Continued*) Cardiovascular bioactive functions of oxylipins.

Substrate	Lipid	Bioactive functions	Reference
	TXB2	Harms: hypertension and vascular dysfunction	Hernandez-Saavedra and Stanford (2022)
	LTB4	Harms: pro-inflammatory, promotes vascular endothelial cell adhesion, related to unstable atherosclerotic plaque	Qiu et al. (2006), Das (2021)
	LTC4	Harms: pro-inflammatory, promotes plaque formation and myocardial ischemia	Nobili et al. (2012)
Ratio	TXB2/ PGF1α	Harms: promoting platelet activation and inducing cardiovascular events	Caligiuri et al. (2017a)

leukotriene C4 synthase (LTC4S) into various metabolites like LTB4, LTC4, LTD4 (Hammarström, 1983). LTs play roles in various acute and chronic inflammations. Especially LTB4, which can induce the release of pro-inflammatory cytokines, recruit and infiltrate leukocytes, and promote inflammation (Das, 2021). LTC4 has been reported to be associated with pro-inflammatory activities, plaque formation, and myocardial ischemia (Nobili et al., 2012). In some animal experiments, researchers also observed changes in LTs. For example, serum LTB4 levels were significantly increased in hyperlipidemic rats (Wang Y. Q. et al., 2020). LTD4 showed high levels in spontaneously hypertensive rats, which may be related to the induction of inflammatory status (Jiang et al., 2015).

2.4 Prostanoids in cardiovascular systems

Prostaglandins (PGs) and thromboxanes (TXs) are collectively referred to as prostanoids. Prostanoids are a class of lipid mediators produced from AA through enzymatic metabolism. Under various physiological and pathological stimuli, AA is catalyzed by phospholipase A2 (PLA2), released from cell membrane phospholipids, and then converted into prostaglandin intermediates PGG2 and PGH under the activity of COX enzymes, which are then metabolized into various bioactive prostaglandins, including PGD2, PGE2, PGF2α, PGI2, TXA2, and others (Beccacece et al., 2023).

Among the different prostanoids, PGD2 is expressed in cells involved in immunity and inflammation (Beccacece et al., 2023). Both PGD2 and its main degradation product, 15-deoxy-Δ-12, 14-Prostaglandin J2 (15d-PGJ2), play roles in inflammation resolution (Yousefnia et al., 2018). PGE2 is one of the most abundant prostaglandins and participates in all processes leading to inflammation (Nakanishi and Rosenberg, 2013). PGF2α is considered a vasoconstrictor of coronary arteries, associated with cardiac dysfunction and hypertrophy (Adams et al., 1998; Kuhn et al., 2015). PGI2 and TXA2 are considered the predominant prostaglandins of the cardiovascular system (Beccacece et al., 2023) produced by vascular endothelial cells and platelets, respectively, exerting opposite effects on vessels and platelets. PGI2 induces vasodilation and inhibits platelet aggregation (Ozen and Norel, 2017), TXA2 induces vasoconstriction and is a potent platelet agonist (Scridon, 2022). The balance between PGI2 and TXA2 is one of the key factors determining the homeostasis of the cardiovascular system. Clinical research shows that for every unit increase in the TXB2 (a metabolite of TXA2)/PGF1α (a downstream metabolite of PGI2) ratio, the likelihood of cardiovascular events increases (Caligiuri et al., 2017a).

Diseases such as thrombosis and atherosclerosis predominantly involve abnormal changes in prostanoids-type oxylipins, closely associated with the activation, adhesion, and aggregation of platelets. Atherosclerosis, a precursor to coronary artery disease and heart failure, involves lipid deposition and thrombus formation, leading to fibrous tissue proliferation and calcification (Tong et al., 2022). These processes thicken and harden the arterial walls, narrow the lumen, induce myocardial ischemia, and ultimately lead to heart failure. Research on oxylipins in atherosclerosis is limited, but increases in TXB2 levels and decreases in 6-keto-PGF1α have been noted (Zhang et al., 2013). Clinical studies have shown that oxylipins, including 11-dehydro-2, 3-dinor-TXB2 is closely associated with blood pressure status (Palmu et al., 2020). In hypertensive patients, elevated levels of TXs (TXA2) and reduced levels of prostanoids have also been observed (Jiang et al., 2015; Xie et al., 2019; Feugray et al., 2022). PGD2/PGE2 and 15d-PGJ2 are inversely correlated with CAD events (Chiang et al., 2022). Compared to healthy volunteers, CAD patients exhibit elevated levels of PGE2 (Theken et al., 2012). Similarly, prostanoids change post-myocardial infarction. Prostanoids like TXB2, TXA2, PGD2, PGE2, PGF2, and 15-Deoxy-PGJ2 rise, while 6-keto-PGF1α and PGI2 decrease (Cao et al., 2016; Li et al., 2016; Jiang et al., 2021; Zhi et al., 2021).

As the terminal stage of various cardiac diseases, heart failure is characterized by structural changes and functional impairments (Snipelisky et al., 2019). Abnormal oxylipins associated with heart failure reflect inflammatory responses, oxidative stress, myocardial fibrosis, and changes in cellular energy metabolism (González et al., 2018; Yin et al., 2019), with notable lipids such as PGE2 mediating inflammation, myocardial fibrosis, and cardiac cell apoptosis. Specifically, in terms of inflammation, prostaglandins like 15R-PGF2α, 11β-DHK-PGF2α, and PGE1 show high relevance to heart failure (Lau et al., 2023). As for myocardial fibrosis, the AA-COX pathway is essential for synthesizing prostanoids (e.g., PGI2, PGD2, PGE2, PGF2, and TXA2), representing the most extensively studied pathway in this area. Studies indicate that in heart failure models in rats, the expression of COX1 and COX2 are significantly upregulated, levels of 13, 14-dihydro-PGF2α, TXB2, PGE2, TXB2/6-keto-PGF1α rise significantly, while 6-keto-PGF1α decreases, concurrently with RAAS system activation, exacerbating the myocardial fibrosis process and inducing heart failure (Wang et al., 2015b).

2.5 Epoxyoctadecaenoic acids (EpOMEs) in cardiovascular systems

EpOMEs are oxides generated by LA via the action of CYP cyclooxygenase. Among the family of EpOMEs, 9, 10-EpOMEs have cardiac inhibitory effects (Sugiyama et al., 1987), and 12, 13-EpOMEs have a higher correlation with heart failure (Lau et al., 2023). Both 9, 10-EpOME and 12, 13-EpOME exhibit elevated levels in CAD patients (Theken et al., 2012). sEH converts EpOMEs to DiHOMEs. Both EpOMEs and DiHOMEs are cytotoxic, cardiotoxic, and can mediate inflammation and vasoconstriction (Hildreth et al., 2020). In CYP2C8-Tie2 mice, hearts perfused in the Langendorff mode with 9, 10-DiHOME or 12, 13-DiHOME showed a reduced recovery rate from reperfusion injury and increased coronary artery resistance (Edin et al., 2011; Bannehr et al., 2019). However, there are also studies supporting the beneficial effects of 12, 13-EpOMEs and 12, 13-DiHOME (Bannehr et al., 2019). In one study, cardiac perfusion of rats with LA, 12, 13-EpOMEs, and 12, 13-DiHOME resulted in a moderate increase in cardiac contraction observed within 10–20 min, with the perfusion effect of 12, 13-DiHOME lasting into the washout period. Accordingly, it is suggested that the impact of EpOMEs and DiHOMEs on cardiovascular function is still uncertain, and the specific effects may be related to other factors such as the dose of oxylipins and the environment.

2.6 Hydroxyoctadecadienoic acids (HODEs) in cardiovascular systems

HODEs are secondary oxidation products of LA, mainly formed through hydroxylation by CYP epoxygenases. The role of HODE in cardiovascular disease remains unclear, as the results of current studies are not consistent. Common HODEs include 9-HODE and 13-HODE. Both 9-HODE and 13-HODE can regulate oxidative stress and inflammation (Folcik and Cathcart, 1994; Krämer et al., 1996; Marmol et al., 1999; Belvisi and Mitchell, 2009). 9-HODE mediates alterations in pro-inflammatory markers associated with chronic inflammation. One study showed that 9-HODE had an inflammation-inducing effect and regulated Forkhead box O nuclear levels through the c-Jun N-terminal protein kinases pathway, linking fatty acid homeostasis, inflammation, and insulin resistance (Kwon et al., 2020). In contrast to 9-HODE, 13-HODE has anti-inflammatory effects (Marmol et al., 1999; Belvisi and Mitchell, 2009), with 13-HODE levels negatively correlated with vascular wall adhesiveness, inhibiting thrombus formation on damaged vascular walls and exerting numerous beneficial effects on cardiovascular health (Buchanan et al., 1991).

Dehydrogenation of HODE by dehydrogenase results in the formation of oxo-ODE. In nested case-control studies of CAD patients, 13-oxo-ODE appears to have a harmful effect (Chiang et al., 2022). The metabolic disorders of HODE and oxo-ODE often occur in acute cardiovascular diseases, such as myocardial infarction (MI) and reperfusion injury after myocardial infarction. However, it is worth noting that HODE and oxo-ODE do not have the same metabolic disturbances in the same disease, probably due to the variability of animal experiments and clinical trials. In clinical trials of myocardial infarction and post-myocardial infarction reperfusion injury, the levels of 9-HODE, 13-HODE, 9-oxo-ODE, and 13-oxo-ODE showed varying degrees of decline (Li et al., 2016; Solati et al., 2023). However, in rats with myocardial infarction, the levels of all these oxylipins were increased (Zhi et al., 2021).

3 Modulation of oxylipins in cardiovascular diseases by traditional Chinese herbal medicines

In China, several traditional Chinese medicine (TCM) formulations are commonly used as adjunct therapies for cardiovascular diseases, including the Xinyue Capsules and Danqi Tongmai Tablets, which are popular used in clinics (Zhi et al., 2021; Wang et al., 2023). Modern pharmacology has shown that these TCM formulations are beneficial for the treatment and prognosis of cardiovascular diseases. As research continues to deepen, the mechanisms by which TCM regulates oxylipins are being gradually revealed, especially in animal experiments and *in vitro* cell studies. Currently, the regulation of oxylipins in cardiovascular diseases by TCM mainly involves lipids such as EETs, HETEs, PGs, HODEs, and EpOMEs produced through the LOX, COX, and CYP pathways (refer to Table 3; Figure 2 for details).

3.1 Regulation of EET by traditional Chinese herbal medicines

TCM formulations, including Xinyue Capsules, Danqi Tongmai Tablets, and Erchen Decoction, regulate four abnormal types of EETs involved in cardiovascular diseases. Xinyue Capsules, a TCM used for treating cardiovascular diseases, primarily consist of Panax quinquefolius saponins (PQS) and are widely used as a supplementary antiplatelet therapy. Recent pharmacological studies have shown that PQS, in combination with antiplatelet drugs, have a synergistic protective effect on platelet adhesion to endothelial cells and reduce the bleeding risk associated with antiplatelet drugs (Wang et al., 2023). This effect is likely due to the activation of the AA-CYP-EET pathway, leading to increased EET synthesis, reduced platelet adhesion and aggregation, and elevated levels of 8, 9-DHET and 11, 12-DHET, thereby ameliorating the cardiac dilation observed in MI rats (Wang et al., 2023).

Danqi Tongmai Tablet, a TCM formula for treating blood stasis-type stable angina pectoris, mainly composed of Salvianolic acid extract and *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae], can increase the levels of 5, 6-EET, 8, 9-EET, 14, 15-EET, 5, 6-DHET, and 11, 12-DHET in the plasma of AMI rats through the CYP2C/2J pathway and downregulate pro-inflammatory cytokines, significantly improving the inflammatory state of AMI rats. The modulation of 5, 6-EET and 8, 9-EET by Danqi Tongmai Tablet at a concentration of 130 mg/kg was the most pronounced, revealing a dose-dependent regulation of arachidonic acid metabolites EET by Danqi Tongmai Tablet (Zhi et al., 2021).

The Erchen Decoction, composed of *Pinellia ternata* (Thunb.) Breit. [Araceae], *Poria cocos* (Schw.)Wolf. [Polyporaceae], *Citrus reticulata* Blanco. [Rutaceae], etc. (names based on the Chinese Pharmacopoeia and http://mpns.kew.org/mpns-portal/), has the

TABLE 3 Summary of Chinese herbal medicines that Regulate Oxylipins mechanisms.

Diseases	Chinese herbal medicine	Main component(s)/ constituent(s)	Oxylipins targets (↑/↓)	Reference
Hypercholesterolemia	Erchen Decoction	*Pinellia ternata* (Thunb.) Breit. [Araceae], *Poria cocos* (Schw.) Wolf. [Polyporaceae], *Citrus reticulata* Blanco. [Rutaceae], etc.	CYP: 14, 15-DHET↑, 20-HETE↓	Chen et al. (2022)
Hypercholesterolemia	Cardiovascular protective mixture	*Salvia miltiorrhiza* Bunge. [Lamiaceae], *Ligusticum chuanxiong* Hort. [Apiaceae], *Angelica sinensis* (Oliv.) Diels. [Apiaceae], etc.	COX: PGI2↑	Tu et al. (2003)
Hypercholesterolemia	Bidens bipinnata L. [Asteraceae]	—	LOX: LTB4↓	Wang et al. (2020b)
Hyperlipidemia	Danhong Injection	*Salvia miltiorrhiza* Bunge. [Lamiaceae], *Carthamus tinctorius* L. [Asteraceae]	COX: 6-keto-PGF1α↑, TXA2↓, PGE2↓ PGI2↑	Wang et al. (2013), Fan et al. (2018)
hypertension	Tengfu Jiangya	*Uncaria rhynchophylla* (Miq.) Miq. ex Havil or *Uncaria macrophylla* Wall or *Uncaria hirsuta* Havil or *Uncaria sinensis* (Oliv.) Havil or *Uncaria sessilifructus* Roxb. [Rubiaceae], *Raphanus sativus* L. [Brassicaceae]	COX: TXB2↓, PGE2↓ LOX: LTD4↓	Jiang et al. (2015)
Thrombosis	*Callicarpa nudiflora* Hook. and Arn. [Lamiaceae]	1,6-di-O-caffeoyl-D-glucopyranoside	COX: TXA2↓	Fu et al. (2017)
Thrombosis	*Callicarpa nudiflora* Hook. and Arn. [Lamiaceae]	luteolin-4′-O-β-D-glucopyranoside	COX: TXA2↓	Xu et al. (2018)
Thrombosis	*Salvia miltiorrhiza* Bunge. [Lamiaceae]	Danshensu	COX: TXB2↓, 6-keto-PGF1α↑ Ratio: TXB2/6-keto-PGF1α↓	Yu et al. (2014)
Thrombosis	*Ilex pubescens* Hook. and Arn. [Aquifoliaceae]	—	COX: TXB2↓, 6-keto-PGF1α↑ Ratio: TXB2/6-keto-PGF1α↓	Cao et al. (2018)
Atherosclerosis	*Whitmania pigra* Whitman or *Hirudo nipponica* Whitman or *Whitmania acranulata* Whitman. [Haemopidae]	—	COX: TXB2↓, 6-keto-PGF1α↑ Ratio: TXB2/6-keto-PGF1α↓	Jiang et al. (2019)
Atherosclerosis	*Crataegus Pinnatifida* Bge. var. *major* N. E. Br. [Rosaceae]	Aqueous extract of *Crataegus Pinnatifida* Bge. var. *major* N. E. Br. [Rosaceae]	COX: TXB2↓, 6-keto-PGF1α↑ Ratio: TXB2/6-keto-PGF1α↓	Zhang et al. (2013)
Coronary heart disease	*Salvia miltiorrhiza* Bunge. [Lamiaceae]	Salvianolic acid B	COX: PGE2↓	Wang et al. (2013)
Myocardial ischemia	*Syringa pinnatifolia* Hemsl. [Oleaceae]	Ethanol extract of *Syringa pinnatifolia* Hemsl	COX: TXB2↓, 6-keto-PGF1α↑ Ratio: TXB2/6-keto-PGF1α↓	Zhang et al. (2022)
Myocardial infarction	Shexiang Boxin Pill	*Moschus berezovskii* Flerov or *Moschus sifanicus* Przewalski or *Moschus moschiferus* Linnaeus. [Cervidae], *Panax ginseng* C. A. Mey. [Araliaceae], and *Liquidambar orientalis* Mill. [Hamamelidaceae R. Br.]	COX: TXB2↓, 6-keto-PGF1α↑ CYP: 20-HETE↑ Ratio: TXB2/6-keto-PGF1α↓	Huang et al. (2017)
Myocardial infarction	Shensong Yangxin Capsule	*Panax ginseng* C. A. Mey. [Araliaceae], *Nardostachys jatamansi* DC. [Caprifoliaceae], *Salvia miltiorrhiza* Bunge. [Lamiaceae] , etc.	COX: TXA2↓, PGI2↑	Jiang et al. (2021)
Myocardial infarction	*Panax quinquefolium* L. [Araliaceae]	Panax quinquefolius saponins	COX: TXA2↓TXB2↓, PGI2↑, 6-keto-PGF1α↑, 6, 15-2keto-13, 14-2h-PGF1α↑ CYP: EET↑, DHET↑ Ratio: TXB2/6-keto-PGF1α↓	Wang et al. (2023)
Acute myocardial infarction	Danqi Tongmai Tablet	Salvianolic acid extract and *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae]	Cox: PGD2↓, PGE2↓, TXB2↓ 15-deoxy-PGJ2↓, PGF2α↓, PGE1↑, PGI1↑, PGI2↑, 6-keto-PGF1α↑	Zhi et al. (2021)

(Continued on following page)

TABLE 3 (*Continued*) Summary of Chinese herbal medicines that Regulate Oxylipins mechanisms.

Diseases	Chinese herbal medicine	Main component(s)/ constituent(s)	Oxylipins targets (↑/↓)	Reference
			Ratio: TXB2/6-keto-PGF1α↓ LOX: 5-HETE↓, 5-oxoETE↓, LTB4↓, 12-HETE↓, 12-oxoETE↓, 15-HETE↓, 15-oxoETE↓, 15-HpETE↓ LXA4↑ CYP: 8-HETE↓, 9-HETE↓, 11-HETE↓, 20- HETE↓ 5, 6-EET↑, 8, 9-EET↑, 11,12-EET↑, 14, 15-EET↑, 5, 6-DHET↑, 8, 9-DHET↑, 11, 12-DHET↑, 16-HETE↑, 17-HETE↑ Oxidation: 9-HODE↓, 13-HODE↓, 9-oxoODE↓, 13-oxoODE↓	
Acute myocardial infarction	Qishen Granule	*Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. [Fabaceae], *Salvia miltiorrhiza* Bunge. [Lamiaceae], *Scrophularia ningpoensis* Hemsl. [Scrophulariaceae], etc.	COX: TXB2↓, PGE2↓, 6-keto-PGF1α↑ Ratio: TXB2/6-keto-PGF1α↓	Li et al. (2016)
Heart failure, Acute myocardial infarction	Qishen Yiqi Dropping Pill	*Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. [Fabaceae], *Salvia miltiorrhiza* Bunge. [Lamiaceae], *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae], etc.	LOX:15-HpETE↓, 15-HETE↓ COX: PGE2↓	Wang et al. (2015a)
Heart failure	Qili Qiangxin	*Panax ginseng* C. A. Mey. [Araliaceae], *Astragalus membranaceus* (Fisch.) Bge.var.*mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. [Fabaceae], *Aconitum carmichaelii* Debeaux. [Ranunculaceae], etc.	CYP: 9, 10-EpOME↓, 12, 13-EpOME↓, 9, 10-DiHOME↓, 5, 6-DHET↑ LOX: 9-OxoODE↓, 13-OxoODE↓, 9, 10, 13-TriHOME↓, 12, 13-DiHODE↓, 20-carboxy-LTB4↓, 5,6-DHET↑	Fu et al. (2018)
Heart failure	Linggui zhugan Decoction	*Poria cocos* (Schw.) Wolf. [Polyporaceae], *Cinnamomum cassia* Presl. [Lauraceae], *Atractylodes macrocephala* Koidz. [Asteraceae], etc.	LOX: 15-HpETE↓, 15-HETE↓	Wang et al. (2020a)
Heart failure	Danqi Pill	*Salvia miltiorrhiza* Bunge. [Lamiaceae], *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae]	COX: TXB2↓, 6-keto-PGF1α↑ Ratio: TXB2/6-keto-PGF1α↓	Wang et al. (2014)
—	Huanglian Jiedu Decoction	*Coptis chinensis* Franch. [Ranunculaceae], *Scutellaria baicalensis* Georgi. [Lamiaceae], *Phellodendron chinense* Schneid. [Rutaceae], etc.	LOX: LTB4↓, 5-HETE↓ COX: PGE2↓	Yuan et al. (2020)

effects of drying dampness and resolving phlegm, regulating qi, and harmonizing the middle. It is often used in the treatment of clinical lipid metabolism disorders (Li S. et al., 2020; Zhang L. et al., 2023). In the formula-disease correspondence group, the concentration of 14, 15-DHET was significantly increased, indicating that Erchen Decoction protected the vascular endothelium of mice with dyslipidemia and stasis syndrome by increasing serum 14, 15-DHET (Chen et al., 2022). Similarly, Qili Qiangxin Capsule, a TCM formula mainly composed of *Panax ginseng* C. A. Mey. [Araliaceae], *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. [Fabaceae] (Usually using *Astragalus membranaceus* (Fisch.) Bge. var.*mongholicus* (Bge.)Hsiao), *Aconitum carmichaelii* Debeaux. [Ranunculaceae], etc., could increase levels of 5, 6-DHET through the AA-CYP450 pathway, regulating inflammatory responses induced by heart failure (Fu et al., 2018).

3.2 Regulation of HETEs by traditional Chinese herbal medicines

Current research indicates that TCM regulation of HETEs primarily focuses on 5-, 12-, 15-, 16-, 17-, and 20-HETE. As previously mentioned, 5-, 12-, and 15-HETE all have harmful effects on the cardiovascular system. The main functions of 16-HETE include promoting vasodilation and inhibiting inflammation mediated by neutrophil adhesion. In AMI model rats, Danqi Tongmai Tablet can elevate levels of 16-HETE and 17-HETE

10.3389/fphar.2024.1454348

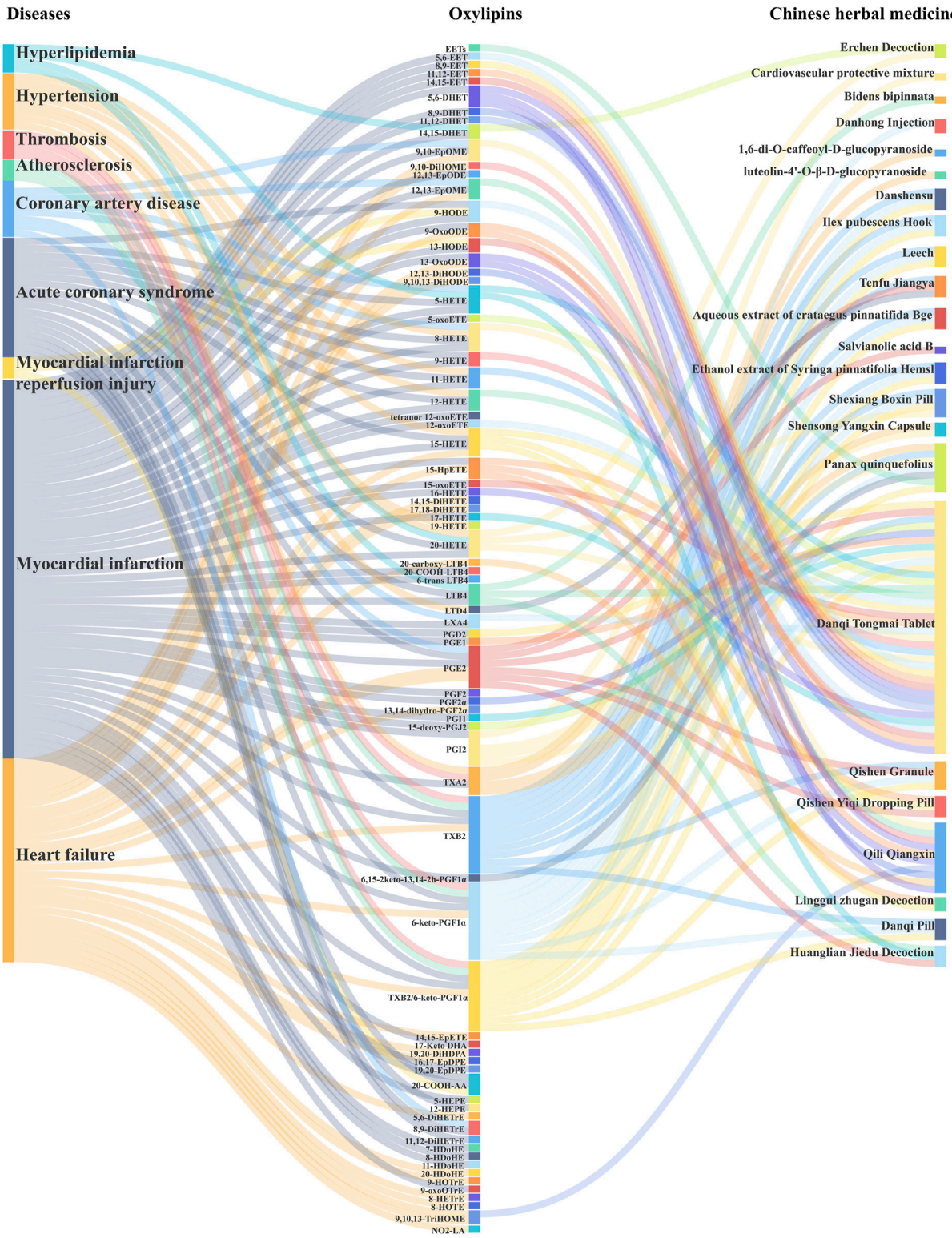


FIGURE 2
Disrupted Oxylipins in Cardiovascular Disease and Oxylipins Targets in Chinese Herbal Medicine. This Sangi diagram is used to demonstrate the oxylipin targets of cardiovascular disease and Chinese herbal medicine, providing a comprehensive overview of the regulation of oxylipins by Chinese herbal medicine in cardiovascular disease.

through the CYP pathway and reduce levels of 5-, 12-, 15-HETE, and 5-, 15-oxoETE through the LOX pathway.

The exact role of 20-HETE in the cardiovascular system needs further exploration. Current research evidence indicates the beneficial effects of 20-HETE but also emphasizes its harm to the cardiovascular system. In dyslipidemic and stasis syndrome model mice (n-5C57BL/6J mice and n-30 apolipoprotein E knockout mice), the serum concentration of 20-HETE was reduced by Erchen Decoction, and the effect of Erchen Decoction on 20-HETE was also related to the prescription-syndrome correspondence. When the prescription-syndrome did not correspond, Erchen Decoction had no significant regulatory effect on 20-HETE compared to the model group (Chen et al., 2022). However, some studies support the beneficial effects of 20-HETE, highlighting its ability to promote endothelial cell proliferation via the VEGF pathway (Chen et al., 2012). Some TCMs, like Shexiang Baoxin Pill, a pill made from *Moschus berezovskii* Flerov or *Moschus sifanicus* Przewalski or *Moschus moschiferus* Linnaeus. [Cervidae] (Usually using *M. berezovskii* Flerov), *Panax ginseng* C. A. Mey. [Araliaceae], and *Liquidambar orientalis* Mill. [Hamamelidaceae R. Br.], etc., commonly used in China for the clinical treatment of angina. Shexiang Baoxin Pill can increase levels of 20-HETE and endothelial progenitor cells (EPCs) in rats with myocardial infarction, along with increasing VEGF expression. Conversely, HET0016 (a 20-HETE synthesis inhibitor) could partially weaken the effects of Shexiang Baoxin Pill on EPCs, VEGF, and angiogenesis. These results strongly suggest that the effects of Shexiang Baoxin Pill on angiogenesis in myocardial infarction are mediated by promoting 20-HETE-induced mobilization of EPCs and VEGF expression (Huang et al., 2017).

3.3 Regulation of LTs by traditional Chinese herbal medicines

Danqi Tongmai Tablet can reduce LTB4 levels through the LOX5 pathway, significantly downregulate pro-inflammatory cytokines, and alleviate the inflammatory status of AMI model rats (Zhi et al., 2021). In spontaneously hypertensive rats, LTD4 levels were elevated, and the Chinese herbal formula Tengfu Jiangya Tablet, main constituents are *Uncaria rhynchophylla* (Miq.) Miq. ex Havil or *Uncaria macrophylla* Wall or *Uncaria hirsuta* Havil or *Uncaria sinensis* (Oliv.) Havil or *Uncaria sessilifructus* Roxb. [Rubiaceae] (Usually using *Uncaria rhynchophylla* (Miq.) Miq. ex Havil) and *Raphanus sativus* L. [Brassicaceae], with the effects of lowering blood pressure) could lower leukotriene LTD4 levels through AA metabolism, suggesting that the interaction between inflammation and hypertension could be one of the potential mechanisms by which leukotrienes exert cardiovascular protective effects (Jiang et al., 2015).

3.4 Regulation of prostaglandins by traditional Chinese herbal medicines

Various herbal formulas have regulatory effects on PGs/TXs oxylipins by COX pathway. For example, Danqi Tongmai Tablet can restore AA metabolism disorder, downregulate metabolic levels of PGD2, PGE2, PGF2α, 15-d-PGJ2, TXB2, and upregulate levels of 6-keto-PGF1α, PGE1, and PGI1 in AMI rats (Zhi et al., 2021). Danhong Injection, a Chinese herbal injection made from *Salvia miltiorrhiza* Bunge. [Lamiaceae] and *Carthamus tinctorius* L. [Asteraceae], is commonly used in the treatment of occlusive cardiovascular diseases (Zhang et al., 2019). It has been shown that Danhong Injection could relax aortic vessels, increase COX mRNA expression, raise 6-keto-PGF1α levels, and promote PGI2 release *in vitro*. Moreover, in hyperlipidemic model rats, Danhong Injection could increase PGE mRNA and 6-keto-PGF1α expression and decrease TXA2 levels, thereby inhibiting platelet aggregation (Wang et al., 2013; Fan et al., 2018). Salvianolic acid, the main component of traditional Chinese herbal medicine *Salvia miltiorrhiza* Bunge. [Lamiaceae], can reduce PGE2 levels and inhibit lipid peroxidation through the AA pathway (Li Y. P. et al., 2020).

In TCM formulations, Qishen Yiqi Dripping Pill, a TCM formula for treating blood stasis-type stable angina pectoris, mainly composed of *Astragalus membranaceus* (Fisch.) Bge. var.*mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. [Fabaceae] (Usually using *Astragalus membranaceus* (Fisch.) Bge. var.*mongholicus* (Bge.) Hsiao, *Salvia miltiorrhiza* Bunge. [Lamiaceae], *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae], etc., can lower NF-κB, COX2, and PGE2 receptor levels, alleviating the inflammatory state (Wang et al., 2015b). Under pathological conditions, inflammation stimulates the production of PGE2 through the COX2/mPGES-1 (membrane-associated prostaglandin E2 synthase 1) pathway, leading to macrophage activation in plaques and matrix metalloproteinase (MMP)2 and MMP9 via the cAMP-dependent pathway. MMPs can degrade the extracellular matrix in the fibrous cap, reducing its components, thinning the fibrous cap, making plaques unstable and prone to rupture, leading to acute ischemic events (Mezzetti, 2005; Sun and Li, 2018). In addition, PGE2 can activate G protein-coupled receptors EP2 and EP4, both of which are associated with vasodilation, stimulation of inflammation, and cardiac hypertrophy (Torres et al., 2015; Sun and Li, 2018; Wang et al., 2019). EP4 is also one of the most important receptors in human inflammation-related diseases (Takayama et al., 2002; Tang et al., 2012), playing a significant role in PGE2-dependent MMP expression. In ankylosing spondylitis patients with concomitant cardiovascular diseases, EP4 expression is much higher than in ankylosing spondylitis patients without clinical manifestations (Cipollone et al., 2005). Thus, it can be inferred that COX2, PGE2, and its receptors EP2, EP4, MMP play significant roles in cardiovascular events. Qishen Yiqi Dripping Pill downregulates AA levels through the AA-COX1/COX2-PGE2 pathway, inhibiting PGE2-mediated apoptosis, regulating PGE2 downstream metabolites EP2 and EP4, reducing MMP2 and MMP9 production, and downregulating p53 and FasL protein. Compared to the model group, the myocardial apoptosis rate in the Qishen Yiqi Dripping Pill group rats was decreased (Wang et al., 2015b; 2015a).

The cardiovascular protective mixture, a TCM formula made from *Salvia miltiorrhiza* Bunge. [Lamiaceae], *Ligusticum chuanxiong* Hort. [Apiaceae], and nine other blood-activating and stasis-removing herbs, can activate the proliferation of vascular endothelial cells *in vitro*, thereby promoting the

synthesis and secretion of PGI2 and playing a protective role in the vascular endothelium (Tu et al., 2003). In the MI model established by left coronary artery ligation, the expression level of PGI2 mRNA decreased and TXA2 increased compared to the MI group. Shensong Yangxin Capsule (main constituents: *Panax ginseng* C. A. Mey. [Araliaceae], *Nardostachys jatamansi* DC. [Caprifoliaceae], *Salvia miltiorrhiza* Bunge. [Lamiaceae], etc., with the effects of benefiting qi and nourishing yin, activating blood and dredging collaterals). could increase plasma PGI2 mRNA levels in MI rabbits, reduce TXA2 levels, thereby balancing vasoconstriction and dilation (Jiang et al., 2021). Among the single herbs in Chinese medicine, *Callicarpa nudiflora* Hook. and Arn. [Lamiaceae], a herb that dispels blood stasis, reduces swelling, and stops bleeding, has an extract, 1,6-di-O-caffeoyl-β-D-glucopyranoside, that has been found to resist P2Y12 and TP2 receptors (prostaglandin-like), thereby inhibiting TXA2 synthesis (Fu et al., 2017). In MI model rats, Panax quinquefolius saponins combined with dual antiplatelet therapy (PQS + DAPT) significantly increased PGI2 synthesis, reduced platelet activation and thrombogenesis agonist TXA2 synthesis and TXB2 levels, while plasma levels of 6-keto-PGF1α increased tenfold, and 6,15-2keto-13,14-2H-PGF1α levels increased threefold. This suggests that the improvement in platelet inhibition by PQS + DAPT may be partly due to the upregulation of AA/PGI2 and the downregulation of AA/TXA2 metabolism (Wang et al., 2023). The downregulation of TXA2 metabolism by PQS + DAPT could be the basis for the enhanced anti-aggregation effect of the combined therapy, possibly helping to reduce cardiovascular events to some extent. Additionally, PGI2 can counteract the thrombotic properties of TXA2, further inhibiting platelet activation. Further analysis found that PGI2 is co-regulated by COX1 and COX2 produced by endothelial cells, which possess vasodilatory properties. In endothelial cells, the use of DAPT alone or in combination with PQS does not affect the expression of COX1 protein; however, it elicits distinct effects on the expression and biological activity of COX2 protein. When DAPT was used alone, COX2 protein expression decreased, and activity declined, whereas PQS + DAPT had no inhibitory effect on COX2 protein expression, and at the same time, COX2 protein activity was enhanced. TXA2 is synthesized in platelets through the COX1 pathway, possessing vasoconstrictive properties. In platelets, compared to the use of DAPT alone, PQS + DAPT showed no significant differences in the regulation of COX1 and COX2 expression and activity. Therefore, compared to the inhibitory effect of the platelet COX1/TXA2 pathway, the regulatory effect of the combined application of PQS with DAPT on the endothelial cell COX2/PGI2 pathway is more optimal (Wang et al., 2023).

Syringa pinnatifolia Hemsl. [Oleaceae] is a Chinese herb mainly produced in Mongolia, China, which has the effect of moving qi and relieving pain and is often made into powder or Chinese medicine formulations for the treatment of myocardial ischemia (Zhang et al., 2022). The peeled extract of *Syringa pinnatifolia* Hemsl. [Oleaceae] downregulated the expression of COX1 and COX2 expression in myocardial ischemia model mice (C57BL/6 mice). Specifically, the strongest inhibitory effects on COX2 and COX1 were observed when the drug concentrations of the extract of *Syringa pinnatifolia* Hemsl. [Oleaceae] were at 20–80 mg/kg and 80 mg/kg, respectively. In addition, *Syringa pinnatifolia* Hemsl. [Oleaceae] pretreatment slightly increased plasma levels and reduced TXB2 production, while the opposite was observed in protein homogenates. Interestingly, the 6-keto-PGF1α/TXB2 ratio in the *Syringa pinnatifolia* Hemsl. [Oleaceae] pretreatment group was strongly dose-dependent, approaching the observed values in the myocardial ischemia sham surgery group, and was significantly superior to the positive drug pretreatment group (Cao et al., 2016).

The balance between 6-keto-PGF1α and TXB2 maintains the homeostasis of the cardiovascular system. Some blood-activating Chinese medicines like aqueous extract of *Crataegus Pinnatifida* Bge. var. *major* N. E. Br. [Rosaceae], Danshensu, Leech powder, the formulas Qishen Granule (main constituents: *Astragalus membranaceus* (Fisch.) Bge. var.*mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. [Fabaceae] (Usually using *Astragalus membranaceus* (Fisch.) Bge. var.*mongholicus* (Bge.) Hsiao, *Salvia miltiorrhiza* Bunge. [Lamiaceae], *Scrophularia ningpoensis* Hemsl. [Scrophulariaceae], etc.), Shexiang Boxin pill, and Danqi Tablet (main constituents: *Salvia miltiorrhiza* Bunge. [Lamiaceae] and *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae]) have mechanisms similar to the peeled extract of *Syringa pinnatifolia* Hemsl. [Oleaceae]. These extracts are all capable of lowering plasma TXB2 levels, increasing plasma 6-keto-PGF1α levels, maintaining a relatively stable 6-keto-PGF1α/TXB2 ratio, reducing lipid peroxidation levels (Zhang et al., 2013; Wang et al., 2014; Yu et al., 2014; Li et al., 2016; Li J. et al., 2020; Huang et al., 2017; Jiang et al., 2019).

3.5 Regulation of EpOMEs by traditional Chinese herbal medicines

In rats with heart failure, levels of LA-produced 9, 10-EpOME and 12, 13-EpOME were elevated, and Qili Qiangxin Capsule reduced these oxylipin levels while maintaining stable levels of 9, 10-DiHOME, thereby controlling cardiac hypertrophy and inflammation associated with heart failure (Fu et al., 2018).

3.6 Regulation of HODEs by traditional Chinese herbal medicines

TCM has been shown to regulate two common types of HODEs. Interestingly, in a study involving Danqi Tongmai Tablets, these tablets significantly reduced the levels of the pro-inflammatory lipid 9-HODE and the anti-inflammatory lipid 13-HODE in rats with myocardial infarction compared to those in acute myocardial infarction and sham operation groups. The levels of their downstream metabolites, 9-OxoODE and 13-OxoODE, were also significantly lowered (Zhi et al., 2021). However, the inflammation status of MI in the Danqi Tongmai Tablet group was still improved, suggesting that Danqi Tongmai Tablet may have a stronger regulatory effect on anti-inflammatory oxylipins, though further research is needed to confirm these results. Similarly, in rats with heart failure, Qili Qiangxin Capsule significantly lowered downstream metabolites of 9-HODE and 13-HODE, such as 9-OxoODE, 13-OxoODE, 12-, 13-DiHODE, and 9-, 10-, 13-TriHOME (Fu et al., 2018), suggesting a regulatory mechanism for HODE metabolites similar to that of Danqi Tongmai Tablet.

3.7 Effects of Chinese herbal medicine on oxidized lipogenesis substrates and related enzymes

Currently, in the research of TCM in treating cardiovascular diseases, some studies have preliminarily revealed the effects of TCM on upstream substrates for oxylipin generation and related enzymes (including PLA2 and COX), such as the formula Xinkeshu Capsules (main constituents: *Salvia miltiorrhiza* Bunge. [Lamiaceae] and *Pueraria lobata* (Willd.) Ohwi. [Fabaceae], used for common cardiovascular diseases such as coronary heart disease, angina, hypertension, arrhythmia, and hyperlipidemia), Huanglian Jiedu Tang (main constituents: *Coptis chinensis* Franch. [Ranunculaceae], *Scutellaria baicalensis* Georgi. [Lamiaceae], *Phellodendron chinense* Schneid. [Rutaceae], etc., commonly used for febrile diseases), and Yixin Shu (main constituents: *Salvia miltiorrhiza* Bunge. [Lamiaceae], *Panax ginseng* C. A. Mey. [Araliaceae], *Ophiopogon japonicus* (L.f). Ker Gawl. [Liliaceae], etc., commonly used to treat coronary heart disease).

The mechanism of Xinke Shu Capsules in treating myocardial infarction involves inhibiting fatty acid β-oxidation, specifically manifested as reversing phospholipase A2ⅡA and regulating the levels of LA and AA in myocardial tissue (Sun et al., 2021). Huanglian Jiedu Decoction and Yixin Shu can restore AA levels in rats with heart failure (Xu et al., 2019; Yuan et al., 2020).

The COX/LOX pathway is an important route for LA and AA to be converted into oxylipins. Studies have shown that some Chinese medicinal herbs can regulate COX and LOX in animals with cardiovascular disease models, thereby improving myocardial injury and protecting the heart. Danshen Dripping Pill downregulates AA metabolism through the AT1-mediated PLA2-COX2/5-LOX metabolic pathway, inhibits RAAS system activation and MMPs expression, and thus inhibits myocardial fibrosis in myocardial failure rats (Zhang et al., 2018). In coronary heart disease models, Danqi pill downregulates the expression of PLA2, COX2, NF-κB on the inflammatory pathway, significantly upregulating PPARα levels on both gene and protein expression levels (Chang et al., 2016). Danqi Tongmai Tablet and Sanhuang Xiexin Decoction (A decoction composed of *Rheum palmatum* L or *Rheum tanguticum* Maxim. ex Balf or *Rheum officinale* Baill. [Polygonaceae] (Usually using *Rheum officinale* Baill), *Coptis chinensis* Franch. [Ranunculaceae], *Scutellaria baicalensis* Georgi. [Lamiaceae], and has the effects of purging fire, detoxifying, and relieving heat). Affected the gene and protein expression levels of COX mRNA, but with different effects. In the myocardial cell oxidative-glucose deprivation/reoxygenation model, Danqi Tongmai Tablet can increase COX2 mRNA, and reduce ALOX5 mRNA levels, alleviating oxidative damage in myocardial cells; in the atherosclerosis model, Sanhuang Xiexin Decoction downregulates COX2 gene expression and protein levels (Wang et al., 2011; Zhi et al., 2021).

The CYP pathway is another route for the conversion of polyunsaturated fatty acids into oxylipins, and many studies have demonstrated the regulatory effects of Chinese medicinal herbs on a variety of CYP enzymes, especially the CYP450 metabolic pathway (Gu et al., 2014; Wang et al., 2018). The cardiovascular protective effect of *Pueraria lobata* (Willd.) Ohwi. [Fabaceae] may be related to the inhibition of CYP2B6, CYP2C9, and CYP3A4 enzymes (Gu et al., 2014). EETs can inhibit tissue factor TF expression and prevent thrombosis, which is related to the activation of the PI3K/AKT pathway to inhibit NF-κB nuclear translocation and target CYP cyclooxygenase (Luo et al., 2023). *Salvia miltiorrhiza* Bunge. [Lamiaceae], a commonly used TCM for treating cardiovascular diseases with blood-activating and stasis-resolving effects, has Tanshinone IIA as its main component. Data mining revealed its potential therapeutic targets might lie in CYP450 3A4, CYP450 A1, and NF-κB1, which may exert an anti-inflammatory and cardiovascular protective effect (Chen, 2015). Ophiopogon D, the main pharmacologically active component of Shenmai Injection, has been used to prevent and treat cardiovascular diseases. Ophiopogon D can alleviate myocardial hypertrophy and inflammation through the CYP450 2J3-NF-κB pathway (Wang et al., 2018).

Most of the Chinese herbal medicines mentioned above are adjunctive therapeutic drugs for CVDs and have good therapeutic effects. Given the important role of oxylipins in CVDs, it is necessary to analyze the regulatory effect of traditional Chinese herbal medicine on oxylipins in CVDs using oxylipins as a therapeutic target. Our review found that traditional Chinese herbal medicine has regulatory effects on the oxylipins' substrate, oxylipins, and downstream metabolites of oxylipins, indicating the enormous potential of traditional Chinese herbal medicine in the treatment of cardiovascular diseases. Further exploration is needed to explore the regulatory effects of more Chinese herbal medicines on oxylipins.

4 Discussion and perspectives

From the perspective of Chinese medicine involved in regulating oxylipins, we have conducted a frequency analysis of the involved Chinese medicines and found that the four most frequently mentioned are *Salvia miltiorrhiza* Bunge. [Lamiaceae] (Danshen in Chinese), *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae] (Sanqi in Chinese), *Panax ginseng* C. A. Mey. [Araliaceae] (Renshen in Chinese), and *Astragalus membranaceus* (Fisch.) Bge. var.*mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. [Fabaceae] (Huangqi in Chinese) (details are provided in the Supplementary Appendix. We have previously mentioned that AA can produce oxylipins such as prostanoids through the COX pathway. Prostanoids are closely related to platelet aggregation, endothelial cell adhesion, and vascular permeability. Some studies have shown that AA-COX-prostanoids are one of the most extensively studied pathways in the COX pathway, closely related to myocardial fibrosis. *Salvia miltiorrhiza* Bunge. [Lamiaceae] is a traditional Chinese herb that promotes blood circulation and improves cardiac fibrosis. In the systematic evaluation of the bioactive components of *Salvia miltiorrhiza* Bunge. [Lamiaceae] in the treatment of thrombotic diseases, Tanshinone, and Salvianolic acids are considered the main active components, including but not limited to Salvianolic Acid B, Tanshinone IIA, and Danshensu (Wei et al., 2023). From Table 2, we know that current research on Chinese medicine has revealed the regulatory effects of Danshensu and Salvianolic acids on oxylipins. Danshensu and Salvianolic acids target the AA-

COX-prostanoids signaling pathway in thrombosis and coronary heart disease, which to some extent explains the anti-fibrotic effect of *Salvia miltiorrhiza* Bunge. [Lamiaceae]. Moreover, we also found that frequently used Chinese medicines *Panax notoginseng* (Burk.) F. H. Chen. [Araliaceae] and *Panax ginseng* C. A. Mey. [Araliaceae] belong to the same genus and have similar active components such as Ginsenoside Rg3 (Wang et al., 2022). Modern pharmacology shows that Ginsenoside Rg3 has antioxidant, anti-inflammatory, antihypertensive, and myocardial ischemia-reperfusion injury preventive effects, which may explain why different Chinese medicines have similar cardiovascular effects in regulating oxylipins (Liu et al., 2020; Wang et al., 2022). Furthermore, this leads us to further speculate that components such as Salvianolic acids and Ginsenoside Rg3, representative of Chinese medicine, may be effective tools for regulating oxylipins, awaiting further research confirmation.

Furthermore, from the current research on TCM, we find that the study of Chinese medicine regulating lipid oxidation not only involves lipid oxidation itself but also its upstream and downstream metabolites. Upstream metabolites of lipid oxidation, such as AA, LA, cPLA, LOX, etc., are closely related to the production of oxylipins and are themselves associated with platelet activation and other cardiovascular risk factors (Yeung et al., 2014), which may play a coordinated role in regulating cardiovascular function with oxylipins. However, it is worth mentioning that the upstream regulatory mechanism of oxylipins usually involves signal cell transduction, and genetic and epigenetic factors in addition to related enzymes and substrates. Various signaling pathways that activate phospholipases can increase the release of free fatty acids from cell membranes, thereby providing substrates for oxylipin synthesis. Hormones, growth factors, and cytokines are examples of signaling molecules that can modulate enzyme expression and activity in oxylipin pathways. Genetic polymorphisms and mutations in genes encoding oxylipin-synthesizing enzymes can significantly affect their expression and function. Additionally, epigenetic modifications such as DNA methylation and histone acetylation can alter gene expression in response to environmental signals. However, there is currently no research on signal cell transduction and genetic correlation in current studies. Looking at the downstream metabolites of oxylipins, they may involve other pathways such as myocardial cell apoptosis, inflammation, and myocardial fibrosis. For example, PGE2 is produced by AA through COX metabolism and has pro-inflammatory and apoptotic effects. The specific mechanism may be related to PGE2-mediated P53 and FasL. TCM has a regulatory effect on the AA-COX-prostanoids-P53/FasL pathway in cardiovascular diseases. For instance, Qishen Yiqi Drop Pills improve myocardial cells by reducing the expression of COX and PGE2 receptors, downregulating PGE2-mediated P53 and FasL proteins; similarly, there is also the PPAR inflammation pathway, where Chinese medicine Danqi Pill can regulate the PPARα/NF-kB signaling pathway related to inflammation, improving the inflammation state mediated by AA. In addition, a large number of oxylipins like 15-HETE, PGJ2, etc., seem to be able to activate PPAR (Chen et al., 2003; Li J. et al., 2019), thereby regulating platelet activation. From the perspective of upstream and downstream metabolites, the mechanism of action of oxylipins in TCM treatment of cardiovascular diseases needs further research to fill the research gap.

Currently, significant progress has been made in the study of the mechanisms by which TCM regulates oxylipins in cardiovascular diseases, yet certain shortcomings persist: (1) Oxylipins have diverse and complex chemical structures, making their detection and analysis methods particularly important. Traditional laboratory methods, such as UV visible and fluorescence spectrophotometry, nuclear magnetic resonance, chemiluminescence analysis, immunoassay, etc., have made some progress in the characterization and quantification of oxidized lipids, but they are very limited (Li L. et al., 2019; Kodali et al., 2020). In recent years, with the advancement of mass spectrometry technology, research on oxylipins in biological samples has been promoted. The combination of mass spectrometry and liquid chromatography can selectively identify individual compounds or compound groups with common characteristics, greatly improving the sensitivity and specificity of detection (Spickett and Pitt, 2015). Thus far, over 100 oxylipins have been identified. Regrettably, most of the experimental techniques employed in the study of TCM regulation of oxylipins still rely on the ELISA method, with only a few studies utilizing lipidomics techniques. Future research in TCM needs to adapt faster to technological developments, selecting new and appropriate lipid oxidation technologies for detection based on the focused lipid oxidation categories, which is conducive to obtaining consistent, reproducible, and reliable lipid oxidation omics results. Additionally, it should be noted that there are still some shortcomings in the current TCM studies using oxidative lipidomics techniques. These studies usually only focus on oxygenases related to inflammation and platelets, rather than the full spectrum. The lipid profiles used in TCM research include up to 71 oxylipins (Fu et al., 2018), while others include 38 oxylipins (Zhi et al., 2021), which is not conducive to a comprehensive revelation of TCM's regulatory mechanisms and its cardiovascular effects. For instance, current research reveals a predominant focus on the AA-COX-prostanoids pathway in most TCM studies, a focus that may reflect researchers' subjective bias. Thus, incorporating the full spectrum of oxylipins in TCM research is imperative. (2) Studies on the regulation of oxylipins by TCM primarily focus on metabolites produced by ω-6 PUFA (AA, LA), with less attention to those derived from ω-3 PUFA. The reason might be that the cardiovascular effects of most ω-3 PUFA-derived oxylipins remain unclear, although research has shown that the risk of cardiovascular diseases is reduced after intake of ω-3 PUFAs and their derivatives. Still, the specific cardiovascular effects of these oxylipins require further study to clarify their roles and regulatory mechanisms in cardiovascular diseases. (3) Current studies on the abnormal regulation of oxylipins in cardiovascular diseases by TCM are primarily based on animal experiments, which yield relatively uniform results, but there is a lack of related clinical studies, particularly large-scale clinical evidence. It remains uncertain whether the regulatory effects of Chinese herbal medicine on oxylipins in cardiovascular patients mirror those observed in animal studies. Also, further research is needed to investigate the impact of Chinese herbal monomers or individual herbs on oxylipins in cardiovascular disease. We also urge more researchers to focus on the significant role of oxylipins in

cardiovascular disease and to conduct large-scale, long-term, high-quality clinical studies on Chinese herbal medicine. Such efforts would provide clearer insights into the regulatory effects and safety of Chinese herbal medicine on oxylipins, enhance the robustness of the data, and increase the potential for broader clinical application.

Author contributions

MqL: Conceptualization, Methodology, Writing–original draft. MH: Conceptualization, Methodology, Writing–original draft, Funding acquisition. MS: Data curation, Investigation, Writing–review and editing. YL: Resources, Visualization, Writing–review and editing. MyL: Project administration, Writing–review and editing. XJ: Resources, Visualization, Writing–review and editing. YW: Supervision, Writing–review and editing. HW: Funding acquisition, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by grants from the National Key R&D Program of China (2022YFC3500705). MH appreciates the support by the Open Scientific Project of Institute of Basic Theory for Chinese Medicine, China Academy of Chinese Medical Sciences (No. YZX-202207).

Acknowledgments

The authors would like to express their gratitude to Dychart for providing us with an online platform for image production.

Conflict of interest

Author YL was employed by Changchun Sino-Russian Science and Technology Park Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1454348/full#supplementary-material

References

Adams, J. W., Sah, V. P., Henderson, S. A., and Brown, J. H. (1998). Tyrosine kinase and c-Jun NH2-terminal kinase mediate hypertrophic responses to prostaglandin F2alpha in cultured neonatal rat ventricular myocytes. *Circ. Res.* 83, 167–178. doi:10.1161/01.res.83.2.167

Alonso-Galicia, M., Falck, J. R., Reddy, K. M., and Roman, R. J. (1999). 20-HETE agonists and antagonists in the renal circulation. *Am. J. Physiol.* 277, F790–F796. doi:10.1152/ajprenal.1999.277.5.F790

Bannehr, M., Löhr, L., Gelep, J., Haverkamp, W., Schunck, W.-H., Gollasch, M., et al. (2019). Linoleic acid metabolite DiHOME decreases post-ischemic cardiac recovery in murine hearts. *Cardiovasc Toxicol.* 19, 365–371. doi:10.1007/s12012-019-09508-x

Beccacece, L., Abondio, P., Bini, C., Pelotti, S., and Luiselli, D. (2023). The link between prostanoids and cardiovascular diseases. *Int. J. Mol. Sci.* 24, 4193. doi:10.3390/ijms24044193

Belvisi, M. G., and Mitchell, J. A. (2009). Targeting PPAR receptors in the airway for the treatment of inflammatory lung disease. *Br. J. Pharmacol.* 158, 994–1003. doi:10.1111/j.1476-5381.2009.00373.x

Breitbart, E., Sofer, Y., Shainberg, A., and Grossman, S. (1996). Lipoxygenase activity in heart cells. *FEBS Lett.* 395, 148–152. doi:10.1016/0014-5793(96)01017-4

Brinkman, H. J., van Buul-Wortelboer, M. F., and van Mourik, J. A. (1990). Involvement of cyclooxygenase- and lipoxygenase-mediated conversion of arachidonic acid in controlling human vascular smooth muscle cell proliferation. *Thromb. Haemost.* 63, 291–297. doi:10.1055/s-0038-1645212

Buchanan, M. R., Bertomeu, M. C., Brister, S. J., and Haas, T. A. (1991). 13-Hydroxyoctadecadienoic acid (13-HODE) metabolism and endothelial cell adhesion molecule expression: effect on platelet vessel wall adhesion. *Wien Klin. Wochenschr* 103, 416–421.

Buchanan, M. R., Horsewood, P., and Brister, S. J. (1998). Regulation of endothelial cell and platelet receptor-ligand binding by the 12- and 15-lipoxygenase monohydroxides, 12-15-HETE and 13-HODE. *Prostagl. Leukot. Essent. Fat. Acids* 58, 339–346. doi:10.1016/s0952-3278(98)90069-2

Buckley, C. D., Gilroy, D. W., and Serhan, C. N. (2014). Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity* 40, 315–327. doi:10.1016/j.immuni.2014.02.009

Caligiuri, S. P. B., Aukema, H. M., Ravandi, A., Lavallée, R., Guzman, R., and Pierce, G. N. (2017a). Specific plasma oxylipins increase the odds of cardiovascular and cerebrovascular events in patients with peripheral artery disease. *Can. J. Physiol. Pharmacol.* 95, 961–968. doi:10.1139/cjpp-2016-0615

Caligiuri, S. P. B., Parikh, M., Stamenkovic, A., Pierce, G. N., and Aukema, H. M. (2017b). Dietary modulation of oxylipins in cardiovascular disease and aging. *Am. J. Physiol. Heart Circ. Physiol.* 313, H903–H918. doi:10.1152/ajpheart.00201.2017

Campbell, W. B., Imig, J. D., Schmitz, J. M., and Falck, J. R. (2017). Orally active epoxyeicosatrienoic acid analogs. *J. Cardiovasc Pharmacol.* 70, 211–224. doi:10.1097/FJC.0000000000000523

Cao, D., Xu, C. C., Xue, Y. Y., Ruan, Q. F., Yang, B., Liu, Z. Q., et al. (2018). The therapeutic effect of Ilex pubescens extract on blood stasis model rats according to serum metabolomics. *J. Ethnopharmacol.* 227, 18–28. doi:10.1016/j.jep.2018.08.026

Cao, Y., Wang, J., Su, G., Wu, Y., Bai, R., Zhang, Q., et al. (2016). Anti-myocardial ischemia effect of Syringa pinnatifolia Hemsl. by inhibiting expression of cyclooxygenase-1 and -2 in myocardial tissues of mice. *J. Ethnopharmacol.* 187, 259–268. doi:10.1016/j.jep.2016.04.039

Carroll, M. A., Balazy, M., Margiotta, P., Huang, D. D., Falck, J. R., and McGiff, J. C. (1996). Cytochrome P-450-dependent HETEs: profile of biological activity and stimulation by vasoactive peptides. *Am. J. Physiol.* 271, R863–R869. doi:10.1152/ajpregu.1996.271.4.R863

Chang, H., Wang, Q., Shi, T., Huo, K., Li, C., Zhang, Q., et al. (2016). Effect of DanQi Pill on PPARα, lipid disorders and arachidonic acid pathway in rat model of coronary heart disease. *BMC Complement. Altern. Med.* 16, 103. doi:10.1186/s12906-016-1083-3

Chen, G. G., Xu, H., Lee, J. F. Y., Subramaniam, M., Leung, K. L., Wang, S. H., et al. (2003). 15-hydroxy-eicosatetraenoic acid arrests growth of colorectal cancer cells via a peroxisome proliferator-activated receptor gamma-dependent pathway. *Int. J. Cancer* 107, 837–843. doi:10.1002/ijc.11447

Chen, J., Ye, C., Yang, Z., Li, P., Wu, H., Xu, B., et al. (2022). Effects of erchen decoction on oxidative stress-related cytochrome P450 metabolites of arachidonic acid in dyslipidemic mice with phlegm-dampness retention syndrome: a randomized, controlled trial on the correspondence between prescription and syndrome. *Evid. Based Complement. Altern. Med.* 2022, 1079803. doi:10.1155/2022/1079803

Chen, L., Ackerman, R., and Guo, A. M. (2012). 20-HETE in neovascularization. *Prostagl. Other Lipid Mediat* 98, 63–68. doi:10.1016/j.prostaglandins.2011.12.005

Chen, S. J. (2015). Drug-target networks for Tanshinone IIA identified by data mining. *Chin. J. Nat. Med.* 13, 751–759. doi:10.1016/S1875-5364(15)30075-3

Chiang, K.-M., Chen, J.-F., Yang, C.-A., Xiu, L., Yang, H.-C., Shyur, L.-F., et al. (2022). Identification of serum oxylipins associated with the development of coronary artery disease: a nested case-control study. *Metabolites* 12, 495. doi:10.3390/metabo12060495

Cipollone, F. (2008). The balance between PGD synthase and PGE synthase is a major determinant of atherosclerotic plaque instability in humans. *Arterioscler. Thromb. Vasc. Biol.* 28, e1. doi:10.1161/ATVBAHA.107.158881

Cipollone, F., Fazia, M. L., Iezzi, A., Cuccurullo, C., De Cesare, D., Ucchino, S., et al. (2005). Association between prostaglandin E receptor subtype EP4 overexpression and unstable phenotype in atherosclerotic plaques in human. *Arterioscler. Thromb. Vasc. Biol.* 25, 1925–1931. doi:10.1161/01.ATV.0000177814.41505.41

Dang, X., Miao, J.-J., Chen, A.-Q., Li, P., Chen, L., Liang, J.-R., et al. (2015). The antithrombotic effect of RSNK in blood-stasis model rats. *J. Ethnopharmacol.* 173, 266–272. doi:10.1016/j.jep.2015.06.030

Das, U. N. (2021). Essential fatty acids and their metabolites in the pathobiology of inflammation and its resolution. *Biomolecules* 11, 1873. doi:10.3390/biom11121873

Edin, M. L., Wang, Z., Bradbury, J. A., Graves, J. P., Lih, F. B., DeGraff, L. M., et al. (2011). Endothelial expression of human cytochrome P450 epoxygenase CYP2C8 increases susceptibility to ischemia-reperfusion injury in isolated mouse heart. *FASEB J.* 25, 3436–3447. doi:10.1096/fj.11-188300

ElKhatib, M., Isse, F. A., and El-Kadi, A. (2023). Effect of inflammation on cytochrome P450-mediated arachidonic acid metabolism and the consequences on cardiac hypertrophy. *Drug Metab. Rev.* 55, 50–74. doi:10.1080/03602532.2022.2162075

El-Sherbeni, A. A., and El-Kadi, A. O. S. (2014). Alterations in cytochrome P450-derived arachidonic acid metabolism during pressure overload-induced cardiac hypertrophy. *Biochem. Pharmacol.* 87, 456–466. doi:10.1016/j.bcp.2013.11.015

Escoubet, B., Griffaton, G., and Lechat, P. (1986). Verapamil depresses the synthesis of lipoxygenase products by hypoxic cardiac rat fibroblasts in culture. *Biochem. Pharmacol.* 35, 1879–1882. doi:10.1016/0006-2952(86)90306-0

Fan, H. J., Li, M., Yu, L., Jin, W. F., Yang, J. H., Zhang, Y. Y., et al. (2018). Effects of Danhong Injection on platelet aggregation in hyperlipidemia rats. *J. Ethnopharmacol.* 212, 67–73. doi:10.1016/j.jep.2017.10.017

Feugray, G., Pereira, T., Iacob, M., Moreau-Grangé, L., Prévost, G., Brunel, V., et al. (2022). Determination of lipoxygenase, CYP450, and non-enzymatic metabolites of arachidonic acid in essential hypertension and type 2 diabetes. *Metabolites* 12, 859. doi:10.3390/metabo12090859

Folcik, V. A., and Cathcart, M. K. (1994). Predominance of esterified hydroperoxy-linoleic acid in human monocyte-oxidized LDL. *J. Lipid Res.* 35, 1570–1582. doi:10.1016/s0022-2275(20)41155-1

Freeman, P. M., Moschonas, K. E., Hinz, C., O'Donnell, V. B., Kinnaird, T. D., James, P. E., et al. (2015). Changes in platelet function independent of pharmacotherapy following coronary intervention in non-ST-elevation myocardial infarction patients. *Atherosclerosis* 243, 320–327. doi:10.1016/j.atherosclerosis.2015.09.024

Fu, J., Chang, L., Harms, A. C., Jia, Z., Wang, H., Wei, C., et al. (2018). A metabolomics study of Qiliqiangxin in a rat model of heart failure: a reverse pharmacology approach. *Sci. Rep.* 8, 3688. doi:10.1038/s41598-018-22074-6

Fu, J. J., Zhu, X. C., Wang, W., Lu, H., Zhang, Z. M., Liu, T., et al. (2017). 1, 6-di-O-caffeoyl-β-D-glucopyranoside, a natural compound from Callicarpa nudiflora Hook impairs P2Y12 and thromboxane A2 receptor-mediated amplification of platelet activation and aggregation. *Phytomedicine* 36, 273–282. doi:10.1016/j.phymed.2017.10.012

Gleim, S., Stitham, J., Tang, W. H., Martin, K. A., and Hwa, J. (2012). An eicosanoid-centric view of atherothrombotic risk factors. *Cell Mol. Life Sci.* 69, 3361–3380. doi:10.1007/s00018-012-0982-9

González, A., Schelbert, E. B., Díez, J., and Butler, J. (2018). Myocardial interstitial fibrosis in heart failure: biological and translational perspectives. *J. Am. Coll. Cardiol.* 71, 1696–1706. doi:10.1016/j.jacc.2018.02.021

Gu, Y. J., Liang, D. L., Xu, Z. S., and Ye, Q. (2014). *In vivo* inhibitory effects of puerarin on selected rat cytochrome P450 isoenzymes. *Pharmazie* 69, 367–370. doi:10.1691/ph.2014.3823

Hammarström, S. (1983). Leukotrienes. *Annu. Rev. Biochem.* 52, 355–377. doi:10.1146/annurev.bi.52.070183.002035

Henein, M. Y., Vancheri, S., Longo, G., and Vancheri, F. (2022). The role of inflammation in cardiovascular disease. *Int. J. Mol. Sci.* 23, 12906. doi:10.3390/ijms232112906

Hernandez-Saavedra, D., and Stanford, K. I. (2022). "Lipid mediators in cardiovascular physiology and disease," in *Cardiovascular signaling in health and disease*. Editors N. L. Parinandi and T. J. Hund (Cham (CH): Springer), 235–258. doi:10.1007/978-3-031-08309-9_8

Hildreth, K., Kodani, S. D., Hammock, B. D., and Zhao, L. (2020). Cytochrome P450-derived linoleic acid metabolites EpOMEs and DiHOMEs: a review of recent studies. *J. Nutr. Biochem.* 86, 108484. doi:10.1016/j.jnutbio.2020.108484

Hoopes, S. L., Garcia, V., Edin, M. L., Schwartzman, M. L., and Zeldin, D. C. (2015). Vascular actions of 20-HETE. *Prostagl. Other Lipid Mediat* 120, 9–16. doi:10.1016/j.prostaglandins.2015.03.002

Huang, C., Chang, M., Leu, H., Yin, W., Tseng, W., Wu, Y. W., et al. (2020). Association of arachidonic acid-derived lipid mediators with subsequent onset of acute myocardial infarction in patients with coronary artery disease. *Sci. Rep.* 10, 8105. doi:10.1038/s41598-020-65014-z

Huang, F., Liu, Y., Yang, X., Che, D., Qiu, K., Hammock, B. D., et al. (2017). Shexiang Baoxin pills promotes angiogenesis in myocardial infarction rats via up-regulation of 20-HETE-mediated endothelial progenitor cells mobilization. *Atherosclerosis* 263, 184–191. doi:10.1016/j.atherosclerosis.2017.06.012

Isse, F. A., Alammari, A. H., El-Sherbeni, A. A., and El-Kadi, A. O. S. (2023). 17-(R/S)-hydroxyeicosatetraenoic acid (HETE) induces cardiac hypertrophy through the CYP1B1 in enantioselective manners. *Prostagl. Other Lipid Mediat* 168, 106749. doi:10.1016/j.prostaglandins.2023.106749

Jiang, C., Wang, X., Dang, S., Wang, X., Deng, Q., Hu, J., et al. (2021). Chinese medicine shensong yangxin Capsule ameliorates myocardial microcirculation dysfunction in rabbits with chronic myocardial infarction. *Chin. J. Integr. Med.* 27, 24–30. doi:10.1007/s11655-018-2578-1

Jiang, H., Shen, Z., Chu, Y., Li, Y., Li, J., Wang, X., et al. (2015). Serum metabolomics research of the anti-hypertensive effects of Tengfu Jiangya tablet on spontaneously hypertensive rats. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 1002, 210–217. doi:10.1016/j.jchromb.2015.08.010

Jiang, Q., Wang, L. N., Hu, J. H., and Zhang, Y. Q. (2019). Oral administration of leeches (Shuizhi): a review of the mechanisms of action on antiplatelet aggregation. *J. Ethnopharmacol.* 232, 103–109. doi:10.1016/j.jep.2018.12.010

Khodadi, E. (2020). Platelet function in cardiovascular disease: activation of molecules and activation by molecules. *Cardiovasc Toxicol.* 20, 1–10. doi:10.1007/s12012-019-09555-4

Kodali, S. T., Kauffman, P., Kotha, S. R., Yenigalla, A., Veeraraghavan, R., Pannu, S. R., et al. (2020). "Oxidative lipidomics: analysis of oxidized lipids and lipid peroxidation in biological systems with relevance to health and disease," in *Measuring oxidants and oxidative stress in biological systems*. Editors L. J. Berliner and N. L. Parinandi (Cham (CH): Springer), 61–92. doi:10.1007/978-3-030-47318-1_5

Krämer, H. J., Stevens, J., Grimminger, F., and Seeger, W. (1996). Fish oil fatty acids and human platelets: dose-dependent decrease in dienoic and increase in trienoic thromboxane generation. *Biochem. Pharmacol.* 52, 1211–1217. doi:10.1016/0006-2952(96)00473-x

Krötz, F., Riexinger, T., Buerkle, M. A., Nithipatikom, K., Gloe, T., Sohn, H. Y., et al. (2004). Membrane-potential-dependent inhibition of platelet adhesion to endothelial cells by epoxyeicosatrienoic acids. *Arterioscler. Thromb. Vasc. Biol.* 24, 595–600. doi:10.1161/01.ATV.0000116219.09040.8c

Kuhn, H., Banthiya, S., and van Leyen, K. (2015). Mammalian lipoxygenases and their biological relevance. *Biochim. Biophys. Acta* 1851, 308–330. doi:10.1016/j.bbalip.2014.10.002

Kwon, S. Y., Massey, K., Watson, M. A., Hussain, T., Volpe, G., Buckley, C. D., et al. (2020). Oxidised metabolites of the omega-6 fatty acid linoleic acid activate dFOXO. *Life Sci. Alliance* 3, e201900356. doi:10.26508/lsa.201900356

Lai, J., and Chen, C. (2021). The role of epoxyeicosatrienoic acids in cardiac remodeling. *Front. Physiol.* 12, 642470. doi:10.3389/fphys.2021.642470

Lai, Q., Yuan, G., Shen, L., Zhang, L., Fu, F., Liu, Z., et al. (2021). Oxoeicosanoid receptor inhibition alleviates acute myocardial infarction through activation of BCAT1. *Basic Res. Cardiol.* 116, 3. doi:10.1007/s00395-021-00844-0

Lau, E. S., Roshandelpoor, A., Zarbafian, S., Wang, D., Guseh, J. S., Allen, N., et al. (2023). Eicosanoid and eicosanoid-related inflammatory mediators and exercise intolerance in heart failure with preserved ejection fraction. *Nat. Commun.* 14, 7557. doi:10.1038/s41467-023-43363-3

Li, C., Wang, J., Wang, Q., Zhang, Y., Zhang, N., Lu, L., et al. (2016). Qishen granules inhibit myocardial inflammation injury through regulating arachidonic acid metabolism. *Sci. Rep.* 6, 36949. doi:10.1038/srep36949

Li, J., Cao, G. Y., Zhang, X. F., Meng, Z. Q., Gan, L., Li, J. X., et al. (2020a). Chinese medicine she-Xiang-Xin-Tong-Ning, containing Moschus, corydalis and ginseng, protects from myocardial ischemia injury via angiogenesis. *Am. J. Chin. Med.* 48, 107–126. doi:10.1142/S0192415X20500068

Li, J., Guo, C., and Wu, J. (2019a). 15-Deoxy-Δ-(12,14)-Prostaglandin J2 (15d-PGJ2), an endogenous ligand of PPAR-γ: function and mechanism. *PPAR Res.* 2019, 7242030. doi:10.1155/2019/7242030

Li, L., Zhong, S., Shen, X., Li, Q., Xu, W., Tao, Y., et al. (2019b). Recent development on liquid chromatography-mass spectrometry analysis of oxidized lipids. *Free Radic. Biol. Med.* 144, 16–34. doi:10.1016/j.freeradbiomed.2019.06.006

Li, S., Xu, Y., Guo, W., Chen, F., Zhang, C., Tan, H. Y., et al. (2020b). The impacts of herbal medicines and natural products on regulating the hepatic lipid metabolism. *Front. Pharmacol.* 11, 351. doi:10.3389/fphar.2020.00351

Li, Y. P., Wang, C. Y., Shang, H. T., Hu, R. R., Fu, H., and Xiao, X. F. (2020c). A high-throughput and untargeted lipidomics approach reveals new mechanistic insight and the effects of salvianolic acid B on the metabolic profiles in coronary heart disease rats

using ultra-performance liquid chromatography with mass spectrometry. *RSC Adv.* 10, 17101–17113. doi:10.1039/d0ra00049c

Liu, X., Mi, X., Wang, Z., Zhang, M., Hou, J., Jiang, S., et al. (2020). Ginsenoside Rg3 promotes regression from hepatic fibrosis through reducing inflammation-mediated autophagy signaling pathway. *Cell Death Dis.* 11, 454. doi:10.1038/s41419-020-2597-7

Luo, L., Yang, Y., Fu, M., Luo, J., Li, W., Tu, L., et al. (2023). 11,12-EET suppressed LPS induced TF expression and thrombus formation by accelerating mRNA degradation rate via strengthening PI3K-Akt signaling pathway and inhibiting p38-TTP pathway. *Prostagl. Other Lipid Mediat* 167, 106740. doi:10.1016/j.prostaglandins.2023.106740

Maayah, Z. H., Abdelhamid, G., and El-Kadi, A. O. (2015). Development of cellular hypertrophy by 8-hydroxyeicosatetraenoic acid in the human ventricular cardiomyocyte, RL-14 cell line, is implicated by MAPK and NF-κB. *Cell Biol. Toxicol.* 31, 241–259. doi:10.1007/s10565-015-9308-7

Manke, M.-C., Ahrends, R., and Borst, O. (2022). Platelet lipid metabolism in vascular thrombo-inflammation. *Pharmacol. Ther.* 237, 108258. doi:10.1016/j.pharmthera.2022.108258

Marmol, F., Puig-Parellada, P., Sanchez, J., and Trullas, R. (1999). Influence of aging on thromboxane A2 and prostacyclin levels in rat hippocampal brain slices. *Neurobiol. Aging* 20, 695–697. doi:10.1016/s0197-4580(99)00069-x

Mezzetti, A. (2005). Pharmacological modulation of plaque instability. *Lupus* 14, 769–772. doi:10.1191/0961203305lu2218oa

Nakanishi, M., and Rosenberg, D. W. (2013). Multifaceted roles of PGE2 in inflammation and cancer. *Semin. Immunopathol.* 35, 123–137. doi:10.1007/s00281-012-0342-8

Nayeem, M. A. (2018). Role of oxylipins in cardiovascular diseases. *Acta Pharmacol. Sin.* 39, 1142–1154. doi:10.1038/aps.2018.24

Nobili, E., Salvado, M. D., Folkersen, L., Castiglioni, L., Kastrup, J., Wetterholm, A., et al. (2012). Cysteinyl leukotriene signaling aggravates myocardial hypoxia in experimental atherosclerotic heart disease. *PLoS One* 7, e41786. doi:10.1371/journal.pone.0041786

Ozen, G., and Norel, X. (2017). Prostanoids in the pathophysiology of human coronary artery. *Prostagl. Other Lipid Mediat* 133, 20–28. doi:10.1016/j.prostaglandins.2017.03.003

Palmu, J., Watrous, J. D., Mercader, K., Havulinna, A. S., Lagerborg, K. A., Salosensaari, A., et al. (2020). Eicosanoid inflammatory mediators are robustly associated with blood pressure in the general population. *J. Am. Heart Assoc.* 9, e017598. doi:10.1161/JAHA.120.017598

Pinckard, K. M., Shettigar, V. K., Wright, K. R., Abay, E., Baer, L. A., Vidal, P., et al. (2021). A novel endocrine role for the BAT-released lipokine 12,13-diHOME to mediate cardiac function. *Circulation* 143, 145–159. doi:10.1161/CIRCULATIONAHA.120.049813

Qiu, H., Gabrielsen, A., Agardh, H. E., Wan, M., Wetterholm, A., Wong, C.-H., et al. (2006). Expression of 5-lipoxygenase and leukotriene A4 hydrolase in human atherosclerotic lesions correlates with symptoms of plaque instability. *Proc. Natl. Acad. Sci. U. S. A.* 103, 8161–8166. doi:10.1073/pnas.0602414103

Reddy, Y. K., Reddy, L. M., Capdevila, J. H., and Falck, J. R. (2003). Practical, asymmetric synthesis of 16-hydroxyeicosa-5(Z), 8(Z), 11(Z), 14(Z)-tetraenoic acid (16-HETE), an endogenous inhibitor of neutrophil activity. *Bioorg Med. Chem. Lett.* 13, 3719–3720. doi:10.1016/j.bmcl.2003.08.005

Rocic, P., and Schwartzman, M. L. (2018). 20-HETE in the regulation of vascular and cardiac function. *Pharmacol. Ther.* 192, 74–87. doi:10.1016/j.pharmthera.2018.07.004

Roman, R. J., and Fan, F. (2018). 20-HETE: hypertension and beyond. *Hypertension* 72, 12–18. doi:10.1161/HYPERTENSIONAHA.118.10269

Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G., Ammirati, E., Baddour, L. M., et al. (2020). Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J. Am. Coll. Cardiol.* 76, 2982–3021. doi:10.1016/j.jacc.2020.11.010

Scridon, A. (2022). Platelets and their role in hemostasis and thrombosis-from physiology to pathophysiology and therapeutic implications. *Int. J. Mol. Sci.* 23, 12772. doi:10.3390/ijms232112772

Shearer, G. C., and Walker, R. E. (2018). An overview of the biologic effects of omega-6 oxylipins in humans. *Prostagl. Leukot. Essent. Fat. Acids* 137, 26–38. doi:10.1016/j.plefa.2018.06.005

Shoieb, S. M., El-Sherbeni, A. A., and El-Kadi, A. (2019). Subterminal hydroxyeicosatetraenoic acids: crucial lipid mediators in normal physiology and disease states. *Chem. Biol. Interact.* 299, 140–150. doi:10.1016/j.cbi.2018.12.004

Snipelisky, D., Chaudhry, S.-P., and Stewart, G. C. (2019). The many faces of heart failure. *Card. Electrophysiol. Clin.* 11, 11–20. doi:10.1016/j.ccep.2018.11.001

Snyder, N. W., Golin-Bisello, F., Gao, Y., Blair, I. A., Freeman, B. A., and Wendell, S. G. (2015). 15-Oxoeicosatetraenoic acid is a 15-hydroxyprostaglandin dehydrogenase-derived electrophilic mediator of inflammatory signaling pathways. *Chem. Biol. Interact.* 234, 144–153. doi:10.1016/j.cbi.2014.10.029

Solati, Z., and Ravandi, A. (2019). Lipidomics of bioactive lipids in acute coronary syndromes. *Int. J. Mol. Sci.* 20, 1051. doi:10.3390/ijms20051051

Solati, Z., Surendran, A., Aukema, H. M., and Ravandi, A. (2023). Impact of reperfusion on plasma oxylipins in ST-segment elevation myocardial infarction. *Metabolites* 14, 19. doi:10.3390/metabo14010019

Spector, A. A. (2009). Arachidonic acid cytochrome P450 epoxygenase pathway. *J. Lipid Res.* 50 (Suppl. l), S52–S56. doi:10.1194/jlr.R800038-JLR200

Spickett, C. M., and Pitt, A. R. (2015). Oxidative lipidomics coming of age: advances in analysis of oxidized phospholipids in physiology and pathology. *Antioxid. Redox Signal* 22, 1646–1666. doi:10.1089/ars.2014.6098

Stanke-Labesque, F., Hardy, G., Cracowski, J. L., and Bessard, G. (2002). Leukotrienes and 12-HETE: key mediators of angiotensin II-mediated vascular effects.Rol in hypertension. *Therapie* 57, 151–156.

Sudhahar, V., Shaw, S., and Imig, J. D. (2010). Epoxyeicosatrienoic acid analogs and vascular function. *Curr. Med. Chem.* 17, 1181–1190. doi:10.2174/092986710790827843

Sugiyama, S., Hayakawa, M., Nagai, S., Ajioka, M., and Ozawa, T. (1987). Leukotoxin, 9, 10-epoxy-12-octadecenoate, causes cardiac failure in dogs. *Life Sci.* 40, 225–231. doi:10.1016/0024-3205(87)90336-5

Sun, L., Jia, H., Yu, M., Yang, Y., Li, J., Tian, D., et al. (2021). Salvia miltiorrhiza and Pueraria lobata, two eminent herbs in Xin-Ke-Shu, ameliorate myocardial ischemia partially by modulating the accumulation of free fatty acids in rats. *Phytomedicine* 89, 153620. doi:10.1016/j.phymed.2021.153620

Sun, X., and Li, Q. (2018). Prostaglandin EP2 receptor: novel therapeutic target for human cancers (Review). *Int. J. Mol. Med.* 42, 1203–1214. doi:10.3892/ijmm.2018.3744

Tacconelli, S., and Patrignani, P. (2014). Inside epoxyeicosatrienoic acids and cardiovascular disease. *Front. Pharmacol.* 5, 239. doi:10.3389/fphar.2014.00239

Takayama, K., García-Cardena, G., Sukhova, G. K., Comander, J., Gimbrone, M. J., and Libby, P. (2002). Prostaglandin E2 suppresses chemokine production in human macrophages through the EP4 receptor. *J. Biol. Chem.* 277, 44147–44154. doi:10.1074/jbc.M204810200

Tang, E. H., Libby, P., Vanhoutte, P. M., and Xu, A. (2012). Anti-inflammation therapy by activation of prostaglandin EP4 receptor in cardiovascular and other inflammatory diseases. *J. Cardiovasc Pharmacol.* 59, 116–123. doi:10.1097/FJC.0b013e3182244a12

Theken, K. N., Schuck, R. N., Edin, M. L., Tran, B., Ellis, K., Bass, A., et al. (2012). Evaluation of cytochrome P450-derived eicosanoids in humans with stable atherosclerotic cardiovascular disease. *Atherosclerosis* 222, 530–536. doi:10.1016/j.atherosclerosis.2012.03.022

Tong, K.-L., Tan, K.-E., Lim, Y.-Y., Tien, X.-Y., and Wong, P.-F. (2022). CircRNA-miRNA interactions in atherogenesis. *Mol. Cell Biochem.* 477, 2703–2733. doi:10.1007/s11010-022-04455-8

Torres, R., Picado, C., and de Mora, F. (2015). The PGE2-EP2-mast cell axis: an antiasthma mechanism. *Mol. Immunol.* 63, 61–68. doi:10.1016/j.molimm.2014.03.007

Troncoso, M. F., Ortiz-Quintero, J., Garrido-Moreno, V., Sanhueza-Olivares, F., Guerrero-Moncayo, A., Chiong, M., et al. (2021). VCAM-1 as a predictor biomarker in cardiovascular disease. *Biochim. Biophys. Acta Mol. Basis Dis.* 1867, 166170. doi:10.1016/j.bbadis.2021.166170

Tu, Z. G., Han, X. D., Wang, X. Y., Hou, Y. Y., Shao, B. Y., Wang, X., et al. (2003). Protective effects of CVPM on vascular endothelium in rats fed cholesterol diet. *Clin. Chim. Acta* 333, 85–90. doi:10.1016/s0009-8981(03)00201-8

Wang, D. D., Fan, G. W., Wang, Y. F., Liu, H. T., Wang, B. Y., Dong, J., et al. (2013). Vascular reactivity screen of Chinese medicine Danhong injection identifies danshensu as a NO-independent but PGI2-mediated relaxation factor. *J. Cardiovasc Pharm.* 62, 457–465. doi:10.1097/FJC.0b013e3182a29657

Wang, J., Li, C., Cao, Y., Wang, Q., Lu, L., Chang, H., et al. (2015a). Mechanism of QSYQ on anti-apoptosis mediated by different subtypes of cyclooxygenase in AMI induced heart failure rats. *BMC Complement. Altern. Med.* 15, 352. doi:10.1186/s12906-015-0869-z

Wang, J., Lu, L., Wang, Y., Wu, Y., Han, J., Wang, W., et al. (2015b). Qishenyiqi Dropping Pill attenuates myocardial fibrosis in rats by inhibiting RAAS-mediated arachidonic acid inflammation. *J. Ethnopharmacol.* 176, 375–384. doi:10.1016/j.jep.2015.11.023

Wang, J., Zeng, L., Zhang, Y., Qi, W., Wang, Z., Tian, L., et al. (2022). Pharmacological properties, molecular mechanisms and therapeutic potential of ginsenoside Rg3 as an antioxidant and anti-inflammatory agent. *Front. Pharmacol.* 13, 975784. doi:10.3389/fphar.2022.975784

Wang, S. L., Lu, J. W., Guan, Y. F., Zhang, X. Y., and Xu, H. (2019). Role of prostaglandin E2 receptor 4 in cardiovascular diseases. *Sheng Li Xue Bao* 71, 361–370.

Wang, W., Song, L., Yang, L., Li, C., Ma, Y., Xue, M., et al. (2023). Panax quinquefolius saponins combined with dual antiplatelet therapy enhanced platelet inhibition with alleviated gastric injury via regulating eicosanoids metabolism. *BMC Complement. Med. Ther.* 23, 289. doi:10.1186/s12906-023-04112-7

Wang, X., Gao, Y., Tian, Y., Liu, X., Zhang, G., Wang, Q., et al. (2020a). Integrative serum metabolomics and network analysis on mechanisms exploration of Ling-Gui-Zhu-Gan Decoction on doxorubicin-induced heart failure mice. *J. Ethnopharmacol.* 250, 112397. doi:10.1016/j.jep.2019.112397

Wang, Y., Huang, X. Y., Ma, Z. C., Wang, Y. G., Chen, X. M., and Gao, Y. (2018). Ophiopogonin D alleviates cardiac hypertrophy in rat by upregulating CYP2J3 *in vitro*

and suppressing inflammation *in vivo*. *Biochem. Bioph Res. Co.* 503, 1011–1019. doi:10.1016/j.bbrc.2018.06.110

Wang, Y., Li, C., Liu, Z. Y., Shi, T. J., Wang, Q. Y., Li, D., et al. (2014). DanQi Pill protects against heart failure through the arachidonic acid metabolism pathway by attenuating different cyclooxygenases and leukotrienes B4. *BMC Complem Altern. M.* 14, 67. doi:10.1186/1472-6882-14-67

Wang, Y. Q., Li, S. J., Man, Y. H., and Zhuang, G. (2020b). Serum metabonomics coupled with HPLC-LTQ/orbitrap MS and multivariate data analysis on the ameliorative effects of Bidens bipinnata L. in hyperlipidemic rats. *J. Ethnopharmacol.* 262, 113196. doi:10.1016/j.jep.2020.113196

Wang, Y. S., Lin, R. T., Cheng, H. Y., Yang, S. F., Chou, W. W., and Juo, S. (2011). Anti-atherogenic effect of San-Huang-Xie-Xin-Tang, a traditional Chinese medicine, in cultured human aortic smooth muscle cells. *J. Ethnopharmacol.* 133, 442–447. doi:10.1016/j.jep.2010.10.018

Wei, B., Sun, C., Wan, H., Shou, Q., Han, B., Sheng, M., et al. (2023). Bioactive components and molecular mechanisms of Salvia miltiorrhiza Bunge in promoting blood circulation to remove blood stasis. *J. Ethnopharmacol.* 317, 116697. doi:10.1016/j.jep.2023.116697

Wittwer, J., and Hersberger, M. (2007). The two faces of the 15-lipoxygenase in atherosclerosis. *Prostagl. Leukot. Essent. Fat. Acids* 77, 67–77. doi:10.1016/j.plefa.2007.08.001

World Heart Federation (2023). World heart report 2023: confronting the world's number one killer. Available at: https://world-heart-federation.org/wp-content/uploads/World-Heart-Report-2023.pdf (Accessed May 27, 2024).

Xie, J., Jiang, H. Q., Li, Y. L., Nie, L., Zhou, H. L., and Yang, W. Q. (2019). Study on the intervention effects of pinggan prescription on spontaneously hypertensive rats based on metabonomic and pharmacodynamic methods. *Chin. J. Integr. Med.* 25, 348–353. doi:10.1007/s11655-015-2126-1

Xu, H. J., Lu, H., Zhu, X. C., Wang, W., Zhang, Z. M., Fu, H. Z., et al. (2018). Inhibitory effects of luteolin-4′-O-β-D-glucopyranoside on P2Y12 and thromboxane A2 receptor-mediated amplification of platelet activation in vitro. *Int. J. Mol. Med.* 42, 615–624. doi:10.3892/ijmm.2018.3634

Xu, J., Li, X., Zhang, F., Tang, L., Wei, J., Lei, X., et al. (2019). Integrated UPLC-Q/TOF-MS technique and MALDI-MS to study of the efficacy of YiXinshu Capsules against heart failure in a rat model. *Front. Pharmacol.* 10, 1474. doi:10.3389/fphar.2019.01474

Xu, S., Ilyas, I., Little, P. J., Li, H., Kamato, D., Zheng, X., et al. (2021). Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. *Pharmacol. Rev.* 73, 924–967. doi:10.1124/pharmrev.120.000096

Yeung, J., Tourdot, B. E., Fernandez-Perez, P., Vesci, J., Ren, J., Smyrniotis, C. J., et al. (2014). Platelet 12-LOX is essential for FcγRIIa-mediated platelet activation. *Blood* 124, 2271–2279. doi:10.1182/blood-2014-05-575878

Yin, J., Lu, X., Qian, Z., Xu, W., and Zhou, X. (2019). New insights into the pathogenesis and treatment of sarcopenia in chronic heart failure. *Theranostics* 9, 4019–4029. doi:10.7150/thno.33000

Yousefnia, S., Momenzadeh, S., Seyed, F. F., Ghaedi, K., and Nasr, E. M. (2018). The influence of peroxisome proliferator-activated receptor γ (PPARγ) ligands on cancer cell tumorigenicity. *Gene* 649, 14–22. doi:10.1016/j.gene.2018.01.018

Yu, C., Qi, D., Lian, W., Li, Q. Z., Li, H. J., and Fan, H. Y. (2014). Effects of danshensu on platelet aggregation and thrombosis: *in vivo* arteriovenous shunt and venous thrombosis models in rats. *PLoS One* 9, e110124. doi:10.1371/journal.pone.0110124

Yu, Z., Wang, L., Wu, S., and Zhao, W. (2023). Dissecting the potential mechanism of antihypertensive effects of RVPSL on spontaneously hypertensive rats via widely targeted kidney metabolomics. *J. Sci. Food Agric.* 103, 428–436. doi:10.1002/jsfa.12157

Yuan, Z., Yang, L., Zhang, X., Ji, P., Hua, Y., and Wei, Y. (2020). Mechanism of Huang-lian-Jie-du decoction and its effective fraction in alleviating acute ulcerative colitis in mice: regulating arachidonic acid metabolism and glycerophospholipid metabolism. *J. Ethnopharmacol.* 259, 112872. doi:10.1016/j.jep.2020.112872

Yuhki, K., Kojima, F., Kashiwagi, H., Kawabe, J., Fujino, T., Narumiya, S., et al. (2011). Roles of prostanoids in the pathogenesis of cardiovascular diseases: novel insights from knockout mouse studies. *Pharmacol. Ther.* 129, 195–205. doi:10.1016/j.pharmthera.2010.09.004

Zhang, F., Deng, H., Kemp, R., Singh, H., Gopal, V. R., Falck, J. R., et al. (2005). Decreased levels of cytochrome P450 2E1-derived eicosanoids sensitize renal arteries to constrictor agonists in spontaneously hypertensive rats. *Hypertension* 45, 103–108. doi:10.1161/01.HYP.0000150782.28485.91

Zhang, J. X., Qi, M. J., Shi, M. Z., Chen, J. J., Zhang, X. Q., Yang, J., et al. (2019). Effects of Danhong injection, a traditional Chinese medicine, on nine cytochrome P450 isoforms *in vitro*. *Biomed. Chromatogr.* 33, e4454. doi:10.1002/bmc.4454

Zhang, J. Y., Liang, R. X., Wang, L., Yan, R. Y., Hou, R., Gao, S. R., et al. (2013). Effects of an aqueous extract of Crataegus pinnatifida Bge. var. major NEBr. fruit on experimental atherosclerosis in rats. *J. Ethnopharmacol.* 148, 563–569. doi:10.1016/j.jep.2013.04.053

Zhang, L., Chen, N., Zhan, L., Bi, T., Zhou, W., Zhang, L., et al. (2023a). Erchen Decoction alleviates obesity-related hepatic steatosis via modulating gut microbiota-drived butyric acid contents and promoting fatty acid β-oxidation. *J. Ethnopharmacol.* 317, 116811. doi:10.1016/j.jep.2023.116811

Zhang, Y., Guallar, E., Blasco-Colmenares, E., Harms, A. C., Vreeken, R. J., Hankemeier, T., et al. (2016). Serum-based oxylipins are associated with outcomes in primary prevention implantable cardioverter defibrillator patients. *PLoS One* 11, e0157035. doi:10.1371/journal.pone.0157035

Zhang, Y., Hong, Z., Yuan, Z., Wang, T., Wu, X., Liu, B., et al. (2020). Extract from Rostellularia procumbens (L.) nees inhibits thrombosis and platelet aggregation by regulating integrin β(3) and MAPK pathways. *ACS Omega* 5, 32123–32130. doi:10.1021/acsomega.0c05227

Zhang, Y., Lu, J., Huang, S., Zhang, Y., Liu, J., Xu, Y., et al. (2023b). CYP2J deficiency leads to cardiac injury and presents dual regulatory effects on cardiac function in rats. *Toxicol. Appl. Pharmacol.* 473, 116610. doi:10.1016/j.taap.2023.116610

Zhang, Y., Lu, J., Ma, Y., Sun, L., Wang, S., Yue, X., et al. (2022). Establishment of fingerprint and mechanism of anti-myocardial ischemic effect of Syringa pinnatifolia. *Biomed. Chromatogr.* 36, e5475. doi:10.1002/bmc.5475

Zhang, Y., Wang, Y., Meng, H., Lu, W. J., Wang, Q. X., Zhang, Q., et al. (2018). Mechanisms of Fufang Danshen tablets on treating heart failure via regulating AT_1-mediated PLA2-COX2/5-LOX metabolic pathway. *Zhongguo Zhong Yao Za Zhi* 43, 2593–2599. doi:10.19540/j.cnki.cjcmm.2018.0083

Zhi, H., Zhang, Z., Deng, Y., Yan, B., Li, Z., Wu, W., et al. (2021). Restoring perturbed oxylipins with Danqi Tongmai Tablet attenuates acute myocardial infarction. *Phytomedicine* 90, 153616. doi:10.1016/j.phymed.2021.153616

Zuo, D., Pi, Q., Shi, Y., Luo, S., and Xia, Y. (2021). Dihydroxyeicosatrienoic acid, a metabolite of epoxyeicosatrienoic acids upregulates endothelial nitric oxide synthase expression through transcription: mechanism of vascular endothelial function protection. *Cell Biochem. Biophys.* 79, 289–299. doi:10.1007/s12013-021-00978-x

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 03 January 2025
DOI 10.3389/fphar.2024.1444967

OPEN ACCESS

EDITED BY
Qing Yong He,
China Academy of Chinese Medical Sciences, China

REVIEWED BY
Neelam S. Sangwan,
Central University of Haryana, India
Wang Shaoping,
Binzhou Medical University, China

*CORRESPONDENCE
Guanlin Xiao,
164669079@qq.com
Xiaoli Bi,
zyfxyjs@gzucm.edu.cn

†These authors have contributed equally to this work

RECEIVED 06 June 2024
ACCEPTED 25 November 2024
PUBLISHED 03 January 2025

CITATION
Tang R, Xiao G, Liu Y, Jia D, Zeng Z, Jia C, Li D, Li Y, Jiang J, Li S and Bi X (2025) Integrated serum pharmacochemistry, pharmacokinetics, and network analysis to explore active components of BuShao Tiaozhi Capsule on hyperlipidemia.
Front. Pharmacol. 15:1444967.
doi: 10.3389/fphar.2024.1444967

Integrated serum pharmacochemistry, pharmacokinetics, and network analysis to explore active components of BuShao Tiaozhi Capsule on hyperlipidemia

Ruiyin Tang[1†], Guanlin Xiao[2†*], Yanchang Liu[1], Dezheng Jia[1], Zhihao Zeng[1], Canchao Jia[1], Dongmei Li[1], Yangxue Li[2], Jieyi Jiang[2], Sumei Li[2] and Xiaoli Bi[2*]

[1]School of the Fifth Clinical Medicine, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China, [2]Guangdong Provincial Engineering Technology Research Institute of Traditional Chinese Medicine, Guangdong Provincial Key Laboratory of Research and Development in Traditional Chinese Medicine, Guangzhou, Guangdong, China

BuShao Tiaozhi Capsule (BSTZC), a novel drug in China, has been used to treat hyperlipidemia (HLP) in clinical practice for many years. Despite our previous studies suggesting that BSTZC can treat HLP, there is a lack of a rapid and systematic method to explore its active components. Therefore, in this study, we aimed to investigate the active components and mechanisms of BSTZC in treating HLP by integrating serum pharmacology, pharmacokinetics, network analysis, and experimental validation. We first established UPLC fingerprints, calibrated 23 common peaks, and identified 13 common peaks, and the similarity was greater than 0.99 for 10 batches. A total of nine metabolites from BSTZC were identified in serum and considered as PK markers. The pharmacokinetic parameters of the PK markers were compared between the control group and the model group through the pharmacokinetics study to determine the dynamic changes of representative components in rats. Compared with the control group, the C_{max} and $AUC_{0\rightarrow t}$ of OXY, IVT, IVL, and KPF-3-G were significantly higher ($P< 0.05$); the $AUC_{0\rightarrow\infty}$ of OXY, PN, and IVT was significantly higher ($P< 0.05$); and the $t_{1/2}$ of IVT, SA, and KPF-3-G was significantly different ($P< 0.05$). *In vivo* experiments showed that BSTZC and its active components could effectively alleviate lipid metabolism disorders and liver injury, with obvious lipid-lowering effects. Further studies showed that BSTZC alleviated HLP by inhibiting the PI3K/Akt signaling pathway, which was consistent with the

Abbreviations: BSTZC, BuShao Tiaozhi Capsule; HLP, hyperlipidemia; IVT, isovitexin; IVL, isoviolanthin; NCS, narcissoside; OXY, oxypaeoniflorin; PN, paeoniflorin; SA, salicylic acid; NAG, neoandrographolide; KPF-3-G, kaempferol-3-glucuronide; APG-7-G, apigenin-7-glucuronide; KEGG, Kyoto Encyclopedia of Genes and Genomes data obtained; PK, pharmacokinetics; QC, quality control; LLOQ, lower limit of quantification; PPI, protein–protein; T_{max}, the time to reach the maximum concentration; $t_{1/2}$, terminal elimination half-life; C_{max}, maximum concentration; $AUC_{0\rightarrow t}$, area under the concentration-time curve from zero to t; $AUC_{0\rightarrow\infty}$, area under the concentration–time curve from zero to infinity; MRT, mean retention time; TC, cholesterol; TG, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TCM, tradition Chinese medicine.

results of the network analysis study. Our results revealed the active components and mechanisms of BSTZC in the treatment of HLP, which could provide useful information to guide the clinical application of BSTZC.

KEYWORDS

BuShao Tiaozhi Capsule, serum pharmacochemistry, pharmacokinetics, network analysis, hyperlipidemia

1 Introduction

Hyperlipidemia (HLP) is a disorder of lipid metabolism disease manifested by an elevation in total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) in blood, or decreased high-density lipoprotein (HDL), which is considered to be a major risk factor for cardiovascular diseases (Vekic et al., 2019). Hypercholesterolemia is associated with an increased risk of cardiovascular disease, and elevated plasma LDL cholesterol levels have become the eighth leading risk factor for death in 2019 (Pirillo et al., 2021). Moreover, the incidence of HLP in some developing countries has increased. At present, the common therapeutic drugs are statins and fibrates, but these drugs are often limited by undesirable side effects, such as abdominal distension, diarrhea, and myasthenia (Bahiru et al., 2021).

BuShao Tiaozhi Capsule (BSTZC) is a traditional Chinese botanical drug formula consisting of four Chinese botanical drugs, namely, Microctis Folium, Paeoniae Radix Rubra, Curcumae Rhizoma, and Andrographis Herba, in the ratio of 4.5:1.5:1:1, which has been used for the treatment of HLP in clinical practice for many years. A clinical trial for new drug approval (2016L02809) has been successfully admitted by the Nation Medical Products Administration (NMPA). It can clear heat, remove food stagnation, and invigorate blood circulation. In the previous research, we analyzed the chemical composition of BSTZC by using a UPLC-TOF-MS/MS method (Xiao et al., 2020), and the quality specification study was established at the same time. In terms of pharmacodynamic effects, BSTZC significantly reduced the serum TC, TG, and LDL-C; improved HDL-C and ApoA1/ApoB; and boosted hepatic LCAT and LXR-α gene expression in HLP rats and mice (Chen et al., 2017; Gan et al., 2018). Furthermore, the lipid-lowering mechanism of BSTZC may be related to the regulation of the FXR signaling pathway, promotion of hepatic CYP7A1 expression, inhibition of ileal bile acid negative feedback regulation, promotion of bile acid excretion, and acceleration of lipid metabolism (Xiao et al., 2022). However, the pharmacological substance basis and metabolic regulation mechanism of BSTZC's real hypolipidemic efficacy are still unclear, which hinders the further clinical application of BSTZC.

According to the theory of serum pharmacochemistry, substances that are absorbed into the blood and reach a certain concentration are likely to be therapeutically effective (Ma, F.X. et al., 2017). In addition, the pharmacokinetics study is focused on dynamic changes and laws of the absorption, distribution, metabolism, and excretion of the effective components of drugs in the body, which was critical in novel medicine research and clinical practice (Li et al., 2015; Tang and Lu, 2009). Network pharmacology is one of the primary techniques to forecast the active components and mechanism of action of drugs, by constructing an interactive network of "disease–drug–targets pathways" (Xiao et al., 2022). Therefore, we established an integrated strategy of serum pharmacochemistry, pharmacokinetics, network analysis, and experimental validation to investigate the active components and mechanisms of BSTZC in treating HLP, which further promoted the study of the pharmacological substance basis and mechanism of BSTZC.

2 Materials and methods

2.1 Chemicals and reagents

The BSTZ (Batch number: 20,230,401) was obtained from Guangdong Provincial Second Hospital of Traditional Chinese Medicine (Guangzhou, China). The information on the reference substances is available in Supplementary Table S1. LC-MS-grade methanol, formic acid, and acetonitrile were purchased from Fisher Scientific (Fair Lawn, NJ, United States). Ultrapure water was purchased from Wahaha Co., Ltd. (Hangzhou, China). Heparin sodium (Batch No. 00321100) was purchased from Chengdu Hepatunn Pharmaceutical Co., Ltd. BSTZC was provided by the manufacturing laboratory of Guangdong Provincial Second Hospital of Traditional Chinese Medicine (Guangzhou, China). Total cholesterol (TC) kit (Batch No. 20230828) and triglyceride (TG) kit (Batch No. 20230830) were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). A high-fat diet (52.2% standard diet, 0.2% bile sodium, 10% casein, 1.2% cholesterol, 0.6% calcium hydrogen phosphate, 0.4% mineral feed, 0.4% premix feed, 15% lard, and 20% saccharose) was purchased from Guangdong Medical Laboratory Animal Center.

2.2 Animal

The Guangdong Medical Laboratory Animal Center (Guangdong Provincial Engineering Technology Research Institute of Traditional Chinese Medicine) SPF Animal Lab provided SD male rats (220 ± 20 g) with license number SCXK (Yue) 2022–0002 and C57BL/6 male mice (18~22 g) with license number SCXK (Yue) 2022–0059. The Animal Ethics Committee of the Guangdong Medical Laboratory Animal Center (Guangdong Provincial Engineering Technology Research Institute of Traditional Chinese Medicine) permitted them to carry out experiments (Approval No. 049097). SD rats were maintained for 1 week in an SPF-grade laboratory with a 12-h light/dark cycle.

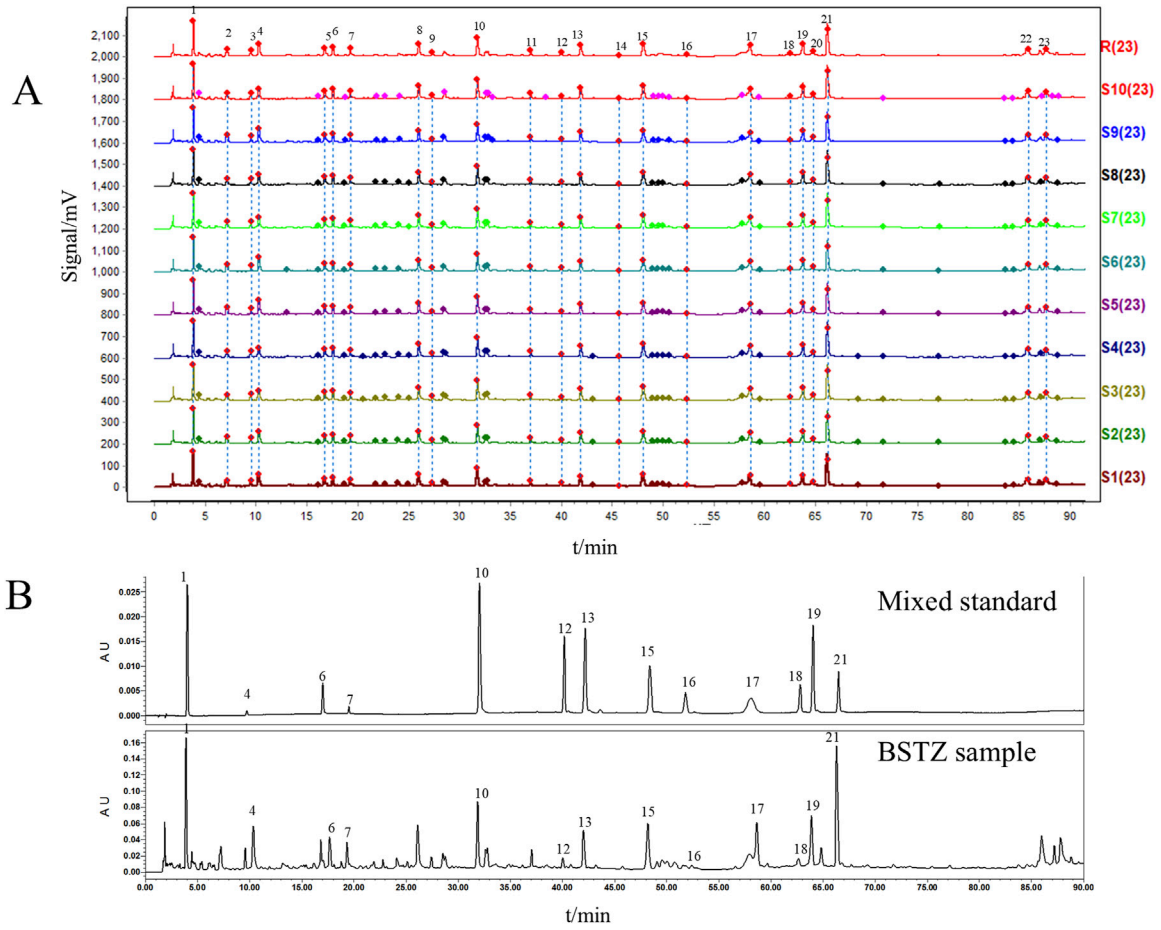


FIGURE 1
BSTZ quality control. **(A)** UPLC fingerprints of BSTZ samples from 10 batches and controls. **(B)** A total of 13 peaks were identified by standards. Peaks 1, 4, 6, 7, 10, 12, 13, 15, 16, 17, 18, 19, and 21 were gallic acid, oxypaeoniflorin, chlorogenic acid, paeoniflorin, ferulic acid, salicylic acid, vitexin, isovitexin, neoandrographolide, isoviolanthin, astragalin, narcissoside, and neoandrographolide.

2.3 UPLC fingerprint analysis of BSTZ

2.3.1 Sample preparation

The BSTZ was pulverized and 2.0 g of the powder was dissolved in 25 mL of 75% methanol–water solution and extracted by sonication for 30 min. The extract was centrifuged and the supernatant was filtered through a 0.22-μm membrane for use. All 10 batches of BSTZ were prepared using the same procedure to facilitate subsequent analysis.

In addition, appropriate quantities of standard samples were weighed accurately. These standard samples were dissolved in 75% methanol and diluted to 10 mL, and the supernatant was filtered through a 0.22-μm filter and used as the reference solution for UPLC analysis.

2.3.2 Chromatographic conditions for UPLC fingerprint

BSTZ analysis was performed on a UPLC (2,695, Waters, United States) connected with a CORTECS UPLC C18 column (2.1 × 150 mm, 1.6 μm, Waters, United States). Methanol (A) and 0.1 formic acid aqueous solvent (B) were used as the mobile phase with a flow rate of 0.20 mL/min, and the solvent gradient used was as follows: 0~35 min, 7~26% A; 35~50 min, 26%~26% A; 50~60 min, 26%~35% A; 60~80 min, 35%~40% A; and 80~90 min, 40%~60% A. The volume temperature was set at 35°C, and the injection volume was 1.0 μL. The result was detected at 300 nm.

2.4 Serum pharmacochemistry

2.4.1 Preparation of sample solution

The contents of BSTZC (about 0.5 g) were precisely weighed and added with 25 mL 75% methanol–water mixture, and then ultrasonically extracted at room temperature for 30 min. Following the extraction process, the mixture was centrifuged at 12,000 rpm for 10 min. The supernatant was filtered through a 0.22-μm Millipore filter before the analysis was performed.

2.4.2 Preparation of reference component solutions

A certain amount of 25 reference components was prepared individually by dissolving each component in methanol at a certain concentration. The stock solutions were diluted and mixed with methanol to obtain standard solutions at a concentration of roughly

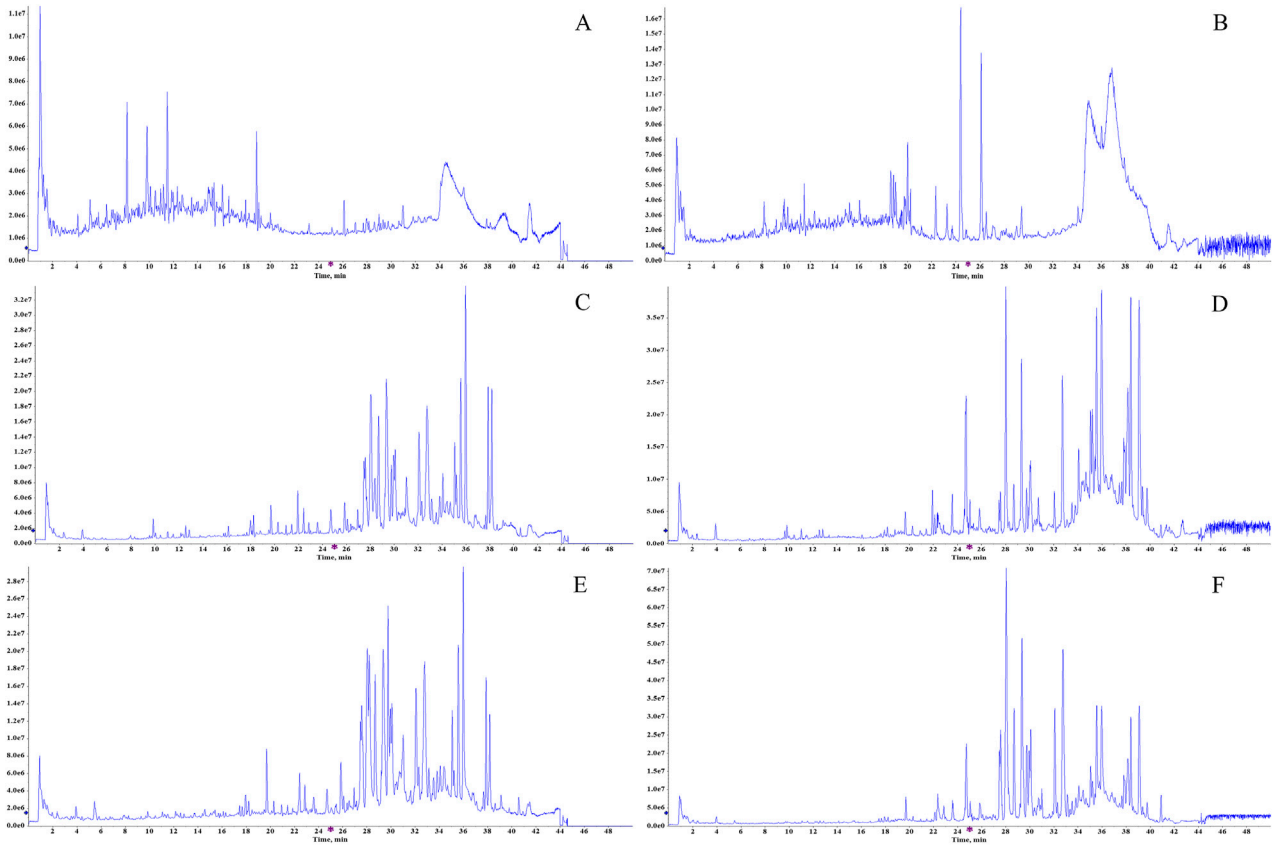


FIGURE 2
Total ion chromatograms of the BSTZC in the positive/negative ion mode **(A, B)**, blank serum in the positive/negative ion mode **(C, D)**, and rat serum after oral administration of BSTZC in the positive/negative ion mode **(E, F)**.

50 μg/mL for each component. The standard solutions were filtered through Millipore filters with a pore size of 0.22 μm before the analysis was performed.

2.4.3 Animal experiment and preparation of plasma sample

Twelve male SD rats (220 ± 20 g) were purchased from Guangdong Medical Laboratory Animal Center (Certificate number 44007200115140). They were given access to normal laboratory food and water for 1 week at a time, and then they were randomly divided into a control group and an administration group. Subjects abstained from food for a duration of 12 h before the experiment and water was provided without restriction. The administration group rats received the human equivalent dose of BSTZC at a dose of 5.76 g/kg, and the control group rats were given an equal dose of water intragastrically. At 10 min, 20 min, 30 min, 60 min, 90 min, and 120 min after administration, blood samples were collected from the fundus venous plexus and centrifuged at 3,000 rpm at 4°C for 15 min. Then, the supernatants of the rats were combined equally at each time point. All blood samples obtained were frozen at −80°C before analysis.

Protein was precipitated by adding 4 mL of methanol to a 1 mL mixture and vortexing for 30 s. After placing at −20°C for 1 h, the mixture was centrifuged at 12,000 rpm at 4°C for 15 min. The supernatant was removed and blown dry at room temperature in nitrogen. The residue was redissolved in 150 μL methanol and vortex mixed for 30 s, and then centrifuged at 12,000 rpm and 4°C for 15 min. Afterward, 90 μL of supernatant was produced for UPLC-Q-TOF-MS analysis.

2.4.4 Chromatography conditions and mass spectrometry conditions

Chromatography analyses were performed on Agilent 1,290II (Agilent, United States). A Waters ACQUITY UPLC BEH C18 column (100 × 2.1 mm, 1.7 μm) was used to separate and analyze samples. Eluent A was 0.1% formic acid water solution, whereas eluent B was acetonitrile with a flow rate of 0.3 mL/min and a temperature of 30°C. The gradient elution was as follows: 0–3 min, 10% B; 3–10 min, 10%–20% B; 10–15 min, 20%–30% B; 15–23 min, 30%–50% B; 23–30 min, 50%–68% B; 30–34 min, 68%–80% B; 34–40 min, 80%–95% B; 40–45 min, 95%–5% B; and 45–50 min, 5% B. The injection volume was 1 μL.

The MS analyses were performed on an X500 Q-TOF/MS system (AB Sciex, United States). The optimized operating parameters were as follows: ion source, 379 KPa; curtain gas, 241.3 KPa; the full scan mass range, *m/z*100-1,000; and ion source temperature, 500°C. The mass spectrometer analysis was conducted in both positive and negative ion modes with an

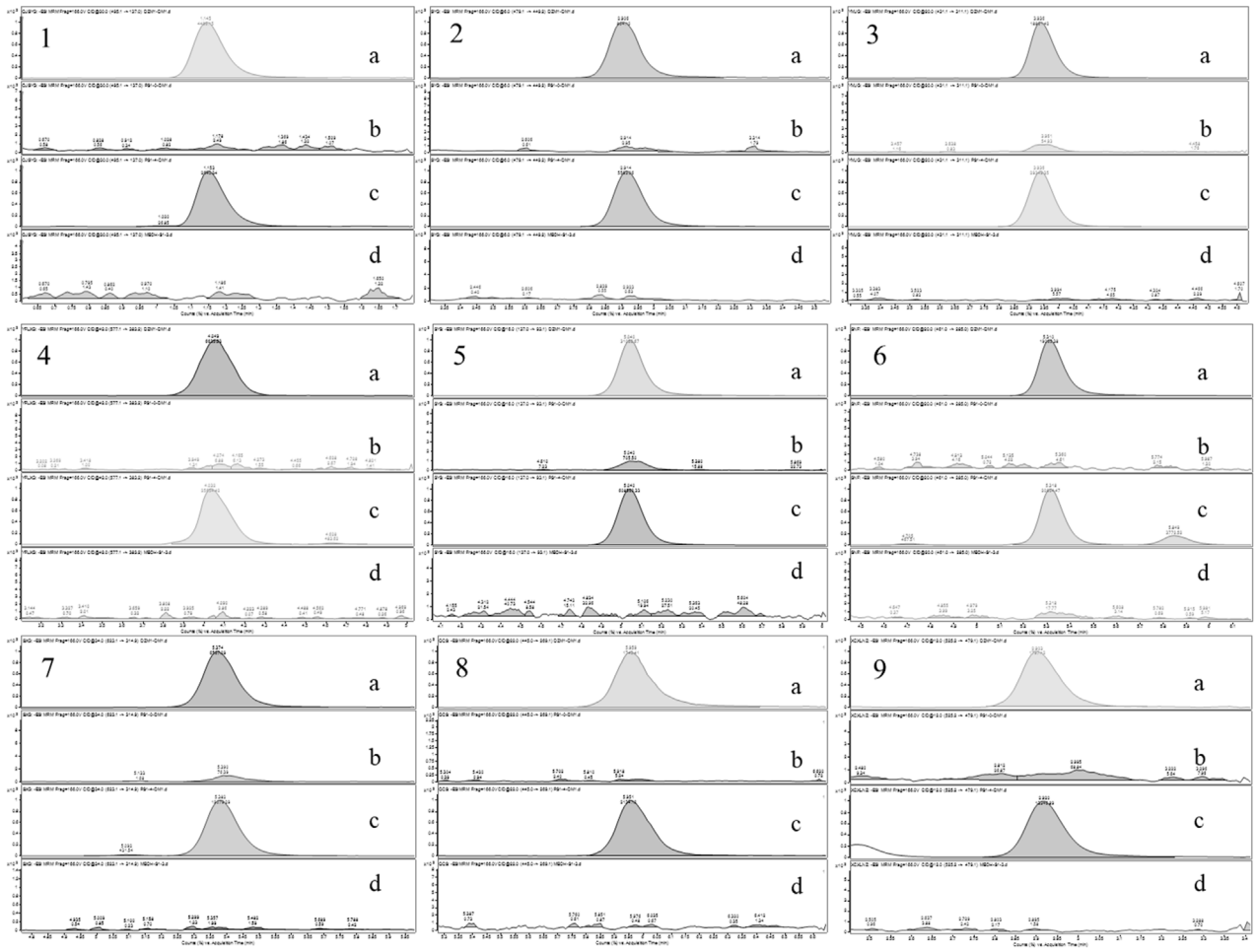


FIGURE 3
Chromatograms of nine tested components (**(A)** mixed standard solution, **(B)** blank plasma, **(C)** serum sample after oral administration of BSTZC, and **(D)** blank solution. 1: OXY; 2: PN; 3: IVT; 4: IVL; 5: SA; 6: KPF-3-G; 7: NCS; 8: APG-7-G; 9: NAG).

TABLE 1 Regression equations, linear ranges, correlation coefficients, and LLOQs of analytes.

Component	Calibration curve	R	Range (ng/mL)	LLOQ (ng/mL)
OXY	$Y = 0.245983X+0.001045$	0.9958	0.0894~496.86	0.1789
PN	$Y = 0.0034332X+0.00094$	0.9984	0.7309~4,060.77	1.4619
IVT	$Y = 1.358451X-0.020610$	0.9979	0.0908~504.70	0.1817
IVL	$Y = 0.433634X+0.013252$	0.9995	0.3613~2007.04	0.5658
SA	$Y = 2.208291X-0.028258$	0.9950	0.9049~5,027.40	1.8099
KPF-3-G	$Y = 0.797102X-0.031415$	0.9978	0.1613~896.11	0.3226
NCS	$Y = 0.642029X-0.014476$	0.9981	0.1413~785.02	0.3226
APG-7-G	$Y = 0.808981X+0.000439$	0.9963	0.3613~2010.96	0.7239
NAG	$Y = 0.093739X-0.000172$	0.9958	0.3612~2007.04	0.7225

electrospray interface (ESI) source. The capillary voltage was 5.5 KV, the declustering potential was 100 V, and collision energy is 35 eV in the ESI^+ mode. The capillary voltage was −4.5 KV, the declustering potential was −80 V, and collision energy is 35 eV in the ESI^- mode. Natural Products HR-MS/MS Spectral Library (Version 1.0, AB Sciex, United States) in Sciex OS v2.1 software was used to analyze the component data. The serum migrating metabolites of BSTZC then were regarded as PK markers.

TABLE 2 Regression equations, linear ranges, correlation coefficients, and LLOQs of analytes (n = 6).

Component	Concentration (ng/mL)	Precision (RSD%)		Accuracy (RE%)	
		Intra-day	Inter-day	Intra-day	Inter-day
OXY	0.60	9.92	11.57	−1.15	3.58
	5.96	8.02	10.65	−0.15	5.90
	397.49	4.95	6.36	9.56	12.92
PN	4.87	9.46	9.91	−9.78	−12.26
	48.72	6.72	10.28	−5.70	−6.98
	3,248.62	10.94	13.66	7.37	−1.79
IVT	0.61	11.32	12.45	−5.50	−5.32
	6.06	6.35	6.33	−0.54	−1.72
	403.76	4.89	6.31	10.07	12.31
IVL	1.89	8.89	10.19	−6.80	−7.51
	18.86	4.27	5.33	11.53	−13.86
	1,257.34	8.53	9.29	12.15	13.00
SA	6.03	8.92	10.94	2.02	−1.03
	60.03	7.35	7.12	5.53	6.36
	4,021.92	3.84	6.73	9.63	12.35
KPF-3-G	1.08	7.75	9.60	6.15	−5.45
	10.75	7.13	9.00	−2.84	−3.57
	716.89	3.13	8.58	−1.18	−1.71
NCS	0.94	13.41	13.10	−3.51	−6.73
	9.42	4.92	5.62	7.62	8.87
	628.02	9.73	9.56	2.27	−0.33
APG-7-G	2.41	10.59	11.80	0.62	−1.74
	24.08	9.08	9.52	−3.10	−6.68
	1,650.63	9.47	9.94	3.81	6.70
NAG	2.41	8.33	10.75	−6.65	−10.21
	24.13	7.64	8.16	5.80	9.06
	1,608.77	10.93	10.61	1.96	4.75

2.5 Pharmacokinetics study

2.5.1 Preparation of standards and control samples

The standards of oxypaeoniflorin (OXY), paeoniflorin (PN), isovitexin (IVT), isoviolanthin (IVL), salicylic acid (SA), kaempferol-3-glucuronide (KPF-3-G), narcissoside (NCS), apigenin-7-glucuronide (APG-7-G), and neoandrographolide (NAG) were accurately weighed and dissolved in methanol to obtain the stock solution. Then, they were diluted with methanol to make mixed standard solution with concentrations of 6.360 μg/mL, 4.873 μg/mL, 6.460 μg/mL, 19.646 μg/mL, 60.329 μg/mL, 11.152 μg/mL, 9.813 μg/mL, 24.084 μg/mL, and 24.132 μg/mL. The stock solution of sulfamethoxazole was accurately weighed, dissolved, and diluted with methanol at a concentration of 2.011 μg/mL.

2.5.2 Sample preparation

A centrifuge tube containing 100 μL plasma was filled with 400 μL methanol–acetonitrile mixed solution (1:1) and IS solution (2.011 μg/mL), and then vortex mixed for 30 s and stored at −20°C for 1 h. The supernatant was separated and dried under a stream of nitrogen at room temperature after the frozen mixture was centrifuged at 4°C and 12,000 rpm for 15 min. The residue was reconstituted in 100 μL of methanol–water (80:20, v/v), vortex mixed, and centrifuged at 4°C, 12,000 rpm for 15 min, and 80 μL supernatant was taken for analysis.

TABLE 3 Stability of results (n = 6).

Component	Concentration	24°C, 24 h	4°C, 12 h		Three cycles of freeze-thaw		−60°C, 30 d	
	(ng/mL)	RE (%)	RSD (%)	RE (%)	RSD (%)	RE (%)	RSD (%)	RE (%)	RSD (%)
OXY	0.60	3.31	11.82	−0.90	14.26	3.14	10.32	10.01	14.74
	5.96	14.65	8.02	11.29	8.18	9.54	7.54	2.93	4.06
	397.49	13.21	7.63	13.69	4.99	9.17	4.95	5.93	6.75
PN	4.87	−13.80	10.59	−12.13	12.15	−7.57	13.04	−0.16	3.82
	48.72	−5.98	12.97	−11.62	8.58	−6.49	11.63	−7.66	12.62
	3,248.62	2.24	14.23	2.87	11.79	4.17	11.10	1.08	12.85
IVT	0.61	−11.20	9.02	−13.20	11.43	−8.43	12.84	−1.23	10.00
	6.06	−2.43	6.12	0.44	9.04	−4.38	6.71	−8.78	2.74
	403.76	13.32	10.08	8.59	4.97	9.77	4.95	2.42	6.49
IVL	1.89	−10.12	13.07	−10.08	10.57	13.58	13.07	4.65	11.21
	18.86	−14.41	7.49	−11.41	5.93	−14.39	7.58	−14.47	5.88
	1,257.34	9.94	9.83	0.76	4.44	−2.90	5.93	−2.95	7.04
SA	6.03	−0.33	11.76	3.71	12.33	−4.29	13.40	−7.96	13.23
	60.03	8.00	7.17	10.43	10.24	10.99	7.34	6.43	1.94
	4,021.92	13.90	10.03	6.98	5.16	1.34	5.48	1.86	6.56
KPF-3-G	1.08	−12.42	7.04	−7.42	14.36	−10.49	11.71	−2.05	7.69
	10.75	−3.21	12.65	−0.70	8.44	−12.42	13.41	−14.58	14.14
	716.89	−4.42	10.37	−5.24	9.01	−3.53	14.97	−8.46	9.67
NCS	0.94	−13.46	11.64	1.90	13.79	3.32	12.97	−10.66	10.99
	9.42	10.00	7.83	11.92	8.40	−8.17	6.32	−9.24	13.12
	628.02	−1.21	10.43	0.08	9.56	0.04	14.05	−5.30	10.18
APG-7-G	2.41	−2.04	7.40	0.76	6.60	−6.79	7.24	−7.57	9.77
	24.08	−5.29	7.76	−2.08	6.29	−3.32	7.20	−8.56	2.06
	1,650.63	12.07	10.65	−1.67	4.50	−5.37	5.86	−8.38	6.71
NAG	2.41	−12.83	12.79	−14.69	9.72	−12.84	12.51	−10.73	9.97
	24.13	8.79	7.26	8.70	10.08	6.98	8.12	−0.58	2.32
	1,608.77	4.81	12.64	8.71	5.20	−13.19	3.82	−12.30	6.30

2.5.3 UPLC-MS/MS conditions for pharmacokinetics

Agilent 1290II (Agilent, United States) was used to analyze plasma on an Agilent Extend-C18 RRHD column (50 × 2.1 mm, 1.8 μm) at 35°C. The mobile phase A and phase B, respectively, were 0.1% formic acid water solution and acetonitrile. The gradient was optimized as follows: 0~0.5 min, 10% B; 0.3~3 min, 10%~16% B; 3~6 min, 16% B; 6~8 min, 16%~20% B; 8~9.5 min, 20%~38% B; 9.5~10.5 min, 38% ~95% B; and 10.5~13 min, 95% B. The flow rate was 0.3 mL/min and the injection volume was 1 μL. Samples were analyzed in negative ionization with the MRM mode in Agilent 6495C (Agilent, United States). The main mass spectral parameters were set as follows: the capillary voltage was 3.0 KV, the ion source temperature was 500°C, the drying gas temperature was 200°C with a gas flow rate of 15 mL/min, the ion source was 30 psi, and sheath gas was 350°C with a gas flow rate of 11 mL/min. The specific mass spectrometry parameters of analytes and IS are shown in Supplementary Table S2.

2.5.4 Method validation

Specificity test: selectivity was assessed by comparing the MRM chromatograms of blank plasma samples, blank plasma spiked with standards, blank solution, and representative plasma samples after oral administration, mixed standard solution, and blank solution were used for the analysis. Linearity and LLOQ: the calibration curves for the quantitative evaluation were determined by graphing the peak area ratio (y) of each component to IS versus the nominal concentration (x)

TABLE 4 Extraction recovery and matrix effects (n = 6).

Component	Concentration (ng/mL)	Extraction recovery		Matrix effect	
		Mean (%)	RSD (%)	Mean (%)	RSD (%)
OXY	0.60	103.26	11.59	90.60	12.38
	5.96	114.70	3.18	85.00	1.37
	397.49	110.10	5.27	88.19	6.30
PN	4.87	94.98	7.28	100.19	7.12
	48.72	98.26	2.26	82.43	3.42
	3,248.62	97.04	5.51	89.31	4.74
IVT	0.61	99.84	4.08	96.62	4.53
	6.06	107.28	3.05	99.83	2.67
	403.76	103.49	5.91	97.96	2.07
IVL	1.89	103.79	8.23	99.94	11.96
	18.86	110.90	2.13	109.13	3.37
	1,257.34	112.36	3.00	103.53	3.49
SA	6.03	104.83	5.80	107.85	6.13
	60.03	113.02	1.70	97.18	1.54
	4,021.92	106.58	1.99	104.98	2.68
KPF-3-G	1.08	100.17	4.62	87.75	10.39
	10.75	108.17	3.91	85.24	1.66
	716.89	105.37	1.96	87.75	3.61
NCS	0.94	101.66	6.65	87.08	8.75
	9.42	102.61	2.45	86.39	4.76
	628.02	98.78	3.51	92.33	9.01
APG-7-G	2.41	108.48	5.94	103.94	2.73
	24.08	112.26	6.12	98.47	9.13
	1,650.63	100.60	1.17	91.54	2.99
NAG	2.41	100.30	5.72	99.71	8.14
	24.13	108.33	6.10	92.76	9.03
	1,608.77	101.63	1.45	93.71	5.73

by using ($1/x^2$) least-squares linear regression. In addition, the analytical signaling of the LLOQ sample should be at least 10 times the signaling of the blank sample. Accuracy and precision test: the QC samples at low, middle, and high concentration levels (n = 6) were analyzed for variation and precision (intra-day and inter-day). Stability test: stability was evaluated by analyzing three concentrations of QC samples (n = 6) under four storage conditions, including room temperature for 24 h, 4°C for 12 h, three cycles of freeze-thaw at −20°C and −60°C for 30 days. Extraction recovery and matrix effect: the peak area of pre-extracted QC samples was recorded as A and the peak area of post-extracted QC samples was recorded as B. Extraction recovery = (B/A) × 100%. The peak area of mixed standard solution with IS was recorded as C. Matrix effect = (C/A) × 100%.

2.5.5 Animal experiment and data analysis

Sixteen male SD rats (220 ± 20 g) were purchased from Guangdong Medical Laboratory Animal Center (Certificate number 44007200122329). They were randomly divided into two groups (n = 8): the control group was administered with a basal diet and the HLP model group was fed with a high-fat diet for 4 weeks. Four weeks after modeling, the levels of TC and TG in plasma were measured to evaluate the model efficiency. Two assays were performed by kit instructions. Then, the livers of three rats in each group were stained with hematoxylin and eosin, combined with TC and TG levels, to evaluate whether the HLP rat model was successfully established.

After the model's successful establishment, all rats were starved overnight before the formal trial. Two group rats were administered

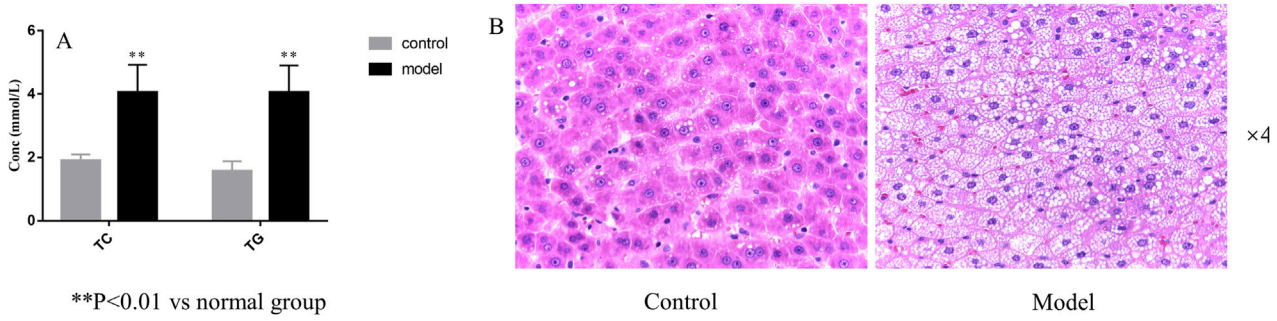


FIGURE 4
Serum biochemical parameters **(A)** and HE staining of liver sections **(B)**.

BSTZC at a dose of 5.76 g/kg. Blood samples (0.5 mL) were collected from the fundus venous plexus and placed into heparinized tubes before the experiment and at 0, 0.083, 0.167, 0.333, 0.146, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after administration. The supernatant was obtained after centrifugation at 10,000 rpm and 4°C for 15 min. All blood samples were stored at −80°C until analysis.

The pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin 8.1 software, including the elimination half-time ($t_{1/2}$), time to the maximum concentration (T_{max}), maximum concentration (C_{max}), area under the plasma concentration-time curve (AUC), and mean retention time (MRT).

2.6 Network analysis

The PK markers of BSTZC were input into the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) to download Canonical SMILES, which could be used to discover the interrelated targets in the Swiss Target Prediction databases (http://www.swisstargetprediction.ch/) and then the target names were standardized from the UniProt database (https://www.uniprot.org/). In the meantime, HLP-related genes were collected from CTD (http://ctdbase.org/) and GeneCards (http://www.genecards.org/) databases, with "hyperlipidemias" and "hyperlipidemia" as keywords. To find out the overlapped targets between the component targets and disease targets, Venny 2.1.0 (http://bioinfogp.cnb.csic.es/tools/venny/) was used. The common targets were imported into the String database (http://string-db.org/), with the screening condition "*Homo sapiens*." Cytoscape 3.7.1 software is used to visualize the protein–protein (PPI) network. Finally, we imported the targets into Bioinformatics (https://www.bioinformatics.com.cn/) to conduct the Kyoto Encyclopedia of Genes and Genomes (KEGG) data obtained pathway enrichment.

2.7 Lipid-lowering experimental validation of active components

2.7.1 Experimental design

The acute HLP model in mice was induced by triton WR-1339 using our previously described method (Xiao et al., 2023). Male C57BL/6 mice were acclimated and fed for 1 week and then randomly divided into 13 groups of six mice each: control, TWR model, fenofibrate (26 mg/kg/day), BSTZC (4.16 g/kg/day), APG (26 mg/kg/day), IVT (26 mg/kg/day), IVL (26 mg/kg/day), KPF (26 mg/kg/day), NCS(26 mg/kg/day), NAG(26 mg/kg/day), OXY (26 mg/kg/day), PN(26 mg/kg/day), and SA (26 mg/kg/day). The animal experiment procedure is shown in Supplementary Figure S1.

2.7.2 Biochemical analysis

The levels of TC, TG, LDL-c, ALT, and AST in serum were determined by using commercial kits according to the manufacturer's instructions.

2.7.3 Real-time PCR

TRIzol reagent was used to extract total RNA from each group of liver tissues. The M-MuLV First Strand cDNA Synthesis Kit and the 2X SG Fast qPCR Master Mix were utilized for reverse transcription and RT-qPCR, respectively. RT-qPCR was performed with the manufacturer's experimental instructions by StepOnePlus (United States), and the gene primer sequences used are shown in Supplementary Table S3. The mRNA expression levels of genes were normalized to GAPDH.

2.8 Statistical analysis

All data were expressed as mean ± SD. Comparisons between multiple groups were evaluated using one-way ANOVA with Tukey's multiple comparison test and analyzed in the study using GraphPad Prism 9.0 software, with statistical significance denoted as $p < 0.05$.

3 Results

3.1 Establishment of fingerprint profiles and similarity evaluation

UPLC prepared and analyzed 10 batches of BSTZ samples. A total of 23 common peaks were obtained based on multipoint correction (Figure 1A). In addition, the UPLC fingerprints of 10 batches of BSTZ samples were evaluated for similarity, and the similarity was more than 0.99 (Supplementary Table S4). This indicates that the quality of the BSTZ samples has been

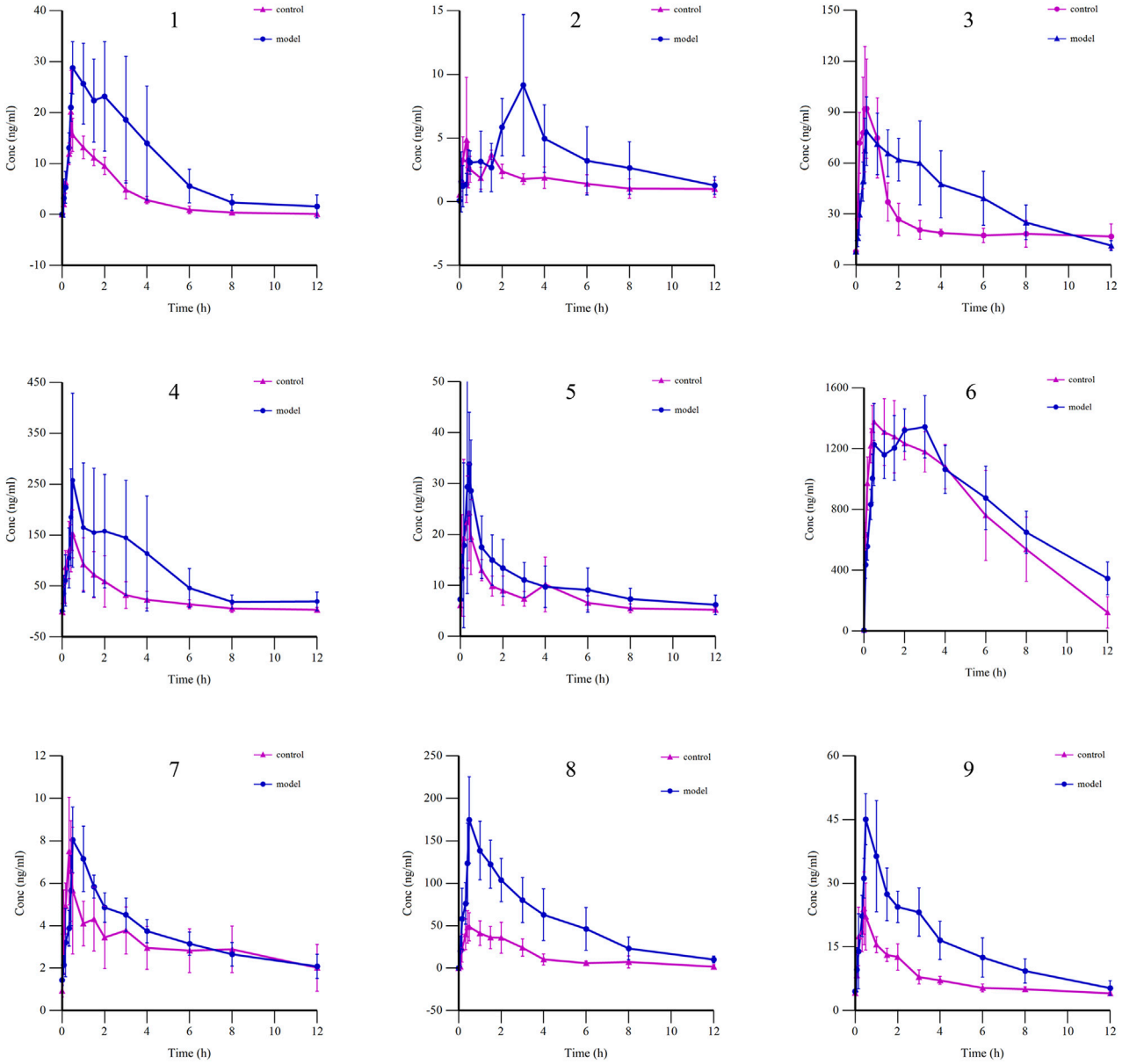


FIGURE 5
Mean plasma concentration–time curves of nine components in control and HLP model groups (1: OXY; 2: PN; 3: IVT; 4: IVL; 5: SA; 6: KPF-3-G; 7: NCS; 8: APG-7-G; 9: NAG).

stable. Thirteen peaks, namely, gallic acid, oxypaeoniflorin, chlorogenic acid, paeoniflorin, ferulic acid, salicylic acid, vitexin, isovitexin, neoandrographolide, isoviolanthin, astragalin, narcissoside, and neoandrographolide, were then identified using standard substances (Figure 1B).

3.2 Identification of absorbed metabolites of BSTZC

A total of 62 components of BSTZC were identified by comparison with standards, mass-to-charge ratio of fragment ions, and internal databases, consisting mainly of 27 flavonoids, 16 organic acids, five monoterpenoids, six diterpene lactones, and eight sesquiterpenes (Figure 2; Supplementary Table S5). Chemical profiling of serum obtained after BSTZC administration was performed to characterize the absorbed metabolites to find possible therapeutic components of BSTZC. Upon comparison with blank serum, nine metabolites were detected in the serum of healthy rats after the administration of BSTZC (OXY, PN, IVT, IVL, SA, NCS, NAG, KPF-3-G, and APG-7-G) (Figure 2; Supplementary Table S5). The two metabolites (KPF-3-G and APG-7-G) were converted from flavonoids through phase II metabolic reaction *in vivo* to glycolaldehyde products.

TABLE 5 Main pharmacokinetic parameters of nine analytes ($\bar{x}\pm s$, n = 6).

Component	Group	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\rightarrow t}$ (h*ng/mL)	$AUC_{0\rightarrow\infty}$ (h*ng/mL)	$MRT_{0\rightarrow t}$ (h)
OXY	Control	1.39 ± 0.55	0.45 ± 0.05	21.66 ± 7.03	39.51 ± 7.43	40.41 ± 7.18	2.03 ± 0.44
	Model	2.16 ± 1.03	1.00 ± 0.61*	33.10 ± 5.36*	115.01 ± 51.02*	122.52 ± 46.68*	3.22 ± 0.47*
PN	Control	1.91 ± 1.12	0.48 ± 0.04	152.52 ± 46.99	326.56 ± 145.09	344.08 ± 152.29	2.48 ± 0.75
	Model	3.55 ± 2.46	1.08 ± 1.10	275.50 ± 148.19	893.99 ± 632.57	1,042.31 ± 584.15*	3.59 ± 1.12
IVT	Control	10.21 ± 6.11	0.33 ± 0.16	27.43 ± 5.90	90.23 ± 9.18	150.43 ± 42.40	4.35 ± 0.22
	Model	5.16 ± 1.54**	0.60 ± 0.22*	48.38 ± 7.83**	183.12 ± 29.55**	222.56 ± 42.67*	4.08 ± 0.41
IVL	Control	2.62 ± 1.84	0.48 ± 0.04	54.70 ± 18.44	164.59 ± 47.19	180.68 ± 54.88	4.10 ± 2.24
	Model	3.37 ± 1.35	0.60 ± 0.22	184.60 ± 41.25**	643.59 ± 182.36**	692.49 ± 186.06**	3.53 ± 0.49
SA	Control	2.13 ± 0.57	0.67 ± 0.31	1,472.74 ± 80.94	9,232.85 ± 1903.57	9,668.54 ± 2,343.94	4.13 ± 0.44
	Model	5.15 ± 2.53*	2.30 ± 0.67**	1,425.11 ± 175.82	10,152.94 ± 1,461.59	12,909.30 ± 2,666.50	4.76 ± 0.15*
KPF-3-G	Control	11.04 ± 3.23	0.38 ± 0.14	110.61 ± 12.48	304.41 ± 49.22	577.34 ± 219.04	4.39 ± 0.69
	Model	4.25 ± 1.57*	1.00 ± 1.11	86.62 ± 17.37*	462.80 ± 116.83*	533.89 ± 101.16	6.39 ± 1.41*
NCS	Control	10.07 ± 5.07	0.35 ± 0.12	33.73 ± 7.70	95.38 ± 13.80	172.36 ± 51.07	4.77 ± 0.32
	Model	15.46 ± 10.72	0.42 ± 0.07	45.38 ± 8.66	122.94 ± 32.61	251.42 ± 67.04	4.65 ± 0.38
APG-7-G	Control	12.35 ± 12.22	0.52 ± 0.56	6.49 ± 4.05	19.25 ± 3.88	46.12 ± 33.46	4.61 ± 1.15
	Model	4.06 ± 1.38	2.28 ± 1.13**	9.80 ± 4.62	42.44 ± 20.35	50.19 ± 23.73	4.56 ± 0.79
NAG	Control	9.95 ± 5.51	0.38 ± 0.07	9.08 ± 1.73	37.51 ± 9.94	72.54 ± 38.77	5.06 ± 0.42
	Model	10.80 ± 3.28	0.60 ± 0.22*	8.14 ± 1.41	42.61 ± 4.07	76.84 ± 23.09	4.78 ± 0.37

* $P< 0.05$, ** $P< 0.01$ vs. normal group.

3.3 Pharmacokinetics study

3.3.1 Method validation

Based on the UPLC-MS technology, a multi-component analytical method was successfully established and methodologically investigated for the analysis of BSTZC in rat plasma. The typical MRM chromatograms of OXY, PN, IVT, IVL, SA, KPF-3-G, NCS, APG-7-G, and NAG are shown in Figure 3. The results presented show that endogenous chemicals did not interfere with the detection of the targeted components in rat plasma and internal standard, indicating the method had a good level of sensitivity and the instrument had adequate distinctiveness. The linear equation, linear ranges, coefficients (r), and LLOQs of these nine analytes are represented in Table 1. These results confirmed that the method was sufficiently sensitive for the pharmacokinetics study. The precision and accuracy values of the intra-day and inter-day of nine analytes are listed in Table 2. The results indicated that the precision and accuracy of the method were acceptable to the requirements of the biological samples. The stability result of the nine components is summarized in Table 3. The RSD of nine analytes was less than 15%, and the RE ranged from −15% to 15%, demonstrating that all the analytes were stable in the rat plasma under the four conditions, including room temperature for 24 h, 4°C for 12 h, three cycles of freeze-thaw at −20°C, and −60°C for 30 days. As shown in Table 4, the extraction recoveries and matrix effects were, respectively, 94.98%–114.70% and 85.00%–109.13%, confirming that the extraction recoveries were reliable and the plasma matrix did not interfere with the determination of the analytes.

3.3.2 Evaluation of the HLP rat model

As shown in Figure 4A, the levels of TC and TG in the model group were significantly increased compared with those in the control group ($P< 0.01$). As shown in Figure 4B, the volume of liver cells in the model group was larger than that in the normal group. In the HLP group, a large number of fat vesicles appeared in the liver tissue, and the hepatocytes were balloon shaped. Meanwhile, many lipid droplets of different sizes accumulated seriously in the hepatocytes, resulting in fatty liver symptoms. The above indicated that the model was constructed successfully.

3.3.3 Pharmacokinetic comparison of BSTZC in control rats and HLP model rats

The mean plasma concentration–time curves of nine components in the control and the HLP model group are shown in Figure 5, whereas the main pharmacokinetic parameters are shown in Table 5. Compared with the control group, mostly the C_{max} and AUC were higher in the model group, whereas the C_{max} and $AUC_{0\rightarrow t}$ of OXY, IVT, IVL, and KPF-3-G were significantly higher in the model group ($P< 0.05$), and the $AUC_{0\rightarrow\infty}$ of OXY, PN, and IVT was significantly higher in the model group ($P< 0.05$). T_{max} reflected the rate of drug absorption. T_{max} parameters were not significantly different between the model group and the normal group except for OXY, IVT, SA, and APG-7-G. On the other hand,

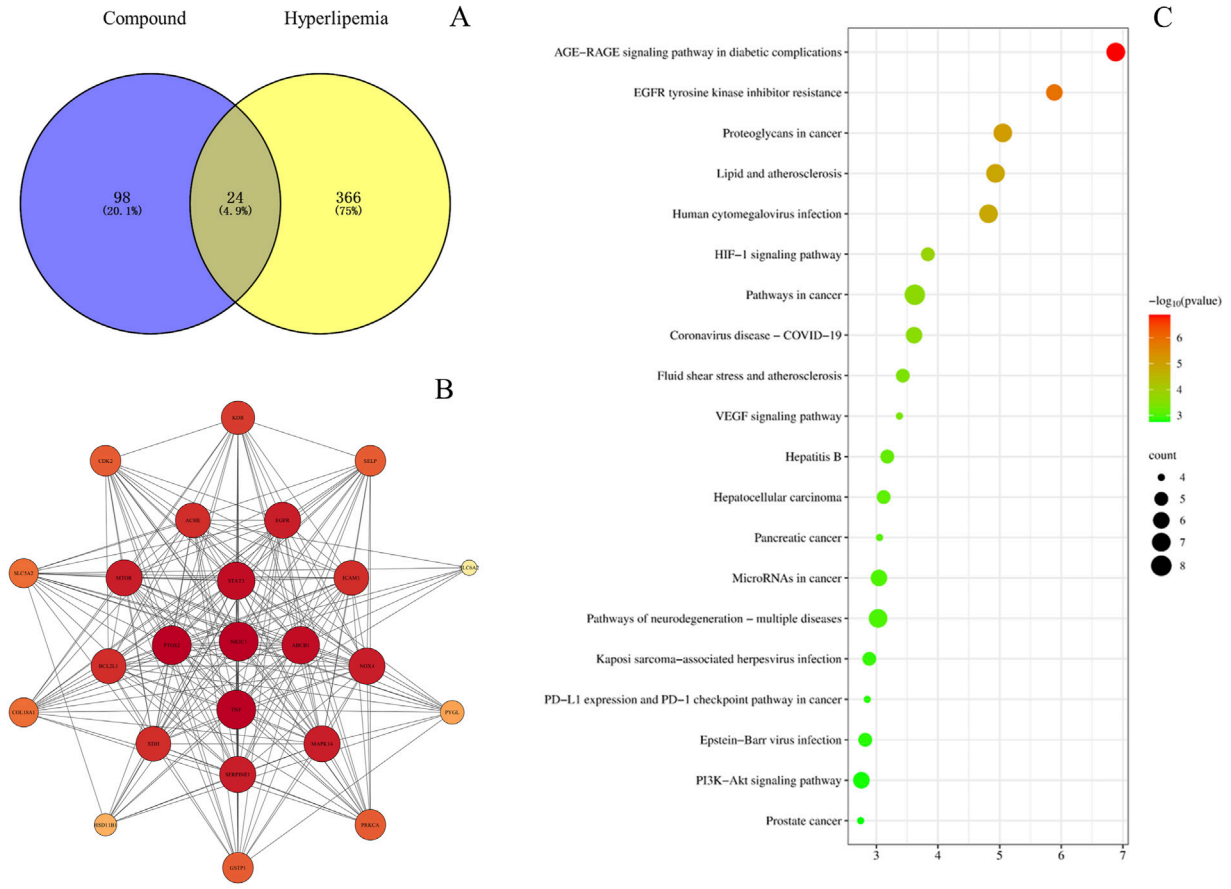


FIGURE 6
Venny diagram **(A)**, PPI network diagram **(B)**, and bubble diagram **(C)**.

the parameters of $t_{1/2}$ and MRT were crucial factors in drug metabolism and elimination. As the result shows, most of the components' MRT were less than 6 h. Moreover, the $t_{1/2}$ of IVT, SA, and KPF-3-G was significantly different ($P< 0.05$).

3.3.4 Network analysis

The PK markers of BSTZC were found in 123 related targets by Swiss Target Prediction databases. The nine components are shown in Supplementary Figure S2. In addition, 390 HLP-related targets were indicated in CTD, GeneCards, DisGeNET, and Drugbank databases. Furthermore, 24 common targets were confirmed by Venny 2.1.0 (Figure 6A), including PTGS2, TNF, NR3C1, ABCB1, STAT3, SERPINE1, MAPK14, NOX4, EGFR, MTOR, ICAM1, ACHE, BCL2L1, XDH, KDR, SELP, CDK2, GSTP1, PRKCA, SLC5A2, COL18A1, PYGL, HSD11B1, and SLC6A2, and then overlapped targets were imported into String and Cytoscape 3.7.1 software to obtain the PPI network, as shown in Figure 6B. The results of the top 20 of the KEGG enrichment pathways are shown in the bubble diagrams in Figure 6C. The results of the KEGG enrichment pathway analysis mainly included lipid, and atherosclerosis pathways, cancer-related pathways, and virus infection. AGE-RAGE signaling pathway, lipid and atherosclerosis, HIF-1 signaling pathway, fluid shear stress and atherosclerosis, VEGF signaling pathway, and PI3K-Akt signaling pathway were relative to the treatment of HLP.

3.4 Results of lipid-lowering experiments with active components

The experimental results showed that the serum levels of TC, TG, LDL-C, ALT, and AST were significantly increased in the model group compared with the control group, indicating that the HLP model was successfully established (Figure 7A). After administration, the monomer components played different degrees of roles in lipid-lowering, compared with the model group, and the KPF group significantly reduced the serum levels of TC, LDL-C, ALT, and AST. The IVT group significantly downregulated the serum levels of TC, TG, LDL-C, and AST. The APG group significantly reduced the serum levels of TG, LDL-C, ALT, and AST. The PN group significantly reduced the levels of TC, TG, LDL-C, and AST in serum, suggesting that these components have good lipid-lowering and liver-protecting effects and that these components may be the active components in the lipid-lowering efficacy of BSTZC. In addition to the above components with lipid-lowering effects, other blood-absorbed components play a protective role for the liver to a certain extent by lowering LDL-C and AST in serum. Among them, the lipid-lowering efficacy of the TCM formula was obvious, and the administration of BSTZC effectively lowered the levels of TC, TG, LDL-C, ALT, and AST in serum, indicating that it could significantly improve the abnormalities of lipid metabolism and liver injury.

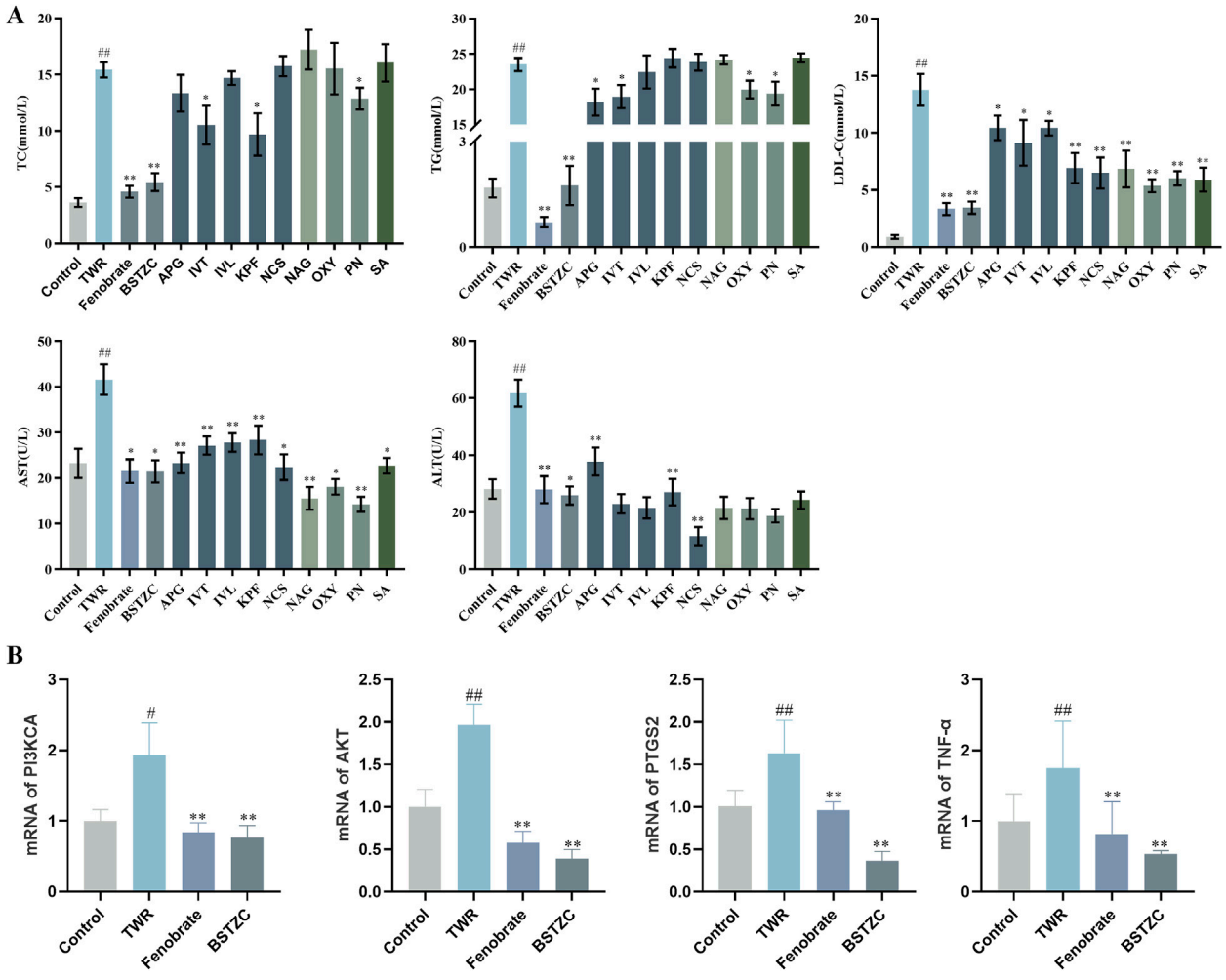


FIGURE 7
Lipid-lowering effect of BSTZC and its active components on triton WR-1339-induced HLP mice. **(A)** Biochemical analyses of serum TC, TG, LDL-c, ALT, and AST. **(B)** mRNA levels of PI3KCA, AKT, PTGS2, and TNF in mice liver. The results are represented as mean ± SD of six mice in each group. $^{\#\#}p < 0.01$ vs. the control group, $^{**}p < 0.01 < 0.01$ vs. the model group.

3.5 Effects of BSTZC on the PI3K/Akt signaling pathway

Combined with the core targets and pathways predicted by the absorption into the blood component network analysis, PTGS2 and TNF may be the key targets of BSTZC, and the ameliorating effect of BSTZC on HLP may be related to the PI3K/Akt signaling pathways. To validate this result, we performed RT-qPCR assays to determine the effect of BSTZC intervention on this pathway. As shown in Figure 7B, compared with the control group, the mRNA levels of AKT, PIK3CA, PTGS2, and TNF were significantly elevated in the TWR model group, and these key targets were significantly reversed after BSTZC treatment. These findings suggested that BSTZC may ameliorate HLP by inhibiting the PI3K/AKT signaling pathways.

4 Discussion

BSTZC is a novel Chinese medicine prepared for the treatment of HLP, which can reduce the risk of hyperlipidemia, atherosclerosis, and coronary heart disease, but there was still insufficient pharmacodynamic substance basis study. Therefore, an effective and quick screening method for active components of BSTZC was established in this work.

The serum pharmacochemistry revealed nine migrating metabolites in rat serum were determined, including five flavonoids, one organic acid, two monoterpenoids, and one diterpene lactone. The migrating metabolites had a certain concentration in the rat blood and high oral bioavailability, which was unambiguously identified by comparing their accurate mass measurements of MS and retention times to reference components. Flavonoids are antioxidant components that can prevent lipid oxidation, especially oxidative damage caused by HLP (Huang et al., 2020). Paeoniflorin and other monoterpenoids can protect the liver by activating AMPK and inhibiting lipid synthesis in hepatocytes (Li, Y.C. et al., 2018). Kaempferol and apigenin have an effect on lipid regulation and antioxidants, which can reduce the level of TC, TG, and MDA, and increase the activities of SOD and GSH-Px in serum (Ochiai et al., 2021; Ren et al., 2016). Furthermore, kaempferol has potential health benefits, which are related to

cardiovascular protective mechanisms, such as anti-aging and cancer-preventive activities (Dabeek and Marra, 2019). However, both the two components were affected by UDP-glucuronosyltransferases (UGT) (Chen et al., 2008), promptly absorbed through the gastrointestinal tract, and metabolized to phase II conjugates (Wang et al., 2014; Zhang et al., 2010). The metabolites were more rapidly eliminated due to the polarity enhancement. The metabolites were spread throughout various botanical drugs in BSTZC prescription (namely, monarch, minister, assistant, and guide), which confirmed each botanical drug was well absorbed. Nevertheless, the metabolites of Curcumae Rhizoma were undetected in rat blood probably because Curcumae Rhizoma contains mainly volatile components, and the next plan was to detect the Curcumae Rhizoma components in blood of rats using GC-MS (Li, W. et al., 2018).

HLP is a chronic systemic metabolic syndrome that becomes a risk factor for atherosclerosis and cardiovascular disease (Barness et al., 2007; Ng et al., 2014). Therefore, we generated the HFD-based rat model to investigate the dynamic changes of BSTZC in rats, compared with the healthy rats. The comparison of the two groups can give a theoretical foundation for clinical administration. The results of pharmacokinetics revealed that the T_{max} of all the components was within 3 h, which indicated that all the analytes were rapidly absorbed into the blood. Relative to rats in the control groups, those in the model group exhibited significantly increased T_{max}, C_{max}, and AUC values for all analytes, which might be attributed to physiological variables. In the pathological condition of HLP, gastrointestinal motility was impaired, leading to prolonged retention time, delayed absorption, and decreased excretion rates (Tong et al., 2012). Based on these cases, the total accumulation in the plasma, especially the flavonoids (Ying et al., 2020), was increased, including the IVT, IVL, and KPF-3-G. The T_{max} of kaempferol was approximately 2 h, whereas KPF-3-G reached the maximum concentration faster, and its $t_{1/2}$ was prolonged, as the metabolite was kaempferol. KPF-3-G can reduce lipid accumulation and the level of reactive oxygen species through the Nrf2/Keap1 pathway (Deng et al., 2021). As the concentration–time profiles show, there was double-peak of KPF-3-G in the control group. The appearance of the double-peak phenomenon may be related to enterohepatic circulation, dual-site absorption, or intestinal efflux (Song et al., 2023). Similarly, we can observe the double-peak phenomenon of *p*N. The pharmacokinetic parameters of PN, as in prior studies, were significantly different in the single drug (Xu et al., 2016), such as T_{max} value 10.00 ± 1.73 min and $t_{1/2}$ value 142.98 ± 30.11 min. Inconsistent with results from prior studies (Luo et al., 2014), the value of T_{max} and $t_{1/2}$ were increased, as well as the residence time in rats was prolonged. PN was orally administrated to HLP model rats, which can activate AMPK, and downregulate the liver fat synthesis pathway, with the appearance of the rising level of APN in the serum, resulting in lipid metabolism acceleration and then having an effect on NAFLD treatment (Ma, Z. et al., 2017). Due to the interaction between components in TCM, the prolonged MRT promoted a therapeutic effect. Moreover, NCS can play an anti-diabetic role by regulating the key target proteins of PTGS2 and TNF, acting on metabolic pathways, and reducing the release of macrophage inflammatory factors to alleviate inflammation (Liu et al., 2023). APG can improve atherosclerosis by stimulating apoptosis of macrophages and downregulating the secretion of cytokines (TNF-α, IL-1β, and IL-6) (Clayton et al., 2021). The blood concentration of NCS and APG increased first and then decreased after oral administration.

To further understand the effectiveness of these nine components of BSTZC in the treatment of HLP, network analysis was an approach to predict the therapeutic pathways. The PPI network showed that common targets including PTGS2, TNF, and ABCB1 were probably the relevant targets for BSTZC in HLP treatment. It was found in these enriched pathways that the common signaling pathways were the HIF-1 signaling pathway, VEGF signaling pathway, and PI3K-Akt signaling pathway associated with the treatment of HLP. HIF-1 is an important transcription factor for hypoxic response, composed of HIF-1α and HIF-1β subtypes. HIF-1 signaling pathway and the protein expression were mediators, resulting in increased vascular endothelial permeability (Thomas et al., 2022). The release of inflammatory mediators leads to increased vascular permeability and angiogenesis in adipose tissue (Manalo et al., 2005). The PI3K-Akt signaling pathway mainly participates in regulating many biological processes, such as cell proliferation, differentiation, migration, and apoptosis (Vivanco and Sawyers, 2002). The risk of atherosclerosis, hypertension, and other cardiovascular diseases was efficiently decreased by suppressing the PI3K-Akt signaling pathway (Shao et al., 2018). NO is a vasodilator secreted by vascular endothelium, which can regulate vascular endothelial function and promote vascular endothelial regeneration and platelet adhesion. The phosphorylation of eNOS was promoted with stimulated Akt so that NO was generated to protect vascular endothelial from dysfunction (Lee et al., 2021). In addition, inhibition of the PI3K/Akt pathway can significantly downregulate LPL expression in macrophages, reduce lipid uptake by macrophages, reduce intracellular lipid accumulation, and delay cell foam formation (Sato et al., 2018). *In vivo* experiments showed that the lipid-lowering effect of BSTZC was obvious, and compared with the model group, BSTZC could effectively reduce the levels of TC, TG, LDL-C, ALT, and AST in mice serum, suggesting that it could alleviate the abnormalities of lipid metabolism and liver injury. Meanwhile, the lipid-lowering effects of APG, KPF, IVT, and PN groups were more obvious in each component group, suggesting that they may serve as the pharmacodynamic substance basis of BSTZC. Interestingly, the lipid-lowering effect of BSTZC was better than that of the single component, which fully reflected the multi-component and multi-target characteristics of BSTZC in the treatment of hyperlipidemia (Zhang et al., 2024). In addition, our study found that BSTZC inhibited the mRNA levels of PI3KCA, AKT, TNF, PTGS2, and TNF, suggesting that BSTZC may alleviate HLP by inhibiting the PI3K/AKT signaling pathway, further validating the results of the network analysis.

In conclusion, in this study, we mainly investigate the active components of BSTZC in treating HLP and verified the lipid-lowering effects of the active components through *in vivo* experiments, which provided the basis for the study of the pharmacological material basis and quality control system of BSTZC. In addition, BSTZC significantly alleviated lipid metabolism disorders and liver injury in the triton WR-1339-induced HLP mice model, and its mechanism may involve the regulation of the PI3K/AKT signaling pathway in the liver to exert lipid-lowering efficacy. In addition, because most preclinical studies have been conducted in male rodents, there are limitations in the

present study in that only male animals were selected first, taking into account the issues of sex hormone effects, stability of experimental results, and efficiency of model building (Beery and Zucker, 2011; Cahill, 2006). Sex differences in metabolic traits such as obesity, diabetes, and cardiovascular disease have been well described in mice, humans, and other species, with females typically exhibiting more beneficial metabolic traits (Chella Krishnan et al., 2018). As the prevalence of lipid metabolism disorders is closely related to age and sex, female mice have relatively high estrogen levels, which has a protective effect and reduces the accumulation of lipids and the development of atherosclerosis. The postmenopausal condition is associated with a high prevalence of many features of the metabolic syndrome, including obesity, steatosis, and oxidative damage to the liver (Hermoso et al., 2016; Yu et al., 2021). In addition, male rats are more likely to develop obesity and metabolic diseases induced by a high-fat diet, and male rats are more sensitive to the catabolic effects of insulin, whereas female rats are more sensitive to the catabolic effects of anorexic leptin, which is determined by the central effect of estrogens. Moreover, female rats showed later diet-induced weight gain and fewer metabolic complications than male rats (Maric et al., 2022). Therefore, taking into account the sex difference, this study will also be conducted in the future to study the sex difference accordingly, and the lipid-lowering effect of BSTZC through this signaling pathway will be confirmed *in vivo* experiments using agonists of the PI3K/AKT signaling pathway.

5 Conclusion

In this work, an effective strategy was developed by integrating serum pharmacological chemistry, pharmacokinetics, network analysis, and experimental validation to explore the active components of BSTZC in the treatment of HLP. In this study, we explored the dynamics of nine migratory components as PK markers by comparing them with normal rats and HLP model rats. In addition, we found that BSTZC and its active components could ameliorate lipid abnormalities and liver injury, and BSTZC could alleviate HLP by modulating the PI3K/Akt pathway. In this study, we provide a systematic approach to explore the active components of TCM and provide useful information to guide the clinical application of BSTZC in treating HLP.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The animal study was reviewed and approved by Guangdong Provincial Engineering Technology Institute of TCM (Guangzhou, China). The study was conducted in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the owners for the participation of their animals in this study.

Author contributions

RT: conceptualization, writing–original draft, writing–review and editing, and data curation. GX: conceptualization, funding acquisition, writing–original draft, and writing–review and editing. YcL: data curation, methodology, and writing–original draft. DJ: methodology, visualization, and writing–original draft. ZZ: data curation and writing–original draft. CJ: investigation and writing–original draft. DL: visualization and writing–original draft. YxL: software, validation, and writing–original draft. JJ: validation and writing–original draft. SL: software and writing–original draft. XB: funding acquisition, supervision, writing–original draft, and writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Basic and Applied Basic Research Foundation of Guangdong Province (Grant No. 2024A1515012809), Major Science and Technology Project on Traditional Chinese Medicine in Guangzhou (Grant No. 2025QN003), and Scientific Research Project of Traditional Chinese Medicine Bureau of Guangdong Province (Grant No. 20251034).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1444967/full#supplementary-material

References

Bahiru, E., Hsiao, R., Phillipson, D., and Watson, K. E. (2021). Mechanisms and treatment of dyslipidemia in diabetes. *Curr. Cardiol. Rep.* 23 (4), 26. doi:10.1007/s11886-021-01455-w

Barness, L. A., Opitz, J. M., and Gilbert-Barness, E. (2007). Obesity: genetic, molecular, and environmental aspects. *Am. J. Med. Genet. A* 143A (24), 3016–3034. doi:10.1002/ajmg.a.32035

Beery, A. K., and Zucker, I. (2011). Sex bias in neuroscience and biomedical research. *Neurosci. and Biobehav. Rev.* 35 (3), 565–572. doi:10.1016/j.neubiorev.2010.07.002

Cahill, L. (2006). Why sex matters for neuroscience. *Nat. Rev. Neurosci.* 7 (6), 477–484. doi:10.1038/nrn1909

Chella Krishnan, K., Mehrabian, M., and Lusis, A. J. (2018). Sex differences in metabolism and cardiometabolic disorders. *Curr. Opin. Lipidol.* 29 (5), 404–410. doi:10.1097/mol.0000000000000536

Chen, Y., Xie, S., Chen, S., and Zeng, S. (2008). Glucuronidation of flavonoids by recombinant UGT1A3 and UGT1A9. *Biochem. Pharmacol.* 76 (3), 416–425. doi:10.1016/j.bcp.2008.05.007

Chen, Y. X., Li, R. Y., Huang, X. J., Zeng, X. H., and N., G. H. (2017). Study on the effect of bushao lipid regulating capsule on lipid metabolism and its related targets in hyperlipidemic rats. *Clin. Med.Eng.* 24 (11), 1525–1527. doi:10.3969/j.issn.1674-4659.2017.11.1525

Clayton, Z. S., Hutton, D. A., Brunt, V. E., VanDongen, N. S., Ziemba, B. P., Casso, A. G., et al. (2021). Apigenin restores endothelial function by ameliorating oxidative stress, reverses aortic stiffening, and mitigates vascular inflammation with aging. *Am. J. Physiol. Heart Circ. Physiol.* 321 (1), H185–H196. doi:10.1152/ajpheart.00118.2021

Dabeek, W. M., and Marra, M. V. (2019). Dietary quercetin and kaempferol: bioavailability and potential cardiovascular-related bioactivity in humans. *Nutrients* 11 (10), 2288. doi:10.3390/nu11102288

Deng, Y., Ma, J., Weng, X., Wang, Y., Li, M., Yang, T., et al. (2021). Kaempferol-3-O-Glucuronide ameliorates non-alcoholic steatohepatitis in high-cholesterol-diet-induced larval zebrafish and HepG2 cell models via regulating oxidation stress. *Life (Basel)* 11 (5), 445. doi:10.3390/life11050445

Gan, H. N., Zeng, X. H., and X., C. Y. (2018). Anti-hyperlipidemia effect of bushao Tiaozhi capsule: an experimental study. *Chin. Manip. Rehabil. Med.* 9 (6), 92–94. doi:10.19787/j.issn.1008-1879.2018.06.044

Hermoso, D. A. M., Shimada, L. B. C., Gilglioni, E. H., Constantin, J., Mito, M. S., Hermoso, A. P. M., et al. (2016). Melatonin protects female rats against steatosis and liver oxidative stress induced by oestrogen deficiency. *Life Sci.* 157, 178–186. doi:10.1016/j.lfs.2016.05.044

Huang, R., Zhang, Y., Shen, S., Zhi, Z., Cheng, H., Chen, S., et al. (2020). Antioxidant and pancreatic lipase inhibitory effects of flavonoids from different citrus peel extracts: an *in vitro* study. *Food Chem.* 326, 126785. doi:10.1016/j.foodchem.2020.126785

Lee, S. K., Kim, M. J., Son, S. H., Kim, K. R., Park, K. K., and Chung, W. Y. (2021). Xanthorrhizol suppresses vascular endothelial growth factor-induced angiogenesis by modulating akt/eNOS signaling and the NF-[Formula: see text]B-dependent expression of cell adhesion molecules. *Am. J. Chin. Med.* 49 (3), 737–751. doi:10.1142/S0192415X21500348

Li, W., Hong, B., Li, Z., Li, Q., and Bi, K. (2018). GC-MS method for determination and pharmacokinetic study of seven volatile constituents in rat plasma after oral administration of the essential oil of Rhizoma Curcumae. *J. Pharm. Biomed. Anal.* 149, 577–585. doi:10.1016/j.jpba.2017.11.058

Li, Y. C., Qiao, J. Y., Wang, B. Y., Bai, M., Shen, J. D., and Cheng, Y. X. (2018). Paeoniflorin ameliorates fructose-induced insulin resistance and hepatic steatosis by activating LKB1/AMPK and AKT pathways. *Nutrients* 10 (8), 1024. doi:10.3390/nu10081024

Li, Y. Z., Wang, Y. L., Tai, W., Yang, L., Chen, Y., Chen, C. Q., et al. (2015). Challenges and solutions of pharmacokinetics for efficacy and safety of traditional Chinese medicine. *Curr. Drug Metab.* 16 (9), 765–776. doi:10.2174/1389200216091512011142223

Liu, T., Cao, L., Zhang, T., and Fu, H. (2023). Molecular docking studies, anti-Alzheimer's disease, antidiabetic, and anti-acute myeloid leukemia potentials of narcissoside. *Arch. Physiol. Biochem.* 129 (2), 405–415. doi:10.1080/13813455.2020.1828483

Luo, N., Li, Z., Qian, D., Qian, Y., Guo, J., Duan, J. A., et al. (2014). Simultaneous determination of bioactive components of Radix Angelicae Sinensis-Radix Paeoniae Alba herb couple in rat plasma and tissues by UPLC-MS/MS and its application to pharmacokinetics and tissue distribution. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 963, 29–39. doi:10.1016/j.jchromb.2014.05.036

Ma, F. X., Xue, P. F., Wang, Y. Y., Wang, Y. N., and Xue, S. Y. (2017). Research progress of serum pharmacochemistry of traditional Chinese medicine. *Chin. J. Chin. Mater Med.* 42 (7), 1265–1270. doi:10.19540/j.cnki.cjcmm.20170224.010

Ma, Z., Chu, L., Liu, H., Wang, W., Li, J., Yao, W., et al. (2017). Beneficial effects of paeoniflorin on non-alcoholic fatty liver disease induced by high-fat diet in rats. *Sci. Rep.* 7, 44819. doi:10.1038/srep44819

Manalo, D. J., Rowan, A., Lavoie, T., Natarajan, L., Kelly, B. D., Ye, S. Q., et al. (2005). Transcriptional regulation of vascular endothelial cell responses to hypoxia by HIF-1. *Blood* 105 (2), 659–669. doi:10.1182/blood-2004-07-2958

Maric, I., Krieger, J.-P., van der Velden, P., Börchers, S., Asker, M., Vujicic, M., et al. (2022). Sex and species differences in the development of diet-induced obesity and metabolic disturbances in rodents. *Front. Nutr.* 9, 828522. doi:10.3389/fnut.2022.828522

Ng, R., Wu, H., Xiao, H., Chen, X., Willenbring, H., Steer, C. J., et al. (2014). Inhibition of microRNA-24 expression in liver prevents hepatic lipid accumulation and hyperlipidemia. *Hepatology* 60 (2), 554–564. doi:10.1002/hep.27153

Ochiai, A., Othman, M. B., and Sakamoto, K. (2021). Kaempferol ameliorates symptoms of metabolic syndrome by improving blood lipid profile and glucose tolerance. *Biosci. Biotechnol. Biochem.* 85 (10), 2169–2176. doi:10.1093/bbb/zbab132

Pirillo, A., Casula, M., Olmastroni, E., Norata, G. D., and Catapano, A. L. (2021). Global epidemiology of dyslipidaemias. *Nat. Rev. Cardiol.* 18 (10), 689–700. doi:10.1038/s41569-021-00541-4

Ren, B., Qin, W., Wu, F., Wang, S., Pan, C., Wang, L., et al. (2016). Apigenin and naringenin regulate glucose and lipid metabolism, and ameliorate vascular dysfunction in type 2 diabetic rats. *Eur. J. Pharmacol.* 773, 13–23. doi:10.1016/j.ejphar.2016.01.002

Sato, K., Shirai, R., Yamaguchi, M., Yamashita, T., Shibata, K., Okano, T., et al. (2018). Anti-atherogenic effects of vaspin on human aortic smooth muscle cell/macrophage responses and hyperlipidemic mouse plaque phenotype. *Int. J. Mol. Sci.* 19 (6), 1732. doi:10.3390/ijms19061732

Shao, D., Lian, Z., Di, Y., Zhang, L., Rajoka, M. S. R., Zhang, Y., et al. (2018). Dietary compounds have potential in controlling atherosclerosis by modulating macrophage cholesterol metabolism and inflammation via miRNA. *NPJ Sci. Food* 2, 13. doi:10.1038/s41538-018-0022-8

Song, J., Liao, W., Deng, X., Zhang, D., Lin, J., Xu, R., et al. (2023). Analysis of the pharmacodynamic difference between Xiaojin Pills taken with Chinese Baijiu and water based on serum pharmacochemistry and pharmacokinetics. *J. Ethnopharmacol.* 300, 115723. doi:10.1016/j.jep.2022.115723

Tang, W., and Lu, A. Y. H. (2009). Drug metabolism and pharmacokinetics in support of drug design. *Curr. Pharm. Des.* 15 (19), 2170–2183. doi:10.2174/138161209788682451

Thomas, C., Leleu, D., and Masson, D. (2022). Cholesterol and HIF-1α: dangerous liaisons in atherosclerosis. *Front. Immunol.* 13, 868958. doi:10.3389/fimmu.2022.868958

Tong, L., Zhou, D., Gao, J., Zhu, Y., Sun, H., and Bi, K. (2012). Simultaneous determination of naringin, hesperidin, neohesperidin, naringenin and hesperetin of Fractus aurantii extract in rat plasma by liquid chromatography tandem mass spectrometry. *J. Pharm. Biomed. Anal.* 58, 58–64. doi:10.1016/j.jpba.2011.05.001

Vekic, J., Zeljkovic, A., Stefanovic, A., Jelic-Ivanovic, Z., and Spasojevic-Kalimanovska, V. (2019). Obesity and dyslipidemia. *Metabolism* 92, 71–81. doi:10.1016/j.metabol.2018.11.005

Vivanco, I., and Sawyers, C. L. (2002). The phosphatidylinositol 3-Kinase AKT pathway in human cancer. *Nat. Rev. Cancer* 2 (7), 489–501. doi:10.1038/nrc839

Wang, X., Zhao, X., Gu, L., Lv, C., He, B., Liu, Z., et al. (2014). Simultaneous determination of five free and total flavonoids in rat plasma by ultra HPLC-MS/MS and its application to a comparative pharmacokinetic study in normal and hyperlipidemic rats. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 953-954, 1–10. doi:10.1016/j.jchromb.2014.01.042

Xiao, G., Xu, A., Jiang, J., Chen, Z., Li, Y., Li, S., et al. (2023). Metabolomics analysis delineates the therapeutic effects of Yinlan Tiaozhi capsule on triton WR-1339 -induced hyperlipidemia in mice. *Front. Pharmacol.* 14, 1252146. doi:10.3389/fphar.2023.1252146

Xiao, G., Zeng, Z., Jiang, J., Xu, A., Li, S., Li, Y., et al. (2022). Network pharmacology analysis and experimental validation to explore the mechanism of Bushao Tiaozhi capsule (BSTZC) on hyperlipidemia. *Sci. Rep.* 12 (1), 6992. doi:10.1038/s41598-022-11139-2

Xiao, G. L., Jiang, J. Y., Xu, A. L., Li, Y. X., and Bi, X. L. (2020). Analysis of chemical constituents in bushao Tiaozhi capsules by UPLC-Q-TOF-MS. *Chin. J. Exp. Trad. Med. Form.* 26 (14), 190–199. doi:10.13422/j.cnki.syfjx.20201613

Xu, W., Zhao, Y., Qin, Y., Ge, B., Gong, W., Wu, Y., et al. (2016). Enhancement of exposure and reduction of elimination for paeoniflorin or albiflorin via Co-administration with total peony glucosides and hypoxic pharmacokinetics comparison. *Molecules* 21 (7), 874. doi:10.3390/molecules21070874

Ying, Y., Wan, H., Zhao, X., Yu, L., He, Y., and Jin, W. (2020). Pharmacokinetic-pharmacodynamic modeling of the antioxidant activity of quzhou fructus aurantii decoction in a rat model of hyperlipidemia. *Biomed. Pharmacother.* 131, 110646. doi:10.1016/j.biopha.2020.110646

Yu, Y.-m., Zhou, B.-h., Yang, Y.-l., Guo, C.-X., Zhao, J., and Wang, H.-w. (2021). Estrogen deficiency aggravates fluoride-induced liver damage and lipid metabolism disorder in rats. *Biol. trace Elem. Res.* 200 (6), 2767–2776. doi:10.1007/s12011-021-02857-1

Zhang, W. D., Wang, X. J., Zhou, S. Y., Gu, Y., Wang, R., Zhang, T. L., et al. (2010). Determination of free and glucuronidated kaempferol in rat plasma by LC-MS/MS: application to pharmacokinetic study. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 878 (23), 2137–2140. doi:10.1016/j.jchromb.2010.06.002

Zhang, Y., Guo, Z., Wang, J., Yue, Y., Yang, Y., Wen, Y., et al. (2024). Qinlian hongqu decoction ameliorates hyperlipidemia via the IRE1-α/IKKB-β/NF-κb signaling pathway: network pharmacology and experimental validation. *J. Ethnopharmacol.* 318 (Pt A), 116856. doi:10.1016/j.jep.2023.116856

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 28 March 2025
DOI 10.3389/fphar.2025.1511486

OPEN ACCESS

EDITED BY
Chen Huei Leo,
National University of Singapore, Singapore

REVIEWED BY
Yuxiang Fei,
China Pharmaceutical University, China
Jinbao Zhang,
Dalian Medical University, China

*CORRESPONDENCE
Hongxu Liu,
lhx_@263.net
Xiang Li,
lixiang11897@bjzhongyi.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 15 October 2024
ACCEPTED 10 March 2025
PUBLISHED 28 March 2025

CITATION
Zhou H, Chen J, Liu H, Li X, Zong H, Zhang S, Shi Y and Li Y (2025) Traditional Chinese medicine injections with Tonifying Qi, equivalent effect of regulating energy metabolism, for acute myocardial infarction: a systematic review and meta-analysis of randomized clinical trials.
Front. Pharmacol. 16:1511486.
doi: 10.3389/fphar.2025.1511486

Traditional Chinese medicine injections with Tonifying Qi, equivalent effect of regulating energy metabolism, for acute myocardial infarction: a systematic review and meta-analysis of randomized clinical trials

Huiwen Zhou[1†], Jiaping Chen[2†], Hongxu Liu[1*], Xiang Li[1,3*], Huiqi Zong[1], Shuwen Zhang[1], Yuxin Shi[1] and Yunze Li[1]

[1]Department of Cardiology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China, [2]Department of Cardiology, Linping Branch of Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, Zhejiang, China, [3]Department of Cardiology, Lhasa People's Hospital, Lhasa, China

Background: Traditional Chinese medicine injections for Tonifying Qi (TCMi-TQs), which exhibits comparable effect of regulating energy metabolism, is commonly used as an adjuvant treatment for acute myocardial infarction (AMI) in China.

Objective: A systematic review and meta-analysis was conducted to contrast the effectiveness and safety of four TCMi-TQs in AMI.

Methods: Eight Databases were thoroughly searched before 31 July 2024, for randomized controlled trials (RCTs) focusing on the application of TCMi-TQs combined with conventional treatments (CT) to treat AMI. The primary outcomes were in-hospital mortality and long-term mortality. Secondary outcomes included malignant arrhythmia, left ventricular ejection fraction (LVEF), and adverse events. Stata17.0 and RevMan 5.4.1 software were employed for meta-analysis. The quality of evidence was evaluated using the GRADE approach.

Results: A total of 113 RCTs involving 10,779 patients were included in the analysis, none of which described in-dependent testing of the purity or potency of the TCMi-TQ product used. 51/113 reported random sequence generation. All RCTs lack adequate description of allocation concealment. 112/113 failed to assess blinding. The meta-analysis results demonstrated that the combined application of TCMi-TQ + CT, compared with CT, significantly reduced in-hospital mortality in AMI patients [RR = 0.58, 95% CI (0.51, 0.67), $P < 0.05$], decreased the incidence of malignant arrhythmia [RR = 0.51, 95%CI(0.42, 0.63), $P < 0.05$], increased LVEF [MD = 6.52, 95%CI(5.54, 7.50), $P < 0.05$], and decreased the incidence of adverse events [RR = 0.70, 95%CI(0.60, 0.81), $P < 0.05$]. The GRADE evidence quality classification indicated that the evidence for in-hospital mortality, malignant arrhythmia, and adverse events was of moderate quality, while the evidence for LVEF was of low quality.

Conclusion: TCMi-TQ demonstrates additional clinical value in reducing mortality, the risk of malignant arrhythmia, and adverse events in patients with AMI. However, further validation of these findings is warranted through high-quality clinical trials due to methodological weaknesses in randomization, blinding, allocation concealment, and insufficient assessment of the purity/potency of botanical drugs and the quantity of active metabolites.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/view/CRD42024573818, identifier PROSPERO (CRD42024573818).

KEYWORDS

Chinese medicine injections, acute myocardial infarction, meta-analysis, traditional Chinese medicine, energy metabolism

1 Introduction

Acute myocardial infarction (AMI) is a significant global health issue characterized by high morbidity and mortality rates, imposing substantial economic and medical burdens (Mensah et al., 2023). AMI is usually caused by coronary artery disease, and research has found that AMI can be associated with cerebrovascular diseases, making clinical diagnosis and treatment more difficult due to comorbidities of the heart and brain (Suzuki et al., 2023). Over the past decade, the management of AMI in China has made some progress. However, the *China Cardiovascular Health and Disease Report 2023 Summary* revealed an increase in AMI mortality in China from 2002 to 2021 (National Center Cardiovascular Diseases, 2024). With the active promotion of secondary prevention measures for coronary heart disease and early reperfusion therapy for AMI, the mortality rate of AMI patients has decreased (Roger et al., 2010). There are still several unresolved issues after reperfusion, including decreased myocardial contractility, ventricular arrhythmia, and no-reflow phenomenon (Thiele et al., 2017). These complications have a significant impact on the prognosis of patients (Heusch and Gersh, 2017). Therefore, exploring additional effective treatment methods remains essential.

Traditional Chinese medicine (TCM) can play a unique role in improving the clinical prognosis of AMI. Research has found that for STEMI patients, on the basis of standardized biomedicine treatment (including reperfusion therapy and optimal drug therapy), Tongxinluo can significantly improve clinical prognosis, and reduce the risk of major adverse cardiovascular and cerebrovascular events at 30°days and 1°year (Yang et al., 2023). Consequently, there is a growing interest among Chinese medical professionals in exploring therapeutic approaches from TCM to help reduce AMI mortality. This research direction aligns with the principles exemplified by Professor Tu Youyou, the Nobel Prize laureate who successfully extracted artemisinin from Artemisia annua, thereby revolutionizing malaria treatment.

One such intervention gaining attention is the use of traditional Chinese medicine injections for tonifying qi (TCMi-TQs), which possess comparable effects of regulating energy metabolism (Li et al., 2023; Wang et al., 2022; Wang A. et al., 2024; Yang et al., 2022). TCMi-TQs have shown promise in reducing mortality and the incidence of re-infarction among AMI patients (Jia et al., 2023; Lu et al., 2018). To obtain high-quality evidence regarding the safety and efficacy of TCMi-TQs in AMI, this study initiated a search for TCMi-TQs used in the treatment of AMI. The search yielded four TCMi-TQs: Shengmai injection (SGMI), Shenmai injection (SMI), Shenfu injection (SFI), and Astragalus injection (AI). Research has demonstrated that these four TCMi-TQs and their main active metabolites play a significant role in modulating myocardial energy metabolism in patients with myocardial ischemia. SGMI increases the number of myocardial cell mitochondria and scavenges oxygen-free radicals (Lu et al., 2005). SMI enhances myocardial microcirculation parameters (Yang and Wang, 2021), while SFI mitigates mitochondrial oxidative stress (Lu and Xiang, 2023). The primary active compound of AI, astragaloside IV, regulates myocardial cell oxidative stress and enhances mitochondrial function (Guan et al., 2023). Detailed information on these four TCMi-TQs is provided in Supplementary Tables S1–S4. The objective of this study is to systematically collect and analyze the data from these four randomized controlled trials (RCTs) investigating TCMi-TQs in the treatment of AMI, with the aim of evaluating its efficacy and safety for AMI patients presenting with relevant indications based on the current evidence. This study has the potential to bridge the gap between TCMi-TQs and modern medicine for AMI treatment and open up avenues for integrative care models for AMI patients.

2 Methods

The systematic review has been registered in the PROSPERO platform for prospective registration with the registration number CRD42024573818. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2015; Page et al., 2021) were employed to conduct our network meta-analysis, as seen in Supplementary Material. To ensure accurate reporting of four TCMIs in this analysis, we adhered to the guidelines established in the consensus statement on the Phytochemical Characterization of Medicinal Plant extract (ConPhyMP) (Supplementary Tables S1–S4) (Heinrich et al., 2022).

2.1 Inclusion and exclusion criteria

The inclusion criteria for this review are as follows:

(1) Study Type: RCTs.
(2) Study Subjects: Patients who meet the diagnostic criteria for AMI.
(3) Type of Intervention: The observation group received any one of the traditional Chinese medicine injections with TCMi-TQ

interventions, including SGMI, SMI, SFI, or AI, in addition to conventional treatment. The control group received conventional treatment (CT), which included general treatment (monitoring vital signs, symptom relief, *etc.*), reperfusion therapy (Percutaneous Coronary Intervention (PCI), thrombolysis, and coronary artery bypass surgery), and pharmacotherapy (antiplatelet agents, anticoagulants, lipid-lowering drugs, *etc.*), while excluding commercial Chinese polyherbal preparation (CCPP), acupuncture, and other traditional medical treatments. The sole difference between the two groups was the administration of TCMi-TQ.

(4) Outcome Measures: The primary outcome measures were in-hospital mortality and long-term mortality. Long-term mortality was defined as mortality occurring at least 1 year after the onset of AMI. Secondary outcomes included the incidence of malignant arrhythmias affecting hemodynamics (such as ventricular fibrillation, polymorphic ventricular tachycardia, and second or third-degree atrioventricular block with hemodynamic disturbance), changes in left ventricular ejection fraction (LVEF) before and after treatment, and adverse safety events (such as dizziness, nausea, and allergic reactions).

The exclusion criteria for this review are as follows:

(1) No mention of diagnostic criteria in the literature or unclear diagnostic criteria.
(2) Control settings of clinical trials that were unreasonable or did not meet the inclusion criteria for this study, such as the inclusion of other CCPP in the experimental group, were excluded.
(3) Duplicate published literature.
(4) Studies that did not include the required effect measures.

2.2 Literature resources

We conducted a comprehensive literature search using multiple databases, including PubMed, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, and Web of Science. Additionally, we searched the China Biological Literature Database, China National Knowledge Infrastructure, VIP database, and Wanfang Data Knowledge Service Platform. The search covered the period from the establishment of each database until July 2024. The search strategy is provided in Supplementary Table S5. In addition to electronic database searches, we also examined the reference lists of relevant articles and manually searched printed books and magazines in the field to ensure a comprehensive literature review. To identify relevant clinical trials, we also searched for registered trials on ClinicalTrials.gov to identify any unpublished articles that met our inclusion criteria.

2.3 Literature screening, information extraction and quality assessment

Two reviewers (YX Shi and YZ Li) independently performed each step according to established search rules. The screening process involved reviewing the title and abstract of each retrieved article and applying predefined inclusion and exclusion criteria. Irrelevant articles were excluded, and no discussion took place until the final results were summarized.

After retrieving the articles, the two reviewers (YX Shi and YZ Li) independently processed the data, identified and removed duplicate articles, retained the most recent publications with the most complete data, excluded articles that did not meet the inclusion or exclusion criteria, and documented the reasons for exclusion. The extracted data included the article title, all authors, year of publication, journal, sample size, participant characteristics, treatment interventions, blinding methods, randomization procedures, outcome measures, adverse events, and other relevant information, which were summarized in a table. In case of any disagreements, a third reviewer (HQ Zong) made the final judgment and resolved the discrepancies.

Risk of bias was assessed by two reviewers (YX Shi and YZ Li) independently, using the Cochrane risk of bias tool (RoB 2.0 Tool) (Sterne et al., 2019). Overall quality of evidence was rated using the Grades of Rec ommendations, Assessment, Development and Evaluation (GRADE) approach (Chen et al., 2018).

Any disagreement between the 2 reviewers (YX Shi and YZ Li) will be resolved by a discussion. Further disagreements will be arbitrated by the third author (HQ Zong).

2.4 Data analysis

RevMan 5.4.1 software was utilized to analyze the extracted clinical research data. Relative risk (RR) analysis was employed for count data, while mean difference (MD) was used for measurement data when the unit of measurement was the same. Standardized mean difference (SMD) was used for measurement data when the unit of measurement differed. All effect sizes were reported with a 95% confidence interval (CI). For continuous outcomes, the change difference was employed for meta-analysis. The mean and standard deviation of the change difference before and after the intervention were calculated using the formula provided in the Cochrane handbook (Higgins et al., 2023).

$$SD_{change} = \sqrt{SD_{pre}^2 + SD_{post}^2 - \left(2 \times Corr \times SD_{pre} \times SD_{post}\right)}$$
$$\text{Corr} = 0.8$$

In this study, the mortality rate, incidence of malignant arrhythmia, and incidence of adverse events were presented using RR. LVEF was presented using the mean and standard deviation of the difference before and after treatment. Heterogeneity among the included studies was assessed using the Q test. A significance level of $P \leq 0.10$ and an I^2 value ≥50% were used as criteria for significant heterogeneity. If the P value was greater than 0.1 and the I^2 value was less than 50%, a fixed-effect model was used for statistical analysis. If the P value was less than or equal to 0.1 and the I^2 value was greater than or equal to 50%, a random-effects model was applied based on sensitivity analysis (Deeks et al., 2023). Statistical significance was defined as $P < 0.05$.

In cases where heterogeneity ($I^2 > 50\%$) was observed among the studies, subgroup analysis and sensitivity analysis were conducted to explore the sources of heterogeneity and verify the stability of the meta-analysis results. Funnel plots were generated using RevMan 5.4.1 software, and Egger's test was performed using

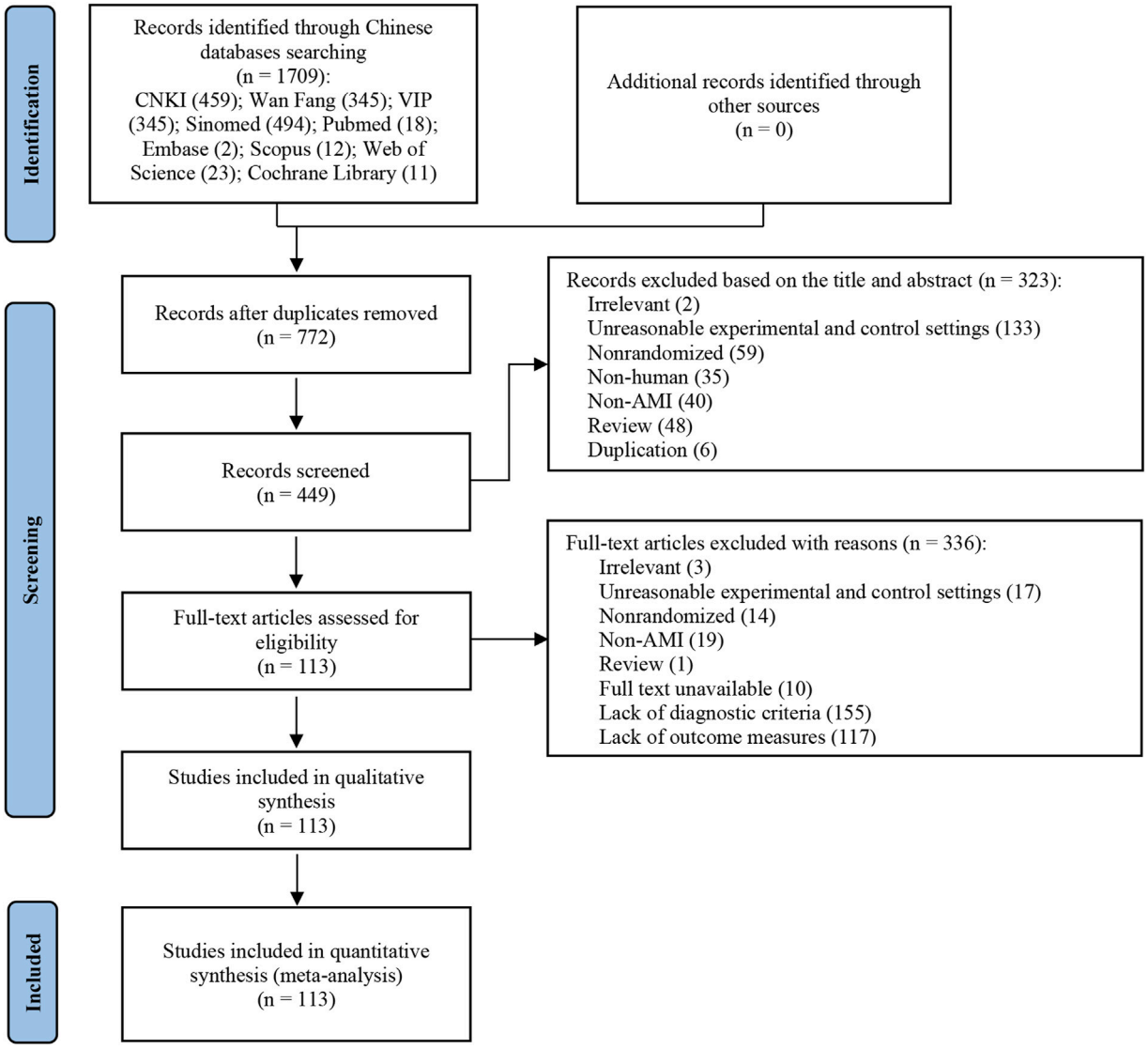


FIGURE 1
Flow chart of the study selection. The initial review yielded 1709 articles, leaving 772 articles after removing duplicates. After selection based on title or abstract, 449 articles were screened for full text review. Of these, 3 articles were irrelevant, 17 articles had unreasonable experimental and control settings, 14 articles were nonrandomized, 19 articles were non-AMI, an article was review, 10 articles' full text were unavailable, 155 articles were lack of diagnostic criteria, 117 articles were lack of outcome measures. Finally, 113 full-text articles were included.

Stata 17.0 software for studies with 10 or more articles to assess potential publication bias. If the *P* value of Egger's test was less than 0.05, it indicated the presence of publication bias among the studies (Egger et al., 1997). For studies exhibiting publication bias, the trim-and-fill method was employed to adjust the results, assuming that missing studies likely occupied symmetrical positions relative to the existing ones—these being studies potentially withheld due to publication bias, such as those reporting negative results (Shi and Lin, 2019).

The evidence quality of outcome indicators was evaluated using the GRADEpro GDT online tool. The default assumption was that the evidence quality of RCTs was high (Guyatt et al., 2008). The evidence quality of outcome indicators was assessed based on five downgrade factors: risk of bias, inconsistency, indirectness, imprecision, and publication bias (Chen et al., 2018).

3 Results

3.1 Literature screening

The process of study selection and identification is depicted in Figure 1. Initially, a total of 1709 potentially relevant articles were retrieved from electronic databases. After removing 937 duplicates, 772 articles remained for further screening. Following title and abstract screening, 323 records were excluded, leaving 449 records. Subsequently, 336 articles were excluded for the following reasons: irrelevant study (n = 3), unreasonable experimental and control settings (n = 17), Nonrandomized (n = 14), Non-AMI (n = 19), review (n = 1), full-text unavailable (n = 10), lack of diagnosis criteria (n = 155), and lack of outcome measures (n = 117). Finally, 113 full-text articles were included.

TABLE 1 Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Shengmai injection												
Cui and Li (2006)	38/36	42/32	56.5/54.2	ALL AMI	Thrombolytic therapy	SGMI 60 mL ivgtt Qd combined with conventional therapy,②, ⑨	Conventional therapy combined with ②, ⑨	14	NR	(1)	NR	NR
Wang et al. (2019a)	53/53	60/46	59.39 ± 10.25/ 59.43 ± 10.31	STEMI	NR	SGMI 60 mL ivgtt Qd combined with conventional therapy, ③, ④, ⑥, ⑧, ⑤, ⑬	Conventional therapy, ③, ④, ⑥, ⑧, ⑤, ⑬	5	NR	(4)	NR	NR
Lu and Yao (2022)	45/45	44/46	57.74 ± 7.28/ 58.67 ± 7.34	STEMI	NR	SGMI 60 mL ivgtt Qd combined with ⑧	⑧	15	NR	(4)	IVVI IX	NR
Xu (2022)	93/93	107/79	66.56 ± 3.35/ 66.69 ± 3.78	STEMI	PCI	SGMI 60 mL ivgtt Qd combined with ①, ③, ⑥, ⑩, ⑭	①, ③, ⑥, ⑩, ⑭	7	3 M	(4)	VI	NR
Chen (2017)	25/25	23/27	56.6 ± 10.2/ 54.9 ± 10.3	STEMI	PCI	SGMI 60 mL ivgtt Qd combined with ①, ②, ③, ⑩	①, ②, ③, ⑩	7	3 M	(1) (4)	NR	NR
Song (2018)	60/60	80/40	54.1 ± 4.6/ 54.8 ± 4.2	ALL AMI	Thrombolytic therapy	SGMI 40 mL ivgtt Qd combined with ⑧, ⑨	⑧, ⑨	7	NR	(4)	NR	YES
Liang (2006)	30/30	34/26	NR	STEMI	Thrombolytic therapy	SGMI 40 mL ivgtt Qd combined with ①, ②, ⑨	①, ②, ⑨	10	NR	(1)	I	NR
Lu (2011)	34/34	44/24	53.2/54.7	STEMI	Thrombolytic therapy	SGMI 40 mL ivgtt Qd combined with ①, ②, ⑥, ⑧	①, ②, ⑥, ⑨	7 to 14	NR	NR	I	NR
Lu (2009)	45/30	44/31	62 ± 8.5/ 64 ± 8.8	ALL AMI	Thrombolytic therapy	SGMI 40–60 mL ivgtt Qd combined with ①, ②, ⑥, ⑧, ⑭	①, ②, ⑥, ⑨, ⑭	10 to 14	NR	NR	I	NR
Ding and Xu (2006)	15/15	16/14	NR	STEMI	Thrombolytic therapy	SGMI 30 mL ivgtt Q12 h combined with conventional therapy, ⑨	Conventional therapy combined with ⑨	7	NR	(1)	NR	NR
Tang (2019)	51/51	58/44	65.68 ± 3.2/ 65.53 ± 3.14	STEMI	Thrombolytic therapy	SGMI 20–50 mL ivgtt Qd combined with ①, ⑥, ⑧	①, ⑥, ⑧	14	NR	NR	IIX	NR
Wang et al. (2010)	32/30	35/27	58 ± 14.9/ 54.9 ± 15.2	STEMI	PCI	SGMI 10 mL iv before surgery, SGMI 50 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑥, ⑩	①, ②, ③, ④, ⑤, ⑥, ⑩	7	NR	(3) (4)	NR	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Wang (2008)	30/30	44/16	54.0 ± 14.9/ 54.9 ± 15.2	STEMI	PCI	SGMI 10 mL iv before surgery, SGMI 50 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑥, ⑩	①, ②, ③, ④, ⑤, ⑥, ⑩	7	NR	(3)	NR	NR
Yang and Cai (2016)	98/98	101/95	57.03 ± 6.74/ 56.27 ± 40.31	ALL AMI	Thrombolytic therapy	SGMI 20–60 mL ivgtt Qd combined with ①, ②, ⑧, ⑨	②, ⑧, ⑨	7	NR	(1) (4)	IIVII	YES
Shenmai injection												
Wei and Liu (2001)	19/15	20/14	56 ± 2.3/ 56 ± 1.8	STEMI	Thrombolytic therapy	SMI 60 mL ivgtt Qd combined with Conventional therapy, ①, ②, ⑨	Conventional therapy combined with ①, ②, ⑨	14–28	NR	(1) (3)	I	NR
Zheng (2016)	34/34	40/28	64.3 ± 4.6/ 66.5 ± 4.7	ALL AMI	NR	SMI 60 mL ivgtt Qd combined with conventional therapy	Conventional therapy	28	NR	(1)	NR	NR
Wang (2016)	50/50	71/29	60.73 ± 14.92/ 60.25 ± 14.35	ALL AMI	NR	SMI 60 mL ivgtt Qd combined with ①, ④. ⑤. ⑥. ⑧. ⑭	①, ④. ⑤. ⑥. ⑧. ⑭	30	NR	(4)	NR	NR
Guo and Zhang (1999)	243/259	355/ 147	64.27/65.12	ALL AMI	Thrombolytic therapy	SMI 60 mL ivgtt Qd combined with ①, ②, ⑨	①, ②, ⑨	14	NR	(1) (3)	I	NR
Zhang (2011)	42/42	47/37	NR	ALL AMI	Thrombolytic therapy	SMI 60 mL ivgtt Qd combined with ①, ②, ⑨	①, ②, ⑨	7	NR	(1) (3)	NR	NR
Yuan (2009)	38/38	47/29	62.4 ± 12.9/ 62.8 ± 13.8	STEMI	Thrombolytic therapy	SMI 60 mL ivgtt Qd combined with ①, ②, ⑥, ⑨	①, ②, ⑥, ⑨	10	NR	(1) (3)	NR	NR
Yang et al. (2014)	30/30	36/24	57.77 ± 10.7/ 57.93 ± 10.37	AMI	PCI	SMI 5 mL iv before surgery, SMI 30 mL ivgtt Qd combined with ①, ②, ⑥, ⑩	①, ②, ⑥, ⑩	3	30D	NR	I	YES
Zhang et al. (2019)	46/46	43/49	58.46 ± 1.99/ 57.69 ± 2.03	ALL AMI	NR	SMI 50 mL ivgtt Qd combined with conventional therapy	Conventional therapy	15	NR	NR	IVV	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Zhao et al. (2005)	20/20	31/9	49.8 ± 11.8/ 50.1 ± 10.3	STEMI	Thrombolytic therapy	SMI 50 mL ivgtt Qd combined with ②, ⑨	②, ⑨	10	NR	(1)	NR	NR
Luo (2016)	46/46	54/38	58.4 ± 6.9/ 59.2 ± 6.5	STEMI	Thrombolytic therapy	SMI 50 mL ivgtt Qd combined with ①, ②, ⑤, ⑨, ⑮	①, ②, ⑤, ⑨, ⑮	14	NR	(4)	NR	NR
Li et al. (2016)	48/48	62/34	58.72 ± 11.63/ 60.19 ± 11.14	STEMI	PCI	SMI 50 mL ivgtt Qd combined with ①, ②, ④, ⑤, ⑩	①, ②, ④, ⑤, ⑩	7	3 M	(3) (4)	NR	NR
Zhao et al. (2016a)	105/105	120/90	61.8 ± 9.5/ 60.2 ± 10.6	STEMI	Thrombolytic therapy	SMI 50 mL ivgtt Qd combined with ①, ②, ④, ⑤, ⑨	①, ②, ④, ⑤, ⑨	14	1Y	(1) (4)	NR	NR
Guo (2014)	39/39	53/25	58.7 ± 11.7/ 58.7 ± 11.7	STEMI	PCI	SMI 50 mL ivgtt Qd combined with ①, ②, ③, ⑥, ⑩	①, ②, ③, ⑥, ⑩	7	3 M	(1) (4)	NR	NR
Xuan et al. (2015)	23/25	26/22	NR	ALL AMI	PCI	SMI 50 mL ivgtt Qd combined with ①, ②, ③, ⑤, ⑥, ⑩, ⑬	①, ②, ③, ⑤, ⑥, ⑩, ⑬	14	1Y	(2) (4)	NR	NR
Qu (2007)	38/30	46/22	NR	ALL AMI	Thrombolytic therapy	SMI 50 mL ivgtt Qd combined with ①, ②, ③, ⑤, ⑥, ⑨	①, ②, ③, ⑤, ⑥, ⑨	10	NR	(1) (3)	NR	NR
Wang et al. (2017)	46/46	58/34	62.72 ± 12.12/ 61.27 ± 10.84	STEMI	PCI	SMI 50 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑩	①, ②, ③, ④, ⑤, ⑩	7	3 M	(3) (4)	NR	NR
Liu (2016)	50/50	61/39	58.41 ± 12.39/ 57.68 ± 12.03	STEMI	PCI	SMI 50 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑥, ⑩	①, ②, ③, ④, ⑤, ⑥, ⑩	7	6 M	(3) (4)	NR	NR
Yang et al. (2017a)	38/38	46/30	35.4 ± 6.7/ 36.8 ± 5.4	STEMI	Thrombolytic therapy	SMI 50 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑥, ⑨, ⑭, ⑮	①, ②, ③, ④, ⑤, ⑥, ⑨, ⑭, ⑮	14	NR	(4)	NR	NR
Yu et al. (2010)	22/26	28/20	NR	NSTEMI	NR	SMI 50 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑥	①, ②, ③, ④, ⑤, ⑥	14	NR	NR	Ⅳ	NR
Ji et al. (2021)	44/45	56/33		STEMI	PCI		①, ③, ④, ⑩	28	NR	(4)	NR	YES

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
			53.91 ± 6.52/ 54.81 ± 6.79			SMI 50 mL ivgtt five times a week combined with ①, ③, ④, ⑩						
Chen (2021)	46/46	60/32	59.41 ± 7.04/ 58.95 ± 7.84	STEMI	Thrombolytic therapy	SMI 50–100 mL ivgtt Qd combined with conventional therapy, ⑨	Conventional therapy combined with ⑨	14	NR	(3)	NR	NR
Zhou (2024)	44/44	40/48	57.82 ± 5.88/ 57.74 ± 5.95	STEMI	NR	SMI 40 mL ivgtt Qd combined with conventional therapy, ①	Conventional therapy, ①	15	NR	(4)	NR	NR
Liu (2016)	44/44	51/37	NR	STEMI	NR	SMI 40 mL ivgtt Qd combined with conventional therapy	Conventional therapy	15	NR	(1) (3) (4)	NR	NR
Yan et al. (2018)	40/40	45/35	56.8 ± 8.4/ 55.9 ± 9.1	STEMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ②, ⑨	②, ⑨	14	NR	(4)	NR	NR
Zhao and Sun (2021)	52/52	53/51	61.3 ± 9.3/ 60.4 ± 7.7	STEMI	PCI	SMI 40 mL ivgtt Qd combined with ①, ⑩	①, ⑩	14	NR	(4)	NR	NR
Ye (2010)	34/34	41/27	NR	ALL AMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ⑥, ⑨, ⑫, ⑬, ⑭	①, ⑥, ⑨, ⑫, ⑬, ⑭	NR	NR	(1) (3)	NR	NR
Zhou (2017)	75/75	95/55	60.7 ± 6.2/ 60.4 ± 7.3	STEMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ③, ④, ⑤, ⑥, ⑧, ⑨, ⑮	①, ③, ④, ⑤, ⑥, ⑧, ⑨, ⑮	NR	NR	(3) (4)	I	NR
Qi et al. (2015b)	60/60	76/44	64.2 ± 2.3/ 62.4 ± 4.5	STEMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ②, ⑨	①, ②, ⑨	14	NR	(4)	NR	YES
Wu et al. (2022)	37/37	43/31	63.55 ± 4.59/ 63.67 ± 4.33	ALL AMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ②, ⑨	①, ②, ⑨	14	3 M	(4)	NR	NR
Du (2017)	44/44	47/41	59.71 ± 6.29/ 59.64 ± 6.38	STEMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ②, ⑤, ⑥, ⑨	①, ②, ⑨	14	NR	(3) (4)	NR	YES
Qi et al. (2015a)	60/60	67/53	56.4 ± 13.8/ 58.7 ± 14.2	STEMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ②, ④, ⑤, ⑨, ⑮	①, ②, ④, ⑤, ⑨, ⑮	14	NR	(4)	NR	NR
Qi et al. (2015a)	60/60	76/44	60.2 ± 13.8/ 61.5 ± 12.5	STEMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ②, ④, ⑤, ⑧, ⑮	①, ②, ④, ⑤, ⑨, ⑮	14	NR	(1)	NR	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Wu et al. (2016)	60/60	NR	NR	STEMI	Thrombolytic therapy	SMI 40 mL ivgtt Qd combined with ①, ②, ④, ⑤, ⑧, ⑨	①, ②, ④, ⑤, ⑧, ⑨	14	NR	(1) (3)	NR	NR
Wang et al. (2021a)	50/51	54/47	60.42 ± 12.39/ 61.27 ± 11.44	STEMI	NR	SMI 40 mL ivgtt Qd combined with ①	①	15	NR	(4)	IVVI	NR
Wang et al. (2019b)	41/41	49/33	62.14 ± 3.58/ 61.94 ± 3.75	STEMI	Thrombolytic therapy	SMI 40 mL iv, SMI 150 mL ivgtt Qd combined with ①, ②, ⑨, ⑭	①, ②, ⑨, ⑭	14	NR	(4)	NR	NR
Xie (2018)	42/42	44/40	61.54 ± 8.73/ 60.85 ± 8.01	ALL AMI	Thrombolytic therapy	SMI 40 mL iv, SMI 100 mL ivgtt Qd combined with ①, ⑨, ⑭	①, ⑨, ⑭	14	NR	(4)	VI	NR
Zong et al. (2014)	34/34	34/34	59.4 ± 9.2/ 60.5 ± 9.4	STEMI	Thrombolytic therapy	SMI 40 mL iv, SMI 100 mL ivgtt Qd combined with ①, ②, ⑨, ⑭	①, ②, ⑨, ⑭	14	NR	(1)	NR	NR
Wang et al. (2017)	35/35	48/22	58.18/58.31	STEMI	Thrombolytic therapy	SMI 40 mL iv, SMI 100 mL ivgtt Bid combined with conventional therapy, ①, ⑨	Conventional therapy, ①, ⑨	15	NR	(4)	NR	NR
Zou (2014)	31/31	40/22	57.69 ± 12.47/ 56.78 ± 11.63	ALL AMI	Thrombolytic therapy	SMI 40 mL iv for 3min (the first dose) and SMI 100 mL ivgtt (the maintenance dose) Qd combined with ②, ③, ④, ⑤, ⑨, ⑮	②, ③, ④, ⑤, ⑨, ⑮	15	NR	(1)	NR	NR
Liu et al. (2004)	41/94	104/33	NR	ALL AMI	Thrombolytic therapy	SMI 40–60 mL ivgtt Qd combined with ②, ⑨	②, ⑨	10–15	NR	(1) (3)	NR	NR
Yu et al. (2021)	49/49	57/41	59.03 ± 4.38/ 58.96 ± 4.35	STEMI	NR	SMI 3 mg/kg iv, SMI 150 mL ivgtt Qd combined with conventional therapy, ④, ⑤	Conventional therapy, ④, ⑤	14	NR	NR	IVVI	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Huang et al. (2015)	74/74	83/65	NR	ALL AMI	NR	SMI 3 mg/kg iv combined with conventional therapy, ③. If the effect was not satisfied after 30 min, an additional 150 mg iv could be given, followed by 0.5–1 mg/min ivgtt to maintain	Conventional therapy combined with ③	28	6 M	(1)	NR	NR
Han et al. (2003)	21/18	25/14	58/58	STEMI	Thrombolytic therapy	SMI 30 mL ivgtt Qd combined with ①, ②, ⑤, ⑥, ⑨	①, ②, ⑤, ⑥, ⑨	14	NR	(1)	I	NR
Shi and Li (2016)	37/35	44/28	61.16 ± 6.51/ 60.85 ± 6.39	STEMI	NR	SMI 20 mL ivgtt Qd combined with conventional therapy, ⑨	Conventional therapy	14	NR	(4)	IIIIVVI	NR
Zhang (2017)	61/61	81/41	68.25 ± 2.1/ 67.74 ± 2.2	STEMI	Thrombolytic therapy	SMI 20 mL ivgtt once combined with conventional therapy, ⑨	Conventional therapy, ⑨	1	NR	(4)	NR	NR
He et al. (2016)	60/60	65/55	61.34 ± 4.21/ 62.16 ± 4.14	STEMI	PCI	SMI 10 mL was infused intracoronary, SMI 100 mL ivgtt Qd/Bid combined with ①, ②, ⑩	①, ②, ⑩	7–14	6 M	(1) (4)	NR	NR
Bai et al. (2002)	62/60	88/34	64.5/61.55	STEMI	Thrombolytic therapy	SMI 100 mL ivgtt Qd/Bid combined with ①, ②, ④, ⑤, ⑥, ⑨	①, ②, ④, ⑤, ⑥, ⑨	10–14	NR	(1)	NR	NR
Zhan and Cui (2023)	34/34	40/28	57.32 ± 5.57/ 57.23 ± 5.43	STEMI	PCI	SMI 100 mL ivgtt Qd combined with conventional therapy, ①, ⑩	Conventional therapy combined with ①, ⑩	14	NR	(4)	II	NR
Sun (2019)	35/35	43/27	57.21 ± 7.93/ 57.79 ± 8.41	ALL AMI	NR	SMI 100 mL ivgtt Qd combined with conventional therapy	Conventional therapy	14	NR	(4)	VI	NR
Wang et al. (2019c)	32/32	35/29	52.18 ± 7.55/ 52.84 ± 7.63	ALL AMI	NR	SMI 100 mL ivgtt Qd combined with conventional therapy	Conventional therapy	7	NR	(4)	NR	NR
Yan et al. (2018)	49/49	57/41	63.27 ± 12.46/ 63.78 ± 12.32	ALL AMI	Thrombolytic therapy	SMI 100 mL ivgtt Qd combined with ⑨	⑨	15	6 M	(4)	NR	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Long (2007)	32/32	37/27	64.9 ± 3.96/ 63.89 ± 5.81	STEMI	Thrombolytic therapy	SMI 100 mL ivgtt Qd combined with ②, ⑥, ⑨	①, ⑤, ⑥, ⑨, ⑬	14	NR	(4)	IV	NR
Zhang et al. (2018b)	65/65	76/54	62 ± 5/ 63 ± 7	STEMI	Thrombolytic therapy	SMI 100 mL ivgtt Qd combined with ①, ②, ⑧, ⑨	①, ②, ⑧, ⑨	3	30 d	(1) (4)	IIIVII	YES
Shi et al. (2018)	56/56	87/25	61.6 ± 7.2/ 60.5 ± 5	STEMI	Thrombolytic therapy	SMI 100 mL ivgtt Qd combined with ①, ②, ③, ⑨	①, ②, ③, ⑨	5	NR	(4)	IVVIIX	NR
Liu (2012)	20/20	25/15	58.2 ± 5.6/ 57.9 ± 8.2	STEMI	Thrombolytic therapy	SMI 100 mL ivgtt Qd combined with ①, ②, ③, ⑤, ⑧, ⑨	①, ②, ③, ⑤, ⑧, ⑨	14	NR	(1)	NR	NR
Xu (2018)	34/35	39/30	62.51 ± 12.37/ 62.43 ± 12.85	ALL AMI	PCI	SMI 100 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑩	①, ②, ③, ④, ⑤, ⑩	15	NR	(4)	NR	NR
Zhao (2020)	40/40	36/44	60 ± 4/ 60 ± 4	ALL AMI	PCI	SMI 100 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤	①, ②, ③, ④, ⑤	15	NR	(4)	NR	NR
Shenfu injection												
Zhu (2006)	52/46	73/25	52.5/53.8	ALL AMI	NR	SFI ivgtt Qd combined with conventional therapy	Conventional therapy	28	NR	(4)	NR	NR
Zhang et al. (2018c)	60/60	76/44	62.97 ± 3.59/ 63.07 ± 3.6	STEMI	PCI	SFI 80 mL ivgtt st combined with ①, ⑩	The same dose of 0.9% saline control combined with ①, ⑩	1	30 d	(1)	VI	NR
Wang et al. (2021a)	20/20	35/5	50.4 ± 10.2/ 58.4 ± 8.6	STEMI	PCI	SFI 80 mL iv before surgery, and maintained for Qd combined with ⑩	Matched placebo, ⑩	5	28 d	(3)	IIVI	NR
Shen et al. (2006)	83/82	88/77	59/61	STEMI	Thrombolytic therapy	SFI 80–100 mL ivgtt Qd combined with conventional therapy, ②, ⑥, ⑨	Conventional therapy combined with ②, ⑥, ⑨	7	NR	(1) (4)	NR	NR
Zhang et al. (2019)	33/32	41/24	NR	STEMI	PCI	SFI 60 mL ivgtt Qd combined with conventional therapy, ⑩	Conventional therapy, ⑩	10	2 M	(4)	NR	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Zhang et al. (2011)	36/38	38/36	54.2/55.7	AMI	NR	SFI 60 mL ivgtt Qd combined with conventional therapy	Conventional therapy	14	NR	(1)	NR	NR
Zhu et al. (2020)	70/70	82/58	65.07 ± 7.24/ 61.67 ± 6.42	NSTEMI	PCI	SFI 60 mL ivgtt Qd combined with ①, ③, ④, ⑤, ⑩	①, ③, ④, ⑤, ⑩	10	30 d	(1)	VI	NR
Ma et al. (2022)	55/55	61/49	57.61 ± 2.1/ 57.62 ± 2.11	NSTEMI	NR	SFI 60 mL ivgtt Qd combined with ①, ③, ④, ⑤	①, ③, ④, ⑤	10	NR	(4)	NR	NR
Pei et al. (2019)	36/36	36/34	63.04 ± 4.69/ 62.38 ± 5.14	STEMI	Thrombolytic therapy	SFI 60 mL ivgtt Qd combined with ①, ②, ③, ⑧	①, ②, ③, ⑨	14	NR	NR	VIII	YES
Li et al. (2017)	67/67	75/59	51.2 ± 8.2/ 51.4 ± 8.3	STEMI	Thrombolytic therapy	SFI 60 mL ivgtt Qd combined with ①, ②, ③, ④, ⑥, ⑧	①, ②, ③, ④, ⑥, ⑨	14	NR	(4)	VIII	NR
Ma et al. (2019)	55/55	63/47	59.14 ± 4.21/ 59.12 ± 4.22	ALL AMI	Thrombolytic therapy	SFI 60 mL ivgtt Bid combined with ①, ②, ③, ⑧, ⑨, ⑭	①, ②, ③, ⑧, ⑨, ⑭	14	NR	(4)	NR	NR
Li (2015a)	32/32	43/21	63.5 ± 11.2/ 63.2 ± 11.5	ALL AMI	Thrombolytic therapy	SFI 60 mL ivgtt Bid combined with ①, ②, ③, ④, ⑤, ⑨, ⑬	①, ②, ③, ④, ⑤, ⑨, ⑬	14	NR	(1) (4)	NR	NR
Zeng (2005)	54/56	61/49	57.6 ± 15.2/ 56.8 ± 15.7	ALL AMI	Thrombolytic therapy	SFI 60–100 mL ivgtt Qd combined with ②, ⑥, ⑧, ⑨	②, ⑥, ⑧, ⑨	10	NR	(1)	NR	NR
Mo and Zhao (2002)	36/38	40/34	55.3 ± 15.6/ 54.9 ± 12.7	ALL AMI	Thrombolytic therapy	SFI 60–100 mL ivgtt Qd combined with ②, ⑥, ⑧, ⑨	②, ⑥, ⑧, ⑨	7	NR	(1)	NR	NR
Chen et al. (2018)	29/29	27/31	54.84 ± 13.93/ 55.61 ± 14.32	STEMI	NR	SFI 50 mL iv-vp Qd combined with ①, ③, ④, ⑤, ⑥	①, ③, ④, ⑤, ⑥	21	NR	(4)	NR	NR
Liu (2018)	50/50	53/47	62.4 ± 8.8/ 63.3 ± 9.1	ALL AMI	NR	SFI 50 mL ivgtt Qd combined with conventional therapy, ③	Conventional therapy, ③	21	NR	(4)	VI	NR
Meng (2014)	30/30	43/17	46.3 ± 11.9/ 46.7 ± 12.1	STEMI	NR	SFI 50 mL ivgtt Qd combined with ⑧	⑧	5	NR	(4)	NR	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Feng et al. (2011)	37/31	37/31	61.2/60.5	ALL AMI	PCI	SFI 50 mL ivgtt Qd combined with ②, ⑤, ⑥, ⑩	②, ⑤, ⑥, ⑩	14	NR	(4)	NR	NR
Kang (2017)	31/31	26/36	54.21 ± 3.52/ 55.32 ± 3.29	STEMI	NR	SFI 50 mL ivgtt Qd combined with ①, ③, ⑤	①, ③, ⑤	14	NR	(4)	NR	NR
Yan et al. (2017)	40/40	43/37	61.68 ± 7.54/ 62.03 ± 7.66	STEMI	NR	SFI 50 mL ivgtt Qd combined with ①, ③, ④, ⑤, ⑥	①, ③, ④, ⑤, ⑥	21	NR	(4)	NR	NR
Wang et al. (2018a)	58/58	71/45	60.8 ± 2.5/ 64.8 ± 2.5	ALL AMI	NR	SFI 50 mL ivgtt once combined with ②, ③, ⑤, ⑧	②, ③, ⑤, ⑧	1	6 M	(4)	NR	NR
Yang et al. (2014)	40/40	56/24	70.4 ± 5.2/ 71.1 ± 4.2	STEMI	PCI OR CABG	SFI 50 mL ivgtt Bid combined with ①, ④, ⑤, ⑨	①, ④, ⑤, ⑨	10	NR	(4)	NR	NR
Lan et al. (2021)	20/20	23/17	58.81 ± 15.21/ 57.37 ± 17.13	STEMI	PCI	SFI 40 mL iv-vp Qd combined with ①, ③, ⑥, ⑩	①, ③, ⑥, ⑩	7	NR	(4)	NR	NR
Li (2006)	37/36	52/21	63.3 ± 16.9/ 59.8 ± 17.2	STEMI	NR	SFI 40 mL ivgtt Qd combined with conventional therapy, ⑥, ⑬	Conventional therapy combined with ⑥, ⑬	14	NR	(1) (4)	NR	NR
Wang et al. (2018b)	31/31	32/30	NR	ALL AMI	NR	SFI 40 mL ivgtt Qd combined with ⑧	⑧	7	6 M	(1) (4)	NR	NR
Feng et al. (2019)	174/160	197/ 137	60.79 ± 9.73/ 61.43 ± 7.22	STEMI	NR	SFI 40 mL ivgtt Qd combined with ①, ②, ④, ⑤, ⑬	①, ②, ④, ⑤, ⑬	10	NR	(1) (4)	NR	NR
Zhao et al. (2016a)	31/30	32/30	NR	AMI including STEMI and non-STEMI in one study	PCI	SFI 40 mL ivgtt Qd combined with ①, ②, ③, ④, ⑥, ⑧, ⑩	①, ②, ③, ④, ⑤, ⑧, ⑩	7	6 M	(1) (4)	NR	NR
Hao et al. (2021)	49/48	42/55	56.98 ± 4.02/ 57.47 ± 3.98	ALL AMI	PCI	SFI 40 mL iv, SFI 40 mL ivgtt Qd combined with ①, ⑩	①, ⑩	7	1 M	(1)	NR	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Li (2015b)	42/41	51/32	56/61	STEMI	Thrombolytic therapy	SFI 40 mL iv every 15 min for 4–8 consecutive times combined with ②, ⑥, ⑨	②, ⑥, ⑨	2	NR	(1) (4)	NR	NR
Chen et al. (2003)	40/38	50/28	NR	STEMI	Thrombolytic therapy	SFI 30 mL ivgtt Qd combined with ①, ②, ⑥, ⑧	①, ②, ⑥, ⑧	14	NR	(4)	NR	NR
Li (2006)	37/36	49/24	63.7 ± 18.6/ 59.8 ± 17.2	STEMI	NR	SFI 20 mL ivgtt Qd combined with conventional therapy, ⑥, ⑬	Conventional therapy combined with ⑥, ⑬	14	NR	(1) (4)	NR	NR
Li et al. (2010)	58/34	55/37	68.2 ± 9.33/ 67.8 ± 10.72	STEMI	NR	SFI 1 mL/kg ivgtt Qd combined with ①, ④, ⑤, ⑥, ⑧, ⑬	①, ④, ⑤, ⑥, ⑧, ⑬	14	NR	(4)	NR	NR
Wang et al. (2017)	64/64	74/54	59.7 ± 14.3/ 58.2 ± 13.6	AMI including STEMI and non-STEMI in one study	PCI	SFI 10 mL/h iv-vp combined with ①, ②, ③, ⑤, ⑥, ⑧, ⑬	①, ②, ③, ⑤, ⑥, ⑧, ⑬	7	NR	(1)	NR	NR
Li et al. (2016)	32/32	40/24	NR	ALL AMI	PCI	SFI 100 mL ivgtt Qd combined with conventional therapy, ①, ②, ⑧, ⑩	Conventional therapy combined with ①, ②, ⑧, ⑩	No more than 14	NR	(1)	NR	NR
Wen (2014)	31/31	36/26	NR	STEMI	Thrombolytic therapy	SFI 100 mL ivgtt Qd combined with ②, ⑨	②, ⑨	15	NR	(4)	NR	NR
Li and Cheng (2014)	35/36	50/21	62.7 ± 16.6/ 61.8 ± 15.2	STEMI	PCI	SFI 100 mL ivgtt Qd combined with ①, ②, ⑩	①, ②, ⑩	10–14	NR	(1)	NR	NR
Li (2013)	30/30	38/22	55.3 ± 15.6/ 54.9 ± 12.7	ALL AMI	Thrombolytic therapy	SFI 100 mL ivgtt Qd combined with ①, ②, ④, ⑤, ⑥, ⑨, ⑭	①, ②, ④, ⑤, ⑥, ⑨, ⑭	14	2 M	(4)	NR	NR
Zhang et al. (2023)	90/90	96/84	75.13 ± 7.26/ 72.56 ± 6.68	STEMI	NR	SFI 100 mL ivgtt Qd combined with ①, ②, ③, ⑧	①, ②, ③, ⑧	3	30 d	(4)	NR	NR
Li et al. (2017)	31/31	34/28	66.38 ± 10.69/ 67.41 ± 11.98	ALL AMI	NR	SFI 100 mL ivgtt Qd combined with ①, ②, ③, ④, ⑤, ⑥, ⑧, ⑬	①, ②, ③, ④, ⑤, ⑥, ⑧, ⑬	14	NR	(1) (4)	I	NR

(Continued on following page)

10.3389/fphar.2025.1511486

TABLE 1 (*Continued*) Characteristics of the included studies.

Study ID	Sample size (E/C)	Sex (M/F)	Age(Y) (E/C)	Type of AMI	Reperfusion therapies	Intervention (E)	Intervention (C)	Course (days)	Follow-up	Outcomes	Adverse events	Treatment based on syndrome differentiation
Zhu et al. (2019)	80/80	94/66	56.4 ± 2.2/ 56.9 ± 2.1	ALL AMI	NR	SFI 100 mL ivgtt Qd combined with ①, ②	Conventional therapy combined with ①, ②	14	NR	(1)	NR	NR
Astragalus injection												
Han et al. (2000)	38/44	50/32	54.3 ± 12.4/ 52.8 ± 11.7	STEMI	Thrombolytic therapy	AI 60 mL ivgtt Qd combined with ①, ②, ⑤, ⑥, ⑨	①, ②, ⑨	10	1 M	(1)	I	NR
Mi et al. (2009)	30/29	36/23	62.33 ± 10.27/ 60.43 ± 10.27	ALL AMI	Thrombolytic therapy	AI 50 mL ivgtt Qd combined with conventional therapy,⑧, ⑨	Conventional therapy combined with ⑧, ⑨	14	NR	(1) (4)	NR	NR
Xian (2019)	48/48	53/43	65.27 ± 7.16/ 64.58 ± 7.32	ALL AMI	PCI	AI 20 mL ivgtt Qd combined with ①, ③, ⑤, ⑧, ⑩	①, ③, ⑤, ⑧, ⑩	14	NR	(4)	VI	NR

Note: N, number; E, experimental group; C, control group; M, male; F, female; Y, years old; AMI, acute myocardial infarction; STEMI, ST, segment elevation myocardial infarction; NSTEMI, non-ST, segment elevation myocardial infarction; ALL AMI, STEMI, and NSTEMI; PCI, percutaneous coronary intervention; CCB, calcium channel blockers; I, intervention measures; d, day; M, month; NR, not report; SGMI: shengmai injection; SMI, shenmai injection; SFI, shenfu injection; AI, astragalus injection; Tid, 3 times a day; Bid, twice a day; Qd, once a day; st, at once; ① anti-platelet; ② anticoagulation; ③ lipid lowering; ④ β -blocker; ⑤ ACEI/ARB; ⑥ antimyocardial ischemia; ⑦ amiodarone; ⑧ vasoactive drugs; ⑨ Thrombolytic therapy; ⑩ PCI; ⑪ Alleviation pain; ⑫ lidocaine; ⑬ Diuretic medication; ⑭ Sedatives; ⑮ CCB; Outcome: (1) fatality rate in hospitalization; (2) fatality rate in the long term; (3) incidence of malignant arrhythmia; (4) left ventricular ejection fraction; Adverse event: I: bleeding events; II: abnormal renal function; III: allergy; IV: headache; V: dizziness; VI: abnormal digestive system; VII: respiratory system dysfunction; VIII: ecchymosis; IX: rash.

10.3389/fphar.2025.1511486

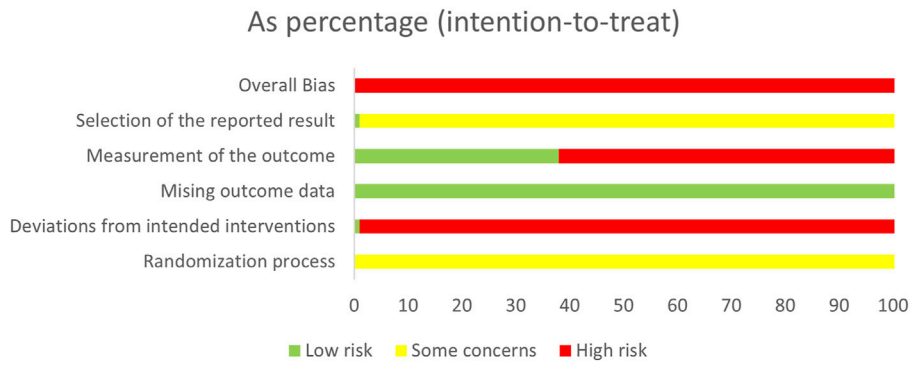


FIGURE 2
Risk-of-bias graph.

3.2 Study characteristics

A total of 113 studies (28–140) met the final eligibility criteria and were included in the meta-analysis (Table 1). All studies were single-center trials conducted in China. Two trial was a three-arm study (Wang, 2016; Li, 2006), while the remaining trials were two-arm studies. The sample sizes ranged from 30 (125) to 502 (139), with the mean age ranging from 35 to 75 years. The duration of treatment varied from once (Wang, 2018; Zhang D. L. et al., 2018; Zhang, 2017) to 30 days (Wang, 2016). We identified two ongoing trials that may be relevant to this review. Supplementary Table S6 provides details of the CCPP included in the study.

3.3 Quality evaluation

All studies (n = 113) were considered to be at high risk of bias. The results are presented in Figure 2 and Supplementary Figure S1. Regarding randomization process, 51 studies described specific randomization methods: 45 studies used the random number table method, one used the simple randomization method, one used the dice throwing method, one used the lottery method, one used the stratified randomization principle, one used the parity randomization method, and one used the randomized parallel grouping method. All included studies were deemed to some concerns risk due to inadequate description of allocation sequence concealment. Regarding deviations from the established intervention, one study specifically described the double-blind method and was rated as having a low risk of bias, and the rest of the studies did not describe the specific randomization or blinding methods and were rated as having a high risk of bias. All included studies were deemed to have a low risk of bias due to missing outcome data. 38 studies assessed no effect on outcome measures and were judged to be at low risk of bias. One study was registered on clinicaltrials.gov and presented all results, so it was judged to be at low risk of bias, while the rest of the studies did not mention registration and were assessed as being at some concerns risk.

3.4 Results of the meta-analysis

3.4.1 Case fatality rate

49 studies (Hao et al., 2021; Zhu et al., 2020; Feng et al., 2019; Zhu et al., 2019; Wang HY. et al., 2018; Zhang DL. et al., 2018; Zhang DM. et al., 2018; Li and Hou, 2017; Wang and Qing, 2017; Chen, 2017; He et al., 2016; Li, 2016; Liu, 2016; Wu et al., 2016; Qi et al., 2015a; Xuan et al., 2015; Li and Cheng, 2014; Zong et al., 2014; Zou, 2014; Liu, 2012; Zhang, 2011; Zhang et al., 2011; Ye, 2010; Mi et al., 2009; Yuan, 2009; Qu, 2007; Cui and Li, 2006; Ding and Xu, 2006; Li, 2006; Liang, 2006; Shen et al., 2006; Zeng, 2005; Zhao et al., 2005; Liu et al., 2004; Han et al., 2003; Bai et al., 2002; Mo and Zhao, 2002; Wei and Liu, 2001; Han et al., 2000; Guo and Zhang, 1999) reported the case fatality rate involving 4,939 patients (Figure 3). The analysis showed no significant heterogeneity (I^2 = 0%), and a fixed-effects model was used for statistical analysis. The meta-analysis results demonstrated that the combined application of TCMi-TQ significantly reduced the mortality of AMI patients compared to CT alone [RR = 0.58, 95%CI (0.51, 0.67), $P < 0.05$]. This effect was observed in both the STEMI subgroup [RR = 0.53, 95%CI (0.50, 0.78), $P < 0.05$] and the subgroup with ALL AMI cases [RR = 0.56, 95%CI (0.46, 0.67), $P < 0.05$]. However, in the long-term mortality subgroup (follow-up time >12 months), the combined application of TCMi-TQ did not significantly reduce the mortality of AMI patients compared to CT alone [RR = 0.22, 95%CI (0.01, 4.29), P = 0.32] (Figure 4).

3.4.2 Malignant arrhythmia

Malignant arrhythmia was reported in 18 studies (1957 patients) (Chen, 2021; Du, 2017; Wang et al., 2017; Zhou, 2017; Li et al., 2016; Liu, 2016; Liu and Tu, 2016; Wu et al., 2016; Zhang et al., 2011; Wang et al., 2010; Ye, 2010; Yuan, 2009; Wang, 2008; Qu, 2007; Liu et al., 2004; Wei and Liu, 2001; Guo and Zhang, 1999; Wang X. et al., 2021). These studies recorded ventricular fibrillation, polymorphic ventricular tachycardia, and second- or third-degree atrioventricular block with hemodynamic disturbances. The meta-analysis, with low heterogeneity between studies (I2 = 36%), indicated that the combination of TCMi-TQ and CT further reduced the incidence of malignant arrhythmia in AMI patients [RR = 0.51.95%CI (0.42, 0.63), $P < 0.05$]. This effect was observed in both the STEMI

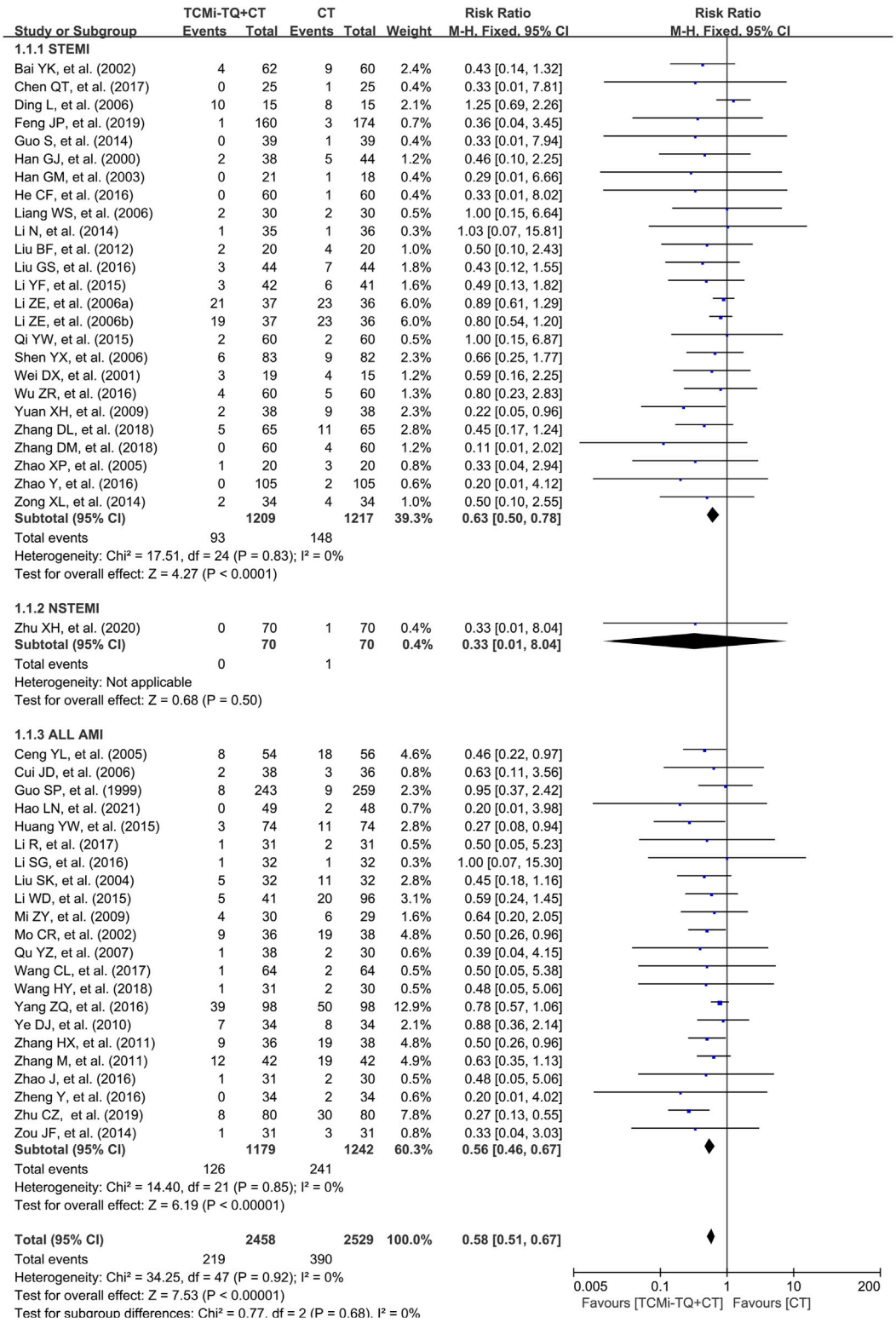


FIGURE 3
Forest plot of the effect of TCMi-TQ combined with conventional biomedicine treatment on in-hospital mortality in patients with AMI Notes: CI, confidence interval; TCMi-TQ, Traditional Chinese medicine injections for Tonifying Qi; CT, conventional treatment; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

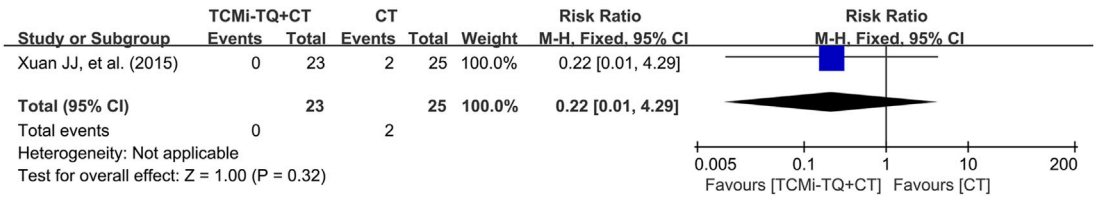


FIGURE 4
Forest plot of the effect of TCMi-TQ combined with conventional biomedicine treatment on long-term mortality in patients with AMI Notes: CI, confidence interval; TCMi-TQ, Traditional Chinese medicine injections for Tonifying Qi; CT, conventional treatment.

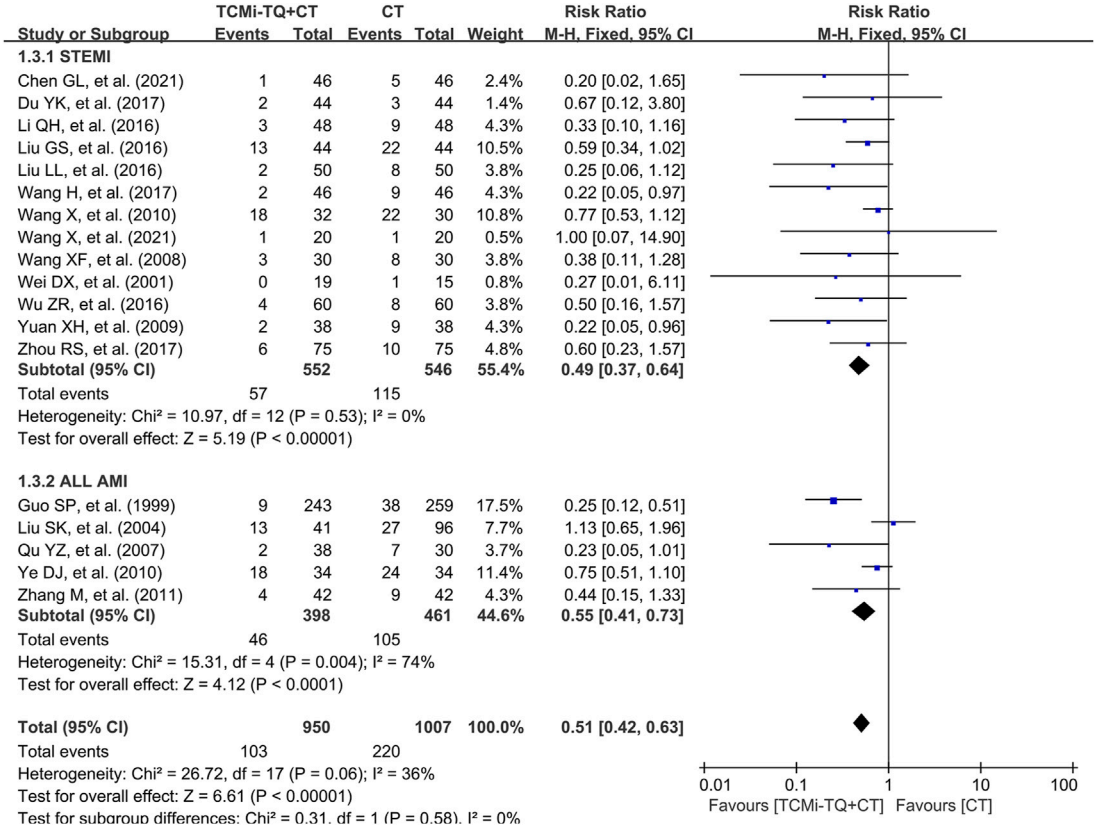


FIGURE 5
Forest plot of the effect of TCMi-TQ combined with conventional biomedicine treatment on the incidence of malignant arrhythmia in patients with AMI. Notes: CI, confidence interval; TCMi-TQ, Traditional Chinese medicine injections for Tonifying Qi; CT, conventional treatment; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

subgroup [RR = 0.49.95%CI (0.37, 0.64), $P < 0.05$] and the subgroup with ALL AMI cases [RR = 0.55.95%CI (0.41, 0.73), $P < 0.05$]. (Figure 5).

3.4.3 LVEF

LVEF data were reported in 71 studies (Zhou, 2024; Zhan and Cui, 2023; Zhang et al., 2023; Lu and Yao, 2022; Ma et al., 2022; Wu et al., 2022; Xu, 2022; Ji et al., 2021; Wang AJ. et al., 2021; Lan et al., 2021; Zhao and Sun, 2021; Zhao, 2020; Feng et al., 2019; Sun, 2019; Wang, 2019; Wang LM. et al., 2019; Wang XY. et al., 2019; Xian, 2019; Zhang et al., 2019; Chen and Qiao, 2018; Liu, 2018; Shi et al., 2018; Song, 2018; Wang HY. et al., 2018; Wang, 2018; Xie, 2018; Xu, 2018; Yan, 2018; Yan et al., 2018; Zhang DL. et al., 2018; Wang and Huang, 2017; Du, 2017; Kang, 2017; Li et al., 2017; Li and Hou, 2017; Wang et al., 2017; Yan et al., 2017; Yang JW. et al., 2017; Zhang, 2017; Zhou, 2017; Chen, 2017; He et al., 2016; Li et al., 2016; Liu, 2016; Liu and Tu, 2016; Luo, 2016; Wang, 2016; Yang and Cai, 2016; Zhao J. et al., 2016; Zhao Y. et al., 2016; Li WD., 2015; Li YF., 2015; Qi et al., 2015b; Qi et al., 2015c; Xuan et al., 2015; Guo, 2014; Meng, 2014; Wen, 2014; Yang, 2014; Li, 2013; Feng et al., 2011; Shi and Li, 2016; Li et al., 2010; Wang et al., 2010; Mi et al., 2009; Long, 2007; Li, 2006; Shen et al., 2006; Zhu, 2006; Chen et al., 2003). High heterogeneity was observed between these studies ($I^2 = 98\%$), and no clear sources of heterogeneity were identified through subgroup

TABLE 2 Subgroup analysis of LVEF based on mean age, TCMi-TQ category, duration of treatment, and sample size.

Grouping criteria	Subgroups	N	I^2 (%)	MD (95%*CI*)	*Z*	*P*
Average age	≥60 years old	34	96	5.23 (4.07, 6.39)	8.82	<0.00001
	60 years old > age ≥40 years old	31	99	7.55 (5.87, 9.22)	8.81	<0.00001
	No report	7	96	7.93 (5.26, 10.61)	5.81	<0.00001
TCMi-TQ variety	Shengmai injection	6	91	4.87 (4.32, 5.43)	17.29	<0.00001
	Shenmai injection	36	98	3.79 (3.62, 3.95)	45.03	<0.00001
	Shenfu injection	28	97	7.51 (7.25, 7.77)	56.36	<0.00001
	Astragalus injection	2	72	7.16 (5.49, 8.83)	8.41	<0.00001
Sessions	≤7 days	22	98	4.00 (3.79, 4.21)	36.84	<0.00001
	>7 days	49	98	5.50 (5.32, 5.67)	60.99	<0.00001
	No report	1	-	3.70 (2.68, 4.72)	7.08	<0.00001
Sample size	<100 people	46	98	4.55 (4.37, 4.72)	50.57	<0.00001
	≤100 people	26	98	5.32 (5.11, 5.53)	49.83	<0.00001

Notes: N, number of studies; CI, confidence interval; MD, mean difference; TCMi-TQ, traditional Chinese medicine injections for Tonifying Qi.

analysis (mean age, type of CCPP, treatment duration, sample size) (see Supplementary Figures S2–S5; Table 2 for details). Despite the heterogeneity, which was deemed acceptable in the overall population analysis, a random-effects model was employed. The meta-analysis results revealed that TCMi-TQ combined with CT significantly improved LVEF in both STEMI and NSTEMI patients compared to treatment with biomedicine alone [MD = 6.52, 95%CI (5.54, 7.50), $P < 0.05$] (Figure 6).

3.4.4 Adverse events

Adverse events were reported in 32 studies (4,896 patients) (Zhan and Cui, 2023; Lu and Yao, 2022; Xu, 2022; Wang AJ. et al., 2021; Yu et al., 2021; Zhu et al., 2020; Pei et al., 2019; Sun, 2019; Tang, 2019; Xian, 2019; Zhang and Jia, 2019; Liu, 2018; Shi et al., 2018; Xie, 2018; Zhang DL. et al., 2018; Zhang DM. et al., 2018; Li et al., 2017; Li and Hou, 2017; Zhou, 2017; Yang and Cai, 2016; Yang et al., 2014; Lu, 2011; Shi and Li, 2016; Yu et al., 2010; Lu, 2009; Long, 2007; Liang, 2006; Han et al., 2003; Wei and Liu, 2001; Han et al., 2000; Guo and Zhang, 1999; Wang X. et al., 2021). These studies recorded bleeding events, abnormal renal function, allergies, headaches, dizziness, abnormal digestive system, respiratory system dysfunction, ecchymosis, and rash. The meta-analysis, with low heterogeneity between studies (I^2 = 18%), indicated that the combination of TCMi-TQ and CT further reduced the incidence of adverse events in AMI patients [RR = 0.70.95%CI (0.60, 0.81), $P < 0.05$] (Figure 7). Specifically, the combination of TCMi-TQ and conventional treatment (CT) reduced the incidence of abnormal digestive system events in AMI patients [RR = 0.31, 95% CI (0.20, 0.47), $P < 0.05$], with heterogeneity I^2 = 33%. Additionally, the combined use of TCMi-TQ and CT did not increase the risk of adverse events such as bleeding events, abnormal renal function, allergies, headaches, dizziness, respiratory system disfunction, ecchymosis, and rash ($P > 0.05$). These findings suggest that the combined use of TCMi-TQ and CT does not increase the incidence of adverse events (Table 3).

3.4.5 Bias and sensitivity analysis

Funnel plots of mortality, malignant arrhythmia, LVEF, and adverse events are presented in Figures 8–11. The Egger test for two outcome indicators indicated no significant publication bias in LVEF ($P = 0.199$) and adverse events ($P = 0.158$). Mortality ($P = 0.000$) and malignant arrhythmia ($P = 0.005$) had significant publication bias. The results were corrected using the trim-and-fill method. No additional studies were included after two iterations using the Linear method. The fixed model results showed no change before and after the iterations, indicating that the meta-analysis results were stable.

Regarding other sources of bias, all included RCTs described the comparability of baseline data, indicating a low risk of bias. For LVEF, the results changed significantly after the removal of Feng et al. (2019) in STEMI, suggesting that this RCT may be the source of heterogeneity (Supplementary Figure S6). The results changed significantly after the removal of Wu et al. (2022) and Yang and Cai (2016) in all AMI cases, suggesting that these RCTs may be the sources of heterogeneity (Supplementary Figure S7). After excluding these three studies one by one, the estimated comprehensive effect points of the remaining studies did not exceed the range, and the results were relatively robust (Supplementary Figures S8–S10).

3.4.6 Results of quality-of-evidence grading

The quality of evidence for the outcomes was assessed using the GRADE method. Due to limitations such as lack of blinding, insufficient allocation concealment, small sample sizes (less than 400 patients), and significant heterogeneity between studies, the quality of evidence for in-hospital mortality, malignant arrhythmias, and adverse events was rated as moderate. The quality of evidence for LVEF was rated as low. A detailed summary of the evidence for each outcome is provided in Table 4.

4 Discussion

In China, the integration of TCM and biomedicine is increasingly becoming an anticipated model of medical

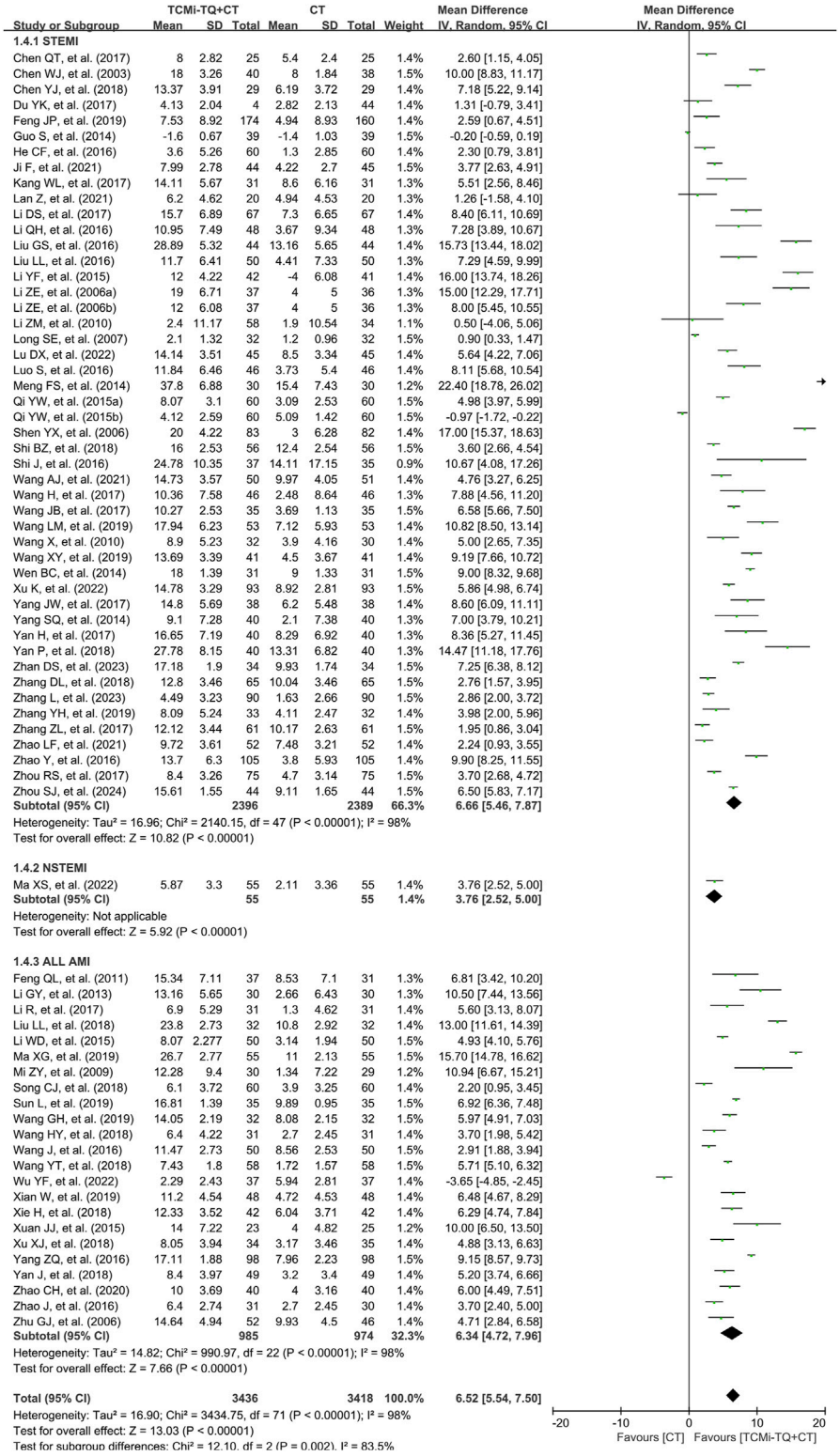


FIGURE 6
Forest plot of the effect of TCMi-TQ combined with conventional biomedicine treatment on LVEF in patients with AMI Notes: CI, confidence interval; MD, mean difference; TCMi-TQ, Traditional Chinese medicine injections for Tonifying Qi; CT, conventional treatment; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left ventricular ejection fraction.

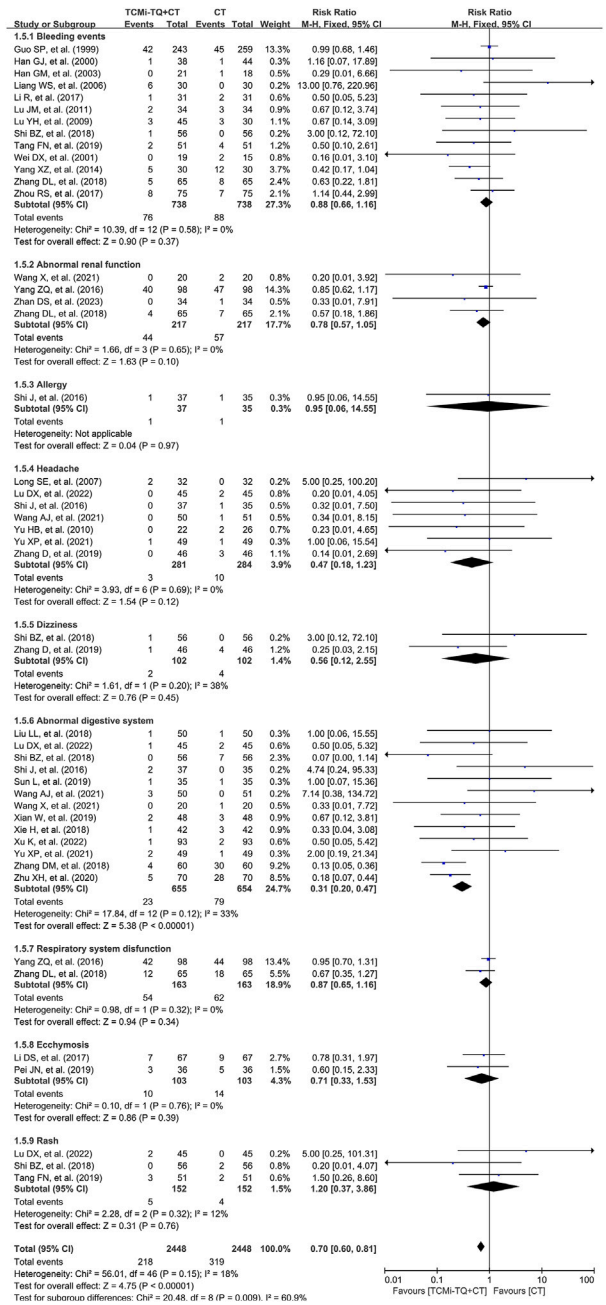


FIGURE 7
Forest plot of the occurrence of adverse events in patients with AMI treated with TCMi-TQ combined with conventional biomedicine. Notes: CI, confidence interval; RR, risk ratio; TCMi-TQ, Traditional Chinese medicine injections for Tonifying Qi; CT, conventional treatment.

development, as it contributes to addressing clinical issues more effectively. Taking AMI as an example, despite the rapid development of modern medical techniques, including PCI, in China, a turning point in the reduction of AMI mortality has not yet been observed (Tsao et al., 2022; GBD 2013 Mortality and Causes of Death Collaborators, 2015). Early intervention and diagnosis of diseases can reduce the incidence rate of AMI, but these areas need further research (Wang et al., 2024b; Wang et al., 2024c; Jaiswal et al., 2023). The standardized application of TCM may serve as a valuable approach to addressing this clinical issue. However, the process of integrating traditional and modern medicine requires support from high-quality evidence-based research. Our study contributes precisely to this by conducting relevant work.

Traditional Chinese Medicine injection (TCMi) refers to a sterile preparation extracted and purified from TCM, which can be in the form of a solution, emulsion, lyophilized powder, or concentrated solution (Zhang et al., 2021; Chen et al., 2022). It is known for its high bioavailability and precise therapeutic effects and has been widely used in China particularly in the treatment of AMI.

It is important to mention a concept in TCM known as "tong zheng yi bing" or "different diseases with the same pattern." Specifically, even if it is not AMI, the same qi deficiency syndrome can be treated with medications that have the function of tonifying qi. Therefore, the use of TCMi may present issues with inappropriate indications. The TCMi selected in this study were those that have the function of tonifying qi. We identified four such TCMi through our search.

In Chinese medicine theory, qi is considered one of the fundamental substances that constitute the human body and maintain vital life activities. Functionally, qi serves roles in promoting, warming, defending, consolidating, and facilitating gasification. Thus, qi can regulate the blood, fluids, and essence; maintain body temperature; defend the body; and sustain the overall connectivity between the interior and exterior of the body. Qi transformation refers to the process of metabolism and the mutual transformation of energy among essence, blood, fluids, and other substances. None of this can be separated from the movement of qi; it can be said that qi, in its forms of ascending, descending, outgoing, and incoming, is the fundamental driving force of all life activities (Wang et al., 2023). It is evident that qi serves as the prime mover of all life activities within the human body. Mitochondria produce ATP, which is the primary source of energy for the body and the main source of power for cardiomyocytes, and the normal structure and function of mitochondria are crucial for myocardial energy metabolism (Lopaschuk and Jaswal, 2010). There is a correlation between qi and mitochondria in terms of their origin, morphology, function, and lesions (Lin et al., 2014; Zhang et al., 2001). Systematic reviews and meta-analyses of RCTs show that Qi-regulating formulations, such as Wenxin Keli and Yangxinshi tablet, may be effective and safe for treating ischemic heart disease (IHD) (Wang et al., 2016; Guo et al., 2023). Research h+as found that they play a certain role in regulating cardiac mitochondrial function (Wu et al., 2020), glucose metabolism, lipid metabolism, and amino acid metabolism (Zhang H. et al., 2018; Jiang et al., 2017). The active metabolite Ginsenoside Rb1 from Panax ginseng, known for its qi-tonifying effects, may promote myocardial recovery in AMI via mechanisms involving mitochondrial autophagy, as demonstrated by both *in vivo* and *in vitro* studies (Hu et al., 2022). Therefore, tonifying qi may have certain potential in regulating cardiac energy metabolism.

SGMI is made up of Ginseng Rubra Radix; Ophiopogonis Radix; Schisandrae Chinensis Fructus, and the main pharmacodynamic substances include ginsenoside metabolites and lignans. Clinical studies have demonstrated that SGMI can inhibit the inflammatory response in acute-phase AMI patients (Wang LM. et al., 2019). For patients in the recovery phase of AMI, SGMI can enhance clinical efficacy, boost cardiac function, improve tissue perfusion, and

TABLE 3 Subgroup analysis of adverse events based on bleeding events, abnormal renal function, allergies, headaches, dizziness, abnormal digestive system, respiratory system dysfunction, ecchymosis, and rash.

Subgroups	Number of studies	Number of patients		I^2 (%)	RR (95%CI)	Z	*P*
		TCMi-TQ + CT	CT				
Bleeding events	13	76 (738)	88 (738)	0	0.88 (0.66, 1.16)	0.90	0.37
Abnormal renal function	4	44 (217)	57 (217)	0	0.78 (0.57, 1.05)	1.63	0.65
Allergies	1	1 (37)	1 (35)		0.95 (0.06, 14.55)	0.04	0.97
Headaches	7	3 (281)	10 (284)	0	0.47 (0.18, 1.23)	1.54	0.12
Dizziness	2	2 (102)	4 (102)	38	0.56 (0.12, 2.55)	0.76	0.45
Abnormal digestive system	13	23 (655)	79 (654)	33	0.31 (0.20, 0.47)	5.38	<0.00001
Respiratory system dysfunction	2	54 (163)	62 (163)	0	0.87 (0.65, 1.16)	0.94	0.34
Ecchymosis	2	10 (103)	14 (103)	0	0.71 (0.33, 1.53)	0.86	0.39
Rash	3	5 (152)	4 (152)	12	1.20 (0.37, 3.86)	0.31	0.76

Notes: CI, confidence interval; CT, conventional treatment; RR, relative risk; TCMi-TQ, traditional Chinese medicine injections for Tonifying Qi.

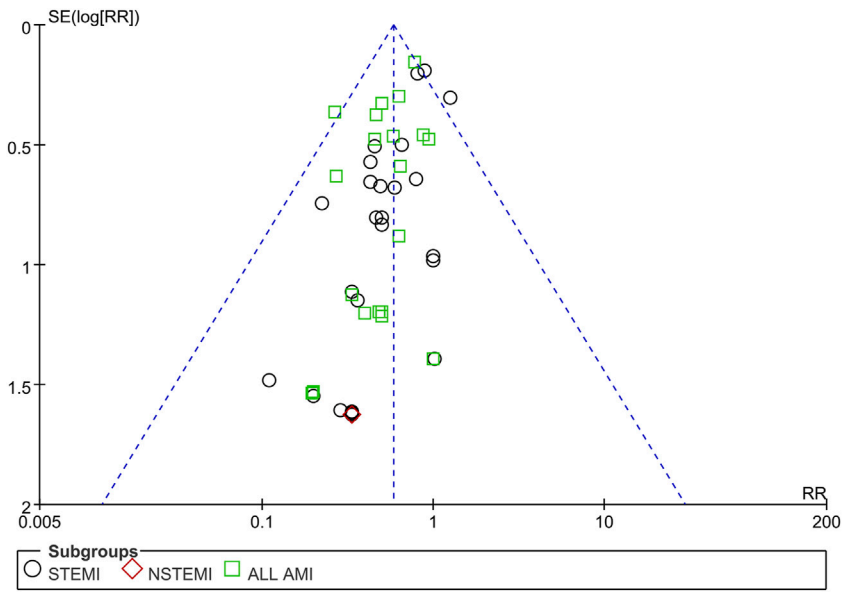


FIGURE 8
Funnel plot of case fatality rate. Notes: STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; AMI, acute myocardial infarction; RR, risk ratio.

optimize oxygen metabolism (Luan et al., 2022). Additionally, it reduces levels of inflammatory factors (Lu and Yao, 2022), restores endothelial function (Tang, 2019), and improves hemorheological parameters (Wang, 2017). Ginsenosides, schizandrin, and ophiopogonin D are the primary active constituents of SGMI. Jiang et al. (2014) investigated the effects of this combination therapy on energy metabolism in rats with AMI and found that it can stimulate fatty acid oxidation and inhibit glycolysis, there by counteracting the metabolic reprogramming associated with AMI (Jiang et al., 2014). Li et al. (2019) found that SGMI can protect the mitochondrial structure of cardiomyocytes from Ang II-induced damage, stabilize mitochondrial membrane potential, and enhance mitochondrial oxygen utilization. Additionally, it can upregulate the expression of genes related to free fatty acid oxidation, glucose oxidation, and mitochondrial biogenesis by activating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, which is crucial for energy metabolism (Li et al., 2019). Zhan et al. (2016) used comparative proteomics techniques to discover that SGMI may exert myocardial protection by modulating multiple energy metabolism pathways: promoting carbohydrate metabolism, inhibiting lipid metabolism, restoring the tricarboxylic acid cycle, and enhancing respiratory chain ATP production (Zhan et al., 2016).

SMI is a compound injection made of Ginseng Rubra Radix and ophiopogonis Radix, and the main pharmacodynamic substances include ginsenosides and ophiopogon saponins (Wang et al., 2020).

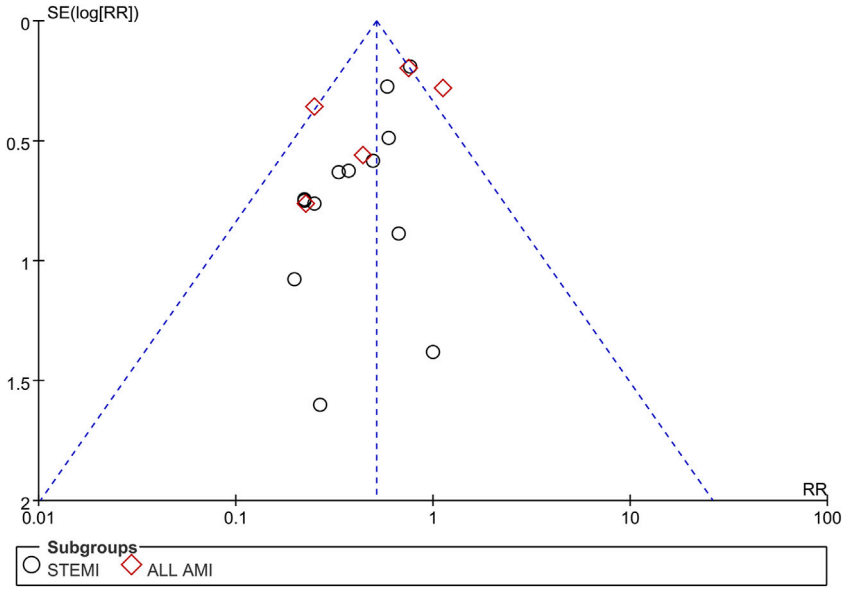


FIGURE 9
Funnel plot of malignant arrhythmia. Notes: STEMI, ST-segment elevation myocardial infarction; AMI, acute myocardial infarction; RR, risk ratio.

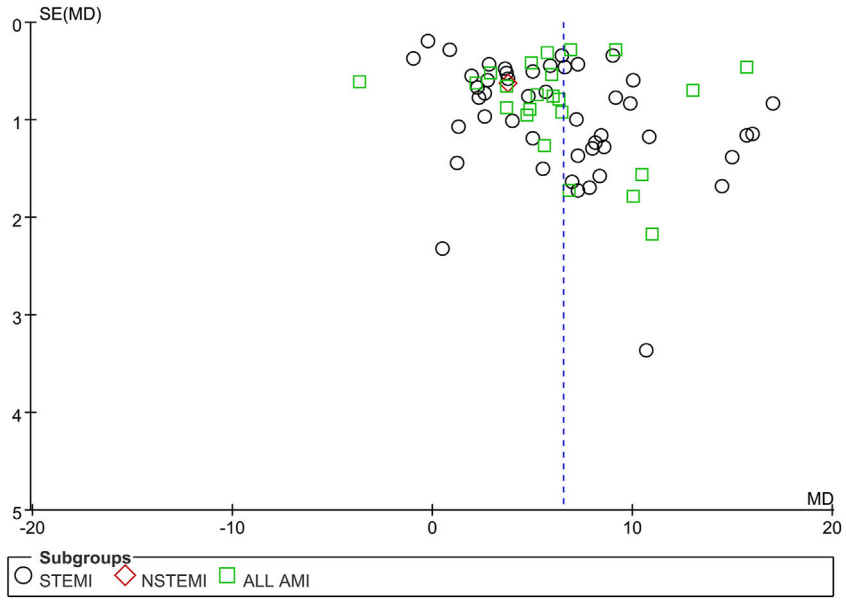


FIGURE 10
Funnel plot of LVEF Notes: STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; MD, mean difference.

Studies have found that SMI can alleviate oxidative stress in patients during the acute phase of AMI (Cao et al., 2022), improve vascular endothelial injury and apoptosis (Yang FF. et al., 2017), and enhance hemodynamic parameters (Qin, 2021). For patients in the recovery phase of AMI, SMI can effectively suppress inflammatory responses, reduce blood viscosity, and improve cardiac function (Zhou, 2024; Zhan and Cui, 2023). Wang et al. (2018) utilized network analysis to discover that SMI can significantly reverse the downregulation of energy metabolism-related proteins such as ATP synthase and malate dehydrogenase caused by ischemia, thereby modulating signaling pathways associated with oxidative phosphorylation and mitochondrial dysfunction. In a primary cardiomyocyte model of hypoxic injury in rats, they found that SMI can stabilize mitochondrial membrane potential, restore intracellular ATP levels, increase maximal mitochondrial respiration rate, and enhance oxygen reserve capacity, thus reversing energy metabolic imbalance (Wang Y.

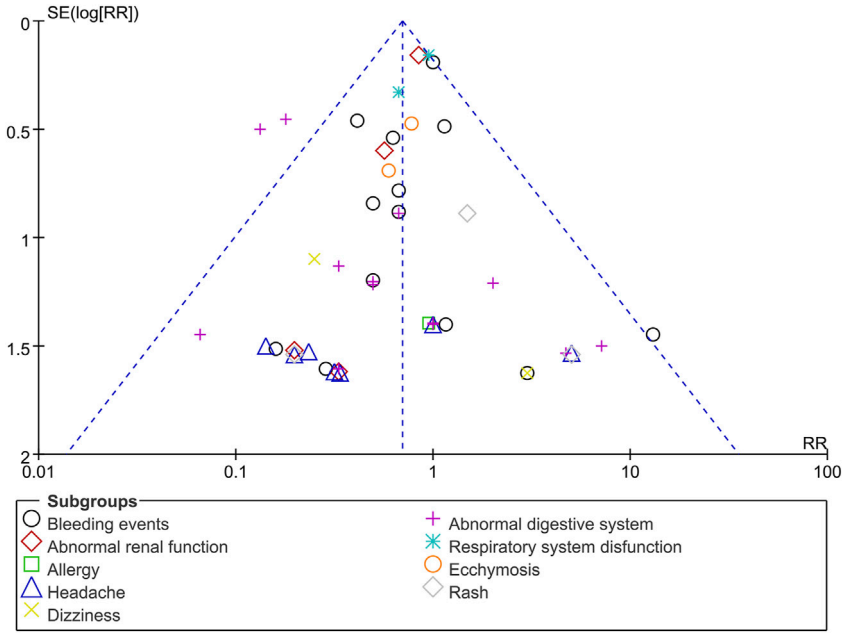


FIGURE 11
Funnel plot of adverse events. Notes: RR, risk ratio.

et al., 2018). Wang et al. (2019) found that SMI can reduce myocardial cell injury following ischemia-reperfusion (I/R). It increases the expression of glucose transporter 4, cluster of differentiation 36, and fructose-6-phosphate kinase, thereby enhancing the utilization of both free fatty acids and glucose (Wang S. et al., 2019).

SFI is made up of Ginseng Rubra Radix and Aconiti Lateralis Radix Praeparata (black shunpian), and the main active metabolites are ginsenosides and panaxynol (Zheng et al., 2022). For patients with acute-phase AMI, SFI can improve hemodynamic parameters (Zhuo et al., 2018) and reduce levels of inflammatory factors (Jin et al., 2017). For patients in the recovery phase of AMI, SFI can mitigate inflammatory responses (Li et al., 2017), improve hemorheological indicators (You and Wang, 2019), enhance fibrinolytic activity (Zhu et al., 2020), improve vascular endothelial function, and reduce oxidative damage (Jia et al., 2016). Studies have found that SFI can protect against myocardial injury by modulating mitochondrial dynamics, improving mitochondrial energy metabolism, reducing mitochondrial oxidative stress, and inhibiting structural damage to mitochondria (Lu and Xiang, 2023). Bai et al. (2018) investigated the effects of SFI on I/R injury in rats and found that it could enhance the clearance of oxygen free radicals, reduce cellular damage, reduce intracellular Ca^{2+} influx, increase ATP levels, and inhibit inflammation (Bo et al., 2018). Zhan et al. (2024) found that SFI can mediate mitochondrial autophagy in rats with I/R injury by regulating the HIF-1α/BNIP3 pathway, thereby protecting the mitochondrial structure and reducing myocardial cell apoptosis (Zhan et al., 2024). Ji et al. (2011) studied the effects of SFI on myocardial dysfunction following cardiac arrest and resuscitation in pigs and found that it could increase the activity of Na^{+}-K^{+}-ATPase and Ca^{2+}-ATPase, and left ventricular superoxide dismutase, thereby modulating energy metabolism and enhancing antioxidant capacity (Ji et al., 2011). Additionally, Huang et al. (2020) found that Shenfu Formula could synergistically mediate metabolic flexibility of fatty acids and glucose in cardiac energy metabolism in heart failure mice induced by transverse aortic constriction through the AMPK-related pathway, thereby inhibiting cardiac metabolic remodeling (Huang et al., 2020).

AI is an injection made from Astragali Radix, and its main active metabolites include flavonoids, saponins, and amino acids (Yu H. et al., 2019). For patients with acute-phase AMI, AI can improve immune-inflammatory responses and ventricular remodeling (Hou et al., 2012). For patients in the recovery phase of AMI, AI can enhance cellular antioxidant capacity (Zhou et al., 2019), protect vascular endothelium, and increase overall antioxidant ability (Chen et al., 2015). Huang et al. (2018) investigated the effects of major extracts from Astragalus membranaceus on tert-butyl hydroperoxide-induced H9C2 cells and found that they could alleviate oxidative stress and increase cell survival by regulating mitochondrial membrane potential and enhancing mitochondrial bioenergetics parameters, including basal respiration, proton leak, maximal respiration, and non-mitochondrial respiration (Huang et al., 2018). Jin et al. (2014) found that Astragalus can correct impaired free fatty acid and glucose metabolism in AMI model rats, increase myocardial ATP, ADP, and total adenine nucleotide levels, thereby protect ischemic myocardium (Jin et al., 2014). Astragaloside IV, the primary active metabolite of AI, plays a crucial role in regulating cardiac energy metabolism. The underlying mechanisms likely involve multiple pathways: it induces the expression of mitochondria-related proteins (Wang Q. et al., 2021; Zang et al., 2020), protects the structural integrity of cardiac mitochondria (Lu et al., 2015), and modulates mitochondrial function (Dong et al., 2017).

These TCMi-TQs exhibit comparable effects. However, the safety of TCMi has become a growing concern. A retrospective

TABLE 4 Evidence summary of outcomes.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCMi-TQ+CT	CT	Relative (95% CI)	Absolute (95% CI)		
Case fatality rate												
48	randomised trials	serious[a]	not serious	not serious	not serious	none	219/ 2,458 (8.9%)	390/ 2,529 (15.4%)	RR 0.58 (0.51–0.67)	65 fewer per 1,000 (from 76 fewer to 51 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Fatality rate in the long term												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	0/23 (0.0%)	2/ 25 (8.0%)	RR 0.22 (0.01–4.29)	62 fewer per 1,000 (from 79 fewer to 263 more)	⊕⊕◯◯ Low	CRITICAL
Incidence of malignant arrhythmia												
18	randomised trials	serious[a]	not serious	not serious	not serious	none	103/ 950 (10.8%)	220/ 1,007 (21.8%)	RR 0.51 (0.42–0.63)	107 fewer per 1,000 (from 127 fewer to 81 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT
LVEF												
72	randomised trials	serious[a]	serious[c]	not serious	not serious	none	3,436	3,418	-	MD 6.52 higher (5.54 higher to 7.5 higher)	⊕⊕◯◯ Low	IMPORTANT
Adverse events												
32	randomised trials	serious[a]	not serious	not serious	not serious	none	218/ 2,448 (8.9%)	319/ 2,448 (13.0%)	RR 0.70 (0.60–0.81)	36 fewer per 1,000 (from 52 fewer to 25 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

Notes: CI, confidence interval; RR, risk ratio; MD, mean difference; TCMi-TQ, traditional Chinese medicine injections for Tonifying Qi; CT, conventional treatment; LVEF, left ventricular ejection fraction.

[a]The blinding method and allocation concealment were not used.

[b]Number of patients included was less than 400.

[c]I square value was large.

10.3389/fphar.2025.1511486

investigation based on China PEACE revealed no benefits of TCMi in patients with acute heart failure (Yu Y. et al., 2019). The annual report on national adverse drug reaction monitoring (2023) revealed 2.627 million cases of suspected adverse drug reactions/events, of which traditional Chinese medicine accounted for 12.6%. Tonifying qi and yin drugs among the top five, and 25.9% of the cases involved injectable drug delivery (National Center For ADR Monitoring C, 2024). Considering the widespread use of TCMi-TQ in the AMI patient population (Spatz et al., 2018), it is necessary to conduct a high-quality systematic evaluation of its efficacy and safety.

This meta-analysis included 113 studies involving 10,779 participants. The results demonstrated that the combined application of TCMi-TQ was more effective in reducing in-hospital mortality, decreasing the occurrence of malignant arrhythmias, reducing the incidence of adverse events, and improving LVEF than biomedicine alone. Safety was also assessed in this meta-analysis, with 32 studies reporting on safety outcomes. No serious adverse events were observed, and the common adverse events included bleeding, ecchymosis, and gastrointestinal discomfort, which could be alleviated through drug withdrawal or symptomatic treatment.

Mortality rate is a crucial indicator reflecting the prognosis of AMI patients (Long et al., 2022). A retrospective study found no significant association between early application of TCMi and in-hospital bleeding or mortality rate in AMI patients (Spatz et al., 2018). However, our study revealed that the combined use of TCMi-TQ significantly reduced AMI mortality, which aligns with the findings of previous systematic reviews examining the effects of SGMI (Lu et al., 2018), SMI (Wang et al., 2015), SFI (Zhu et al., 2018), and AI (Su et al., 2017) in AMI treatment. These findings suggest that TCMi with the specific function of tonifying qi plays a unique role in reducing AMI mortality, possibly due to its comparable effects of regulating energy metabolism. Additionally, this study attempted to investigate the impact of TCMi-TQ combined with CT on the long-term mortality rate of AMI patients. However, due to the limited number of studies evaluating long-term mortality, we were unable to identify potential benefits of TCMi-TQ in long-term mortality, highlighting the need for further research.

Malignant arrhythmia is a significant cause of death in patients with acute myocardial infarction (AMI) (Eryol et al., 2002; Nasution et al., 2020). Studies have consistently demonstrated that malignant arrhythmia accompanies 60%–100% of deaths during the acute phase of AMI (Eldar et al., 1994; Berg et al., 2001). Unfortunately, the benefits of antiarrhythmic drugs for such patients are limited (Piccini et al., 2011). Although a few clinical cases have suggested that TCMi may have adverse effects leading to the occurrence of malignant arrhythmias (Jin, 2013; Zhao et al., 1995; Wu and Li, 1988), a meta-analysis revealed that the combined use of TCMi with tonifying qi properties can reduce the risk of malignant arrhythmias during hospitalization in AMI patients. This reduction in risk may be attributed to the clinical effect of TCMi-TQ in improving myocardial ischemia.

Following myocardial infarction, the loss of myocardial cells leads to myocardial remodeling and the development of heart failure (Author Anonymous, 2020), which significantly impacts the patients' quality of life and long-term prognosis. LVEF is an essential indicator of cardiac function (McDonagh et al., 2021). This study found that the combined use of TCMi-TQ demonstrates clinically relevant improvements in cardiac function, consistent with previous meta-analysis results (Zhu et al., 2018; Wei et al., 2021). The protective effect of TCMi-TQ on ischemic myocardium may explain this improvement. However, significant heterogeneity was observed in the analysis results, and subgroup analysis and sensitivity analysis did not identify a clear source of heterogeneity. This heterogeneity may be attributed to differences in the ultrasound equipment and technical standards used for LVEF assessment. Therefore, caution must be exercised when interpreting the aforementioned results due to the presence of these heterogeneity factors.

Our meta-analysis results demonstrate that the combined administration of TCMi-TQ does not increase the occurrence of adverse events in AMI patients. Nevertheless, TCMi, when administered through direct bloodstream injection, can be influenced by various factors such as co-solvents, particulates during the manufacturing process, and solvents. This often leads to a higher occurrence of adverse reactions compared to other TCM formulations (Zhang and Niu, 2018). Therefore, healthcare providers should exercise caution in prescribing medications, prioritizing oral formulations. For patients with complex or severe conditions requiring traditional TCM injections, intramuscular administration should be preferred. In emergency situations, TCM injections via intravenous infusion may be necessary (Gao et al., 2012). Healthcare providers should strictly adhere to medication guidelines for the rational and standardized use of TCM injections. Providers should carefully prepare medications, standardize dosages and treatment plans, and accurately identify and document the evidence basis for medication use (Yu et al., 2023). Hospitals should enhance quality control and inspection during the procurement of medications. These TCM injections should be classified, stored separately, and subjected to enhanced supervision and consultation to ensure their proper use. Additionally, hospitals should integrate the quality of TCM intravenous formulations into clinical safety monitoring systems to enable traceability (Peng and Li, 2019). Assigning specialized TCM pharmacists to systematically manage these formulations can further enhance oversight and safety. Research has shown that pharmacist involvement in prescription review, dispensing, drug preparation, and patient counseling significantly reduces the incidence of adverse reactions (Deng et al., 2024). Therefore, hospitals should establish standardized management systems for TCMi and foster effective communication between pharmacists, clinical doctors, and patients to reduce the incidence of adverse reactions.

In summary, this study has the following characteristics compared to previous meta-analyses on TCMi (Mensah et al., 2023): The TCMi included in this study all possess the function of tonifying qi. This is because energy metabolism is one of the main therapeutic principles in TCM for treating AMI, reflecting the representativeness of this study (Suzuki et al., 2023). This study primarily focuses on the observing mortality rate. Meta-analyses of TCMi with mortality, a hard endpoint, as the primary outcome have been relatively rare. The conclusions of this study will provide a more valuable reference for clinical decision-making by healthcare professionals.

The present study underwent a rigorous research process, adhering strictly to a pre-registered protocol. Nonetheless, this meta-analysis still has certain limitations (Mensah et al., 2023): Regarding methodological quality, the overall quality of the included studies is suboptimal, particularly due to insufficient reporting of random sequence generation, allocation concealment methods, blinding implementation, medical follow-up, and independent assessment of the purity/potency of the TCMi-TQ utilized in the studies. These factors may introduce risks of selection bias and performance bias. Researchers

should adhere to RCT design standards (Chan et al., 2013) and reporting guidelines (Butcher et al., 2022). In future clinical studies, independent collaborative laboratories should be incorporated, utilizing advanced technologies such as HPLC and GC-MS to assess the purity and efficacy of TCMi-TQ, accurately identify and quantitatively analyze active ingredients, and promote the scientific and standardized generation of high-quality clinical evidence in TCM. This will enhance the rigor and reliability of clinical trials (Suzuki et al., 2023). Regarding long-term efficacy, the included studies fail to evaluate long-term mortality, which limits the assessment of the long-term prognosis of AMI patients receiving TCMi-TQs. It is recommended to expand the evaluation of long-term survival outcomes in AMI patients who receive TCMi-TQs. This would provide a more comprehensive assessment of the clinical significance and practical application value of these treatments (National Center Cardiovascular Diseases, 2024). Regarding heterogeneity, there is notable heterogeneity in the results concerning LVEF, thereby affecting the certainty of the outcomes. These discrepancies may stem from variations in ultrasound equipment and technical standards for LVEF evaluation. To minimize the impact of human factors and ensure consistent, reliable results, it is recommended to enhance the standardization of ultrasound equipment and evaluation techniques (Roger et al., 2010). Regarding the generalizability of research results, all the included studies were conducted within China and involved a single ethnic group. While our findings provide a preliminary foundation for multicenter research, further evaluation is necessary to determine the generalizability of the conclusions. We recommend conducting multicenter trials outside of China to generate more reliable and generalizable clinical evidence.

5 Conclusion

The present study proposes that integrating TCMi-TQ with conventional biomedicine treatment has a favorable impact on reducing mortality rates, the incidence of malignant arrhythmias, the incidence of adverse events, and enhancing cardiac function among patients with AMI. Given the low methodological quality observed in the included studies, it is imperative to approach this conclusion with caution. Nevertheless, these findings hold significant potential for informing clinical practice guidelines, and we look forward to achieving the scientific integration of TCMi-TQ with standard care in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

HwZ: Conceptualization, Formal Analysis, Methodology, Validation, Visualization, Writing–original draft. JC: Conceptualization, Formal Analysis, Methodology, Validation, Writing–original draft. HL: Funding acquisition, Methodology, Supervision, Writing–review and editing. XL: Funding acquisition, Methodology, Supervision, Writing–review and editing. HqZ: Formal Analysis, Investigation, Writing–review and editing. SZ: Investigation, Writing–review and editing. YS: Formal Analysis, Investigation, Writing–review and editing. YL: Investigation, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by Grants from the National Natural Science Foundation of China (No. 82104767, No. 82174315); Beijing major and difficult diseases collaborative research project of traditional Chinese and Western medicine (No. 2023BJSZDYNJBXTGG-011); Beijing "The Fourteenth Five-Year" key specialty of Traditional Chinese Medicine cardiovascular Department (demonstration class) (BJZKLC0011); Research and Translational Application of Clinical Specialized Diagnosis and Treatment Techniques in the Capital (No. Z221100007422127); Scientific Research Program of Hebei Provincial Administration of Traditional Chinese Medicine (No. B2025055); And Training Fund for Open Projects at Clinical Institutes and Departments of Capital Medical University (No. CCMU2024ZKYXY012); Youth Talent Support Project of the Chinese Association of Traditional Chinese Medicine (No. CACM-2024-QNRC2-B20); Beijing Traditional Chinese Medicine New Era 125 Project Promotes Talents. Capital Health Development Research Special Project (No. 2022-1-2231).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1511486/full#supplementary-material

References

Author Anonymous (2020). Expert consensus on prevention and treatment of heart failure after myocardial infarction. *Chin. Cardiocirc. J. Chin.* (35), 1166–1180. doi:10.3969/j.issn.1000-3614.2020.12.002

Bai, Y. K., Wang, Y. H., Hao, Y. L., Liang, Y. Q., and Li, X. X. (2002). Clinical observation of 999 Shenmai injection and western medicine on 62 patients with acute myocardial infarction. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.*, 285–286. doi:10.3969/j.issn.1008-8849.2002.04.003

Berg, R. A., Sanders, A. B., Kern, K. B., Hilwig, R. W., Heidenreich, J. W., Porter, M. E., et al. (2001). Adverse hemodynamic effects of interrupting chest compressions for rescue breathing during cardiopulmonary resuscitation for ventricular fibrillation cardiac arrest. *Circulation* 104, 2465–2470. doi:10.1161/hc4501.098926

Bo, B. J., Tian, Y. C., Kang, X. Q., Qiao, Y. G., and Zhao, D. (2018). Effect of Shenfu injection on Ca^{2+} and KATP channels in MIRI rats. *Clin. Res. Pract. Chin.* 3, 5–6. doi:10.19347/j.cnki.2096-1413.201826002

Butcher, N. J., Monsour, A., Mew, E. J., Chan, A. W., Moher, D., Mayo-Wilson, E., et al. (2022). Guidelines for reporting outcomes in trial reports: the consort-outcomes 2022 extension. *JAMA* 328, 2252–2264. doi:10.1001/jama.2022.21022

Cao, J. C., Guo, L., and Sun, Q. Y. (2022). Curative effect of shenmai injection combined with western medicine on No-reflow after PCI in patients with acute myocardial infarction and its effect on myocardial injury and oxidative stress. *J. New Chin. Med. Chin.* 54, 48–52. doi:10.13457/j.cnki.jncm.2022.15.010

Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., et al. (2013). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 346 (8), e7586. doi:10.1136/bmj.e7586

Chen, G. L. (2021). Ginseng-assisted intravenous thrombolysis in acute ST-segment elevation myocardial infarction. Practical Clinical J of Integr. *Tradit. Chin. West. Med. (Chin.)* 21, 64–65. doi:10.13638/j.issn.1671-4040.2021.13.031

Chen, H., Ceng, X. T., Gu, W. J., Bai, Z. G., and Gu, Y. H. (2018). The introduction of using new version of guideline development tool (GRADE pro GDT) in the systematic reviews of the intervention studies. *Chin. J. Evid. Based Med. Chin.* 18, 1135–1142.

Chen, J. D., Zhang, L. T., Chen, X. H., and Qian, J. (2015). Clinical observation on Astragalus injection for treatment of acute myocardial infarction after percutaneous coronary intervention. *Chin. J. Integr. Med. Cardio/Cerebrovasc. Dis. Chin.* 17, 1924–1926. doi:10.3969/j.issn.1672-1349.2015.17.002

Chen, Q. T. (2017). Effect of Shengmai injection on cardiac function after PCI in patients with ST-segment elevation myocardial infarction. Bachelor's degree. Qingdao (China): Qingdao University.

Chen, W. J., Zeng, W. T., Hong, J. L., Guo, S. B., and Zhang, M. Y. (2003). The effect of shenfu injection on left heart function in patients with acute myocardial infarction--with a report of 40 cases. *New Med. Chin.*, 746–747. doi:10.3969/j.issn.0253-9802.2003.12.016

Chen, Y. J., and Qiao, W. (2018). Effects of shenfu injection on cardiac function in patients with acute myocardial infarction. *J. Rare Uncommon Dis. (Chin.)* 25, 11–13. doi:10.3969/j.issn.1009-3257.2018.06.005

Chen, Z. Y., Liu, Y., Wei, Y., Deng, L. Y., and Zhang, Q. (2022). Efficacy of traditional Chinese medicine injection in preventing oxaliplatin-induced peripheral neurotoxicity: an analysis of evidence from 3598 patients. *Evid. Based Complement. Altern. Med.* 2022, 6875253. doi:10.1155/2022/6875253

Cui, J. D., and Li, X. F. (2006). Clinical observation on 38 cases of acute myocardial infarction treated with auxiliary treatment of Shengmai injection. *J. Pract. Med. Tech. Chin.*, 3598–3599. doi:10.3969/j.issn.1671-5098.2006.20.055

Deeks, J. J., Higgins, J. P. T., and Altman, D. G. (2023). On behalf of the Cochrane statistical methods group Cochrane handbook for systematic reviews of interventions. in *Chapter 10: analysing data and undertaking meta-analyses*. Available online at: https://training.cochrane.org/handbook/archive/v6.4/chapter-10 (Accessed October 1, 2024).

Deng, S. Q., Luo, X. H., and Xu, D. L. (2024). Analysis of the effect of pharmacist intervention on the rational use of traditional Chinese medicine injections. *Chin. Sci. Technol. J. Database (Abstr. Ed.) Med. Health (Chin.)* (10), 153–156.

Ding, L., and Xu, M. H. (2006). Clinical observation on the adjuvant treatment of acute myocardial infarction complicated with cardiogenic shock with Shengmai Injection. *Gansu Tradit. Chin. Med. Chin.* 19, 11. doi:10.3969/j.issn.1004-6852.2006.08.006

Dong, Z., Zhao, P., Xu, M., Zhang, C., Guo, W., Chen, H., et al. (2017). Astragaloside IV alleviates heart failure via activating PPARα to switch glycolysis to fatty acid β-oxidation. *Sci. Rep.* 7, 2691. doi:10.1038/s41598-017-02360-5

Du, Y. K. (2017). Clinical study of Shenmai injection combined with thrombolytic therapy legislation riverstone anterior wall acute myocardial infarction reperfusion injury. *Shaanxi J. Tradit. Chin. Med. Chin.* 38, 171–173. doi:10.3969/j.issn.1000-7369.2017.02.015

Egger, M., Davey, S. G., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629–634. doi:10.1136/bmj.315.7109.629

Eldar, M., Ohad, D., Bor, A., Varda-Bloom, N., Swanson, D. K., and Battler, A. (1994). A closed-chest pig model of sustained ventricular tachycardia. *Pacing Clin. Electrophysiol.* 17, 1603–1609. doi:10.1111/j.1540-8159.1994.tb02353.x

Eryol, N. K., Topsakal, R., Oguzhan, A., Abaci, A., Basar, E., Ergin, A., et al. (2002). Is the change of late potential over time related to enzyme levels? Ischemic burden in acute myocardial infarction. *Ann. Noninvasive Electrocardiol.* 7, 242–246. doi:10.1111/j.1542-474x.2002.tb00170.x

Feng, J. P., Liang, M. F., Wang, Y. H., and Yan, W. (2019). Effect analysis on Shenfu Injection combined with enoxaparin sodium in treatment of acute myocardial infarction complicated with heart failure. *Drug Eval. Res. Chin.* 42, 2057–2061. doi:10.7501/j.issn.1674-6376.2019.10.028

Feng, Q. L., Yao, A. Q., and Dang, Y. H. (2011). Effect of shenfu injection on ventricular remodeling in patients with acute myocardial infarction and clinical observations. *J. Emerg. Trad. Chin. Med. Chin.* 20, 1183–1184. doi:10.3969/j.issn.1004-745X.2011.07.101

Gao, R., Weng, W. L., and Li, R. (2012). The principle and methods of reasonable application of traditional Chinese medicine injection. China licens. *Pharm. Chin.* 9, 5–8. doi:10.3969/j.issn.1672-5433.2012.12.002

GBD 2013 Mortality and Causes of Death Collaborators (2015). Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 385, 117–171. doi:10.1016/S0140-6736(14)61682-2

Guan, J., Huang, F. K., Zhou, Y. L., Li, B. Q., Chen, Y. W., Wang, Y., et al. (2023). Research progress on the mechanism of astragaloside IV in preventing ischemia hypoxia myocardial injury in patients with heart failure. *Pract. J. Card. Cereb. Pneumal Vasc. Dis. Chin.* 31, 111–114. doi:10.12114/j.issn.1008-5971.2023.00.180

Guo, H., Zhu, M., Yu, R., Li, X. Y., and Zhao, Q. F. (2023). Efficacy of Chinese traditional patent medicines for heart failure with preserved ejection fraction: a Bayesian network meta-analysis of 64 randomized controlled trials. *Front. Cardiovasc Med.* 10, 1255940. doi:10.3389/fcvm.2023.1255940

Guo, S. (2014). Study on the myocardial protective effect of shenmai injection on patients with acute myocardial infarction after emergency PCI surgery. Bachelor's degree. Henan (China): Xinxiang Medical University, 7–14.

Guo, S. P., and Zhang, Y. Z. (1999). Antimyocardial thwarting effect of shenmai injection in urokinase thrombolysis for acute myocardial infarction. *Acta Acad. Med. Weifang Chin.* 21, 271–273.

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., et al. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336, 924–926. doi:10.1136/bmj.39489.470347.AD

Han, G. J., Ma, Z. X., Xue, X. R., Lu, L. Y., and Zhang, Y. (2000). Effect of astragalus injection on reperfusion injury in acute myocardial infarction treated with intravenous thrombolysis. *Chin. J. Integr. Tradit. West. Med. Intensive Crit. Care (Chin)*, 107–108. doi:10.3321/j.issn:1008-9691.2000.02.015

Han, G. M., Han, X. Y., and Meng, Y. H. (2003). Twenty-one cases of acute myocardial infarction with western and traditional Chinese medicine. *Shandong J. Tradit. Chin. Med. Chin.*, 485–487. doi:10.16295/j.cnki.0257-358x.2003.08.028

Hao, L. N., Pei, G. X., and Li, Y. P. (2021). Effect of shenfu injection on myocardial reinfusion TIMI flow grading and fibrinolytic indexes in patients undergoing PCI for AMI. *Chin. J. Conval. Med. Chin.* 30, 429–431. doi:10.13517/j.cnki.ccm.2021.04.035

He, C. F., Ji, Q. J., Zhang, L., Xie, X. F., Han, X. L., and Li, C. (2016). Investigate the influence on cardiac structure and function of patients with acute myocardial infarction treated with Shenmai combined with tirofiban after interventional therapy. *J. Clin. Emerg. Chin.* 17, 671–674. doi:10.13201/j.issn.1009-5918.2016.09.004

Heinrich, M., Jalil, B., Abdel-Tawab, M., Echeverria, J., Kulić, Ž., McGaw, L. J., et al. (2022). Best Practice in the chemical characterisation of extracts used in pharmacological and toxicological research-The ConPhyMP-Guidelines. *Front. Pharmacol.* 13, 953205. doi:10.3389/fphar.2022.953205

Heusch, G., and Gersh, B. J. (2017). The pathophysiology of acute myocardial infarction and strategies of protection beyond reperfusion: a continual challenge. *Eur. Heart J.* 38, 774–784. doi:10.1093/eurheartj/ehw224

Higgins, J. P. T., Li, T. J., and Deeks, J. J. (2023). *Chapter 6: choosing effect measures and computing estimates of effect*. Available online at: https://training.cochrane.org/handbook/archive/v6.4/chapter-06 (Accessed October 1, 2024).

Hou, Y., Chen, Z. H., Wang, Y., Yang, L., and Wu, Y. X. (2012). Impact of Huangqi injection on inflammation and ventricular remodeling in patients with acute myocardial infarction. *J. Clin. Cardiol. Chin.* 28, 766–768.

Hu, J., Zhang, L., Fu, F., Lai, Q., Zhang, L., Tao, L., et al. (2022). Cardioprotective effect of ginsenoside Rb1 via regulating metabolomics profiling and AMP-activated protein kinase-dependent mitophagy. *J. Ginseng Res.* 46, 255–265. doi:10.1016/j.jgr.2021.06.011

Huang, Y., Kwan, K., Leung, K. W., Wang, H., Kong, X. P., Dong, T., et al. (2018). The extracts and major compounds derived from Astragali Radix alter mitochondrial bioenergetics in cultured cardiomyocytes: comparison of various polar solvents and compounds. *Int. J. Mol. Sci.* 19, 1574. doi:10.3390/ijms19061574

Huang, Y., Zhang, K., Jiang, M., Ni, J., Chen, J., Li, L., et al. (2020). Regulation of energy metabolism by combination therapy attenuates cardiac metabolic remodeling in heart failure. *Int. J. Biol. Sci.* 16, 3133–3148. doi:10.7150/ijbs.49520

Huang, Y. W., Lin, B., and Zhang, M. Y. (2015). Observation of shenmai injection and atorvastatin in treatment of patients with acute myocardial infarction. *Chin. Arch. Tradit. Chin. Med. Chin.* 33, 2558–2560. doi:10.13193/j.issn.1673-7717.2015.10.079

Jaiswal, V., Wajid, Z., Suresh, V., Hanif, M., Rajak, K., Halder, A., et al. (2023). Procedural safety of transcatheter aortic valve replacement with Portico valve: a systematic review. *Int. J. Surg.* 109, 3602–3608. doi:10.1097/JS9.0000000000000645

Ji, F., Ren, Y. L., Zhang, Y. B., and Chen, X. B. (2021). Application of shenmai injection in patients with ST-segment elevation myocardial infarction with deficiency of both qi and yin. *World Chin. Med. Chin.* 16, 643–647. doi:10.3969/j.issn.1673-7202.2021.04.021

Ji, X. F., Yang, L., Zhang, M. Y., Li, C. S., Wang, S., and Cong, L. H. (2011). Shen-fu injection attenuates postresuscitation myocardial dysfunction in a porcine model of cardiac arrest. *Shock* 35, 530–536. doi:10.1097/SHK.0b013e31820e2058

Jia, F. Y., Gao, S. W., Zhang, Q., Pang, J. Z., and Xu, Q. (2023). Meta-analysis of efficacy and safety of Shenfu Injection combined with conventional western medicine in treatment of acute myocardial infarction after PCI. *Drug Eval. Res. Chin.* 46, 1323–1333. doi:10.7501/j.issn.1674-6376.2023.06.021

Jia, P., Zi, H. Y., and Ceng, Y. J. (2016). Influence of Shenfu injection on effect and endothelial function in patients with acute inferior wall ST-elevation myocardial infarction complicated with hypotension after percutaneous coronary intervention. *China Med. Chin.* 11, 789–792. doi:10.3760/cma.j.issn.1673-4777.2016.06.002

Jiang, M., Kang, L., Wang, Y., Zhao, X., Liu, X., Xu, L., et al. (2014). A metabonomic study of cardioprotection of ginsenosides, schizandrin, and ophiopogonin D against acute myocardial infarction in rats. *BMC Complement. Altern. Med.* 14, 350. doi:10.1186/1472-6882-14-350

Jiang, M., Wang, Q., Chen, J., Wang, Y., Fan, G., and Zhu, Y. (2017). Comparative metabonomics of Wenxin Keli and Verapamil reveals differential roles of gluconeogenesis and fatty acid β-oxidation in myocardial injury protection. *Sci. Rep.* 7, 8739. doi:10.1038/s41598-017-09547-w

Jin, Y., Chen, Q., Li, X., Fan, X., and Li, Z. (2014). Astragali Radix protects myocardium from ischemia injury by modulating energy metabolism. *Int. J. Cardiol.* 176, 1312–1315. doi:10.1016/j.ijcard.2014.07.154

Jin, Y. Y., Gao, H., Yan, Y., and Zhang, H. (2017). The effect of Shenfu injection on IL-6 and TNF - α in patients with acute ST segment elevation myocardial infarction complicated by cardiogenic shock. *Chin. J. Integr. Med. Cardio/Cerebrovasc. Dis. Chin.* 15, 59–63. doi:10.3969/j.issn.1672-1349.2017.01.016

Jin, Y. Z. (2013). A case of ventricular tachycardia induced by shengmai injection. *Chin. J. Trauma Disabil. Med. Chin.* 21, 220–221.

Kang, W. L. (2017). Clinical efficacy analysis of shenfu injection in the treatment of patients with acute myocardial infarction. *Chin. Prim. Health Care (Chin)* 31, 82–83. doi:10.3969/j.issn.1001-568X.2017.07.0034

Lan, Z., Tuo, P., Gao, Y. G., Li, B., Yan, N. Z., Chen, X. H., et al. (2021). Study on the efficacy of shenfu injection combined with sodium creatine phosphate in the treatment of acute ST-segment elevation inferior wall myocardial infarction. J. Emerg. Trad. *Chin. Med. Chin.* 30, 1374–1377. doi:10.3969/j.issn.1004-745X.2021.08.014

Li, D. K., Zhu, J., Hu, X. L., Gao, Z., Xing, G., and Yu, L. F. (2017). Clinical efficacy of shenfu injection and reteplase in the treatment of acute ST elevation myocardial infarction. *Chin. J. Integr. Med. Cardio/Cerebrovasc. Dis. (Chin)* 15, 3007–3010. doi:10.3969/j.issn.1672-1349.2017.23.019

Li, G. Y. (2013). Clinical study on the intervention of shenfu injection in the formation of ventricular wall tumor in patients with acute myocardial infarction. *Chin. Manip. and Rehabilit. Med. (Chin.)* 4, 36–39. doi:10.3969/j.issn.1008-1879.2013.03.018

Li, N., and Cheng, W. L. (2014). Clinical research of Shenfu Injection used in treating acute myocardial infarction accompanied right heart failure. *China J. Tradit. Chin. Med. Pharm. Chin.* 29, 3061–3063.

Li, Q., Zhang, S., Yang, G., Wang, X., Liu, Y., Chen, Y., et al. (2023). Energy metabolism: a critical target of cardiovascular injury. *Biomed. Pharmacother.* 165, 115271. doi:10.1016/j.biopha.2023.115271

Li, Q. H., Deng, X., Zhou, X. Y., and Jiang, H. M. (2016). Influence of shenmai injection on myocardia of patients with acute myocardial infarction after PCI operation. Henan tradit. *Chin. Med. Chin.* 36, 430–433. doi:10.16367/j.issn.1003-5028.2016.03.0187

Li, R., and Hou, A. J. (2017). Clinical study of shenfu injection in the treatment of acute myocardial infarction with pump failure. *Clin. J. Tradit. Chin. Med. Chin.* 29, 1874–1877. doi:10.16448/j.cjtcm.2017.0622

Li, S. G. (2016). Clinical study on the treatment of combined cardiogenic shock after PCI for acute myocardial infarction with shenfu injection. Asia-Pacific Tradit. *Med. Chin.* 12, 140–141. doi:10.11954/ytctyy.201617067

Li, W. D. (2015a). Treatment of acute myocardial infarction with heart failure with injection of reference. *Jilin J. Tradit. Chin. Med. Chin.* 35, 901–903. doi:10.13463/j.cnki.jlzyy.2015.09.011

Li, Y., Ruan, X., Xu, X., Li, C., Qiang, T., Zhou, H., et al. (2019). Shengmai injection suppresses angiotensin II-induced cardiomyocyte hypertrophy and apoptosis via activation of the AMPK signaling pathway through energy-dependent mechanisms. *Front. Pharmacol.* 10, 1095. doi:10.3389/fphar.2019.01095

Li, Y. F. (2015b). Analysis of the clinical efficacy of ginseng injection applied to rescue the early stage of acute extensive anterior wall myocardial infarction in emergency medical treatment. *China Health Care and Nutr. (Chin)* 25, 120–121.

Li, Z. E. (2006). A clinical study on the treatment of acute myocardial infarction (ST elevation type) complicated with left heart failure by different dosage of shenfu injection. *J. New Chin. Med. Chin.*, 19–20. doi:10.13457/j.cnki.jncm.2006.06.012

Li, Z. M., Hu, Q., Mao, Y., and Li, H. J. (2010). Effect of shenfu injection with conventional therapy on heart failure in elderly patients with myocardial infarction. *Chin. J. Integr. Med. Chin.* 30, 996–998.

Liang, W. S. (2006). Clinical study on the treatment of acute myocardial infarction in the elderly by combining Chinese and Western medicine. *China Med. Chin.*, 275–277. doi:10.3760/cma.j.issn.1673-4777.2006.05.010

Lin, F., Guo, L. L., and Wang, J. (2014). Explaining the role of qi in Chinese medicine based on the function of mitochondria. *Chin. J. Integr. Med. Chin.* 34, 903–906. doi:10.7661/CJIM.2014.08.0903

Liu, B. F. (2012). Clinical efficacy of 20 cases of acute inferior wall combined right ventricular myocardial infarction treated with traditional Chinese and western medicines. *World Health Dig. Chin.* 9, 118–119. doi:10.3969/j.issn.1672-5085.2012.29.108

Liu, G. S. (2016). Effectiveness and pharmacologic analysis of shenmai injection in the treatment of acute myocardial infarction. *Strait Pharm. J. Chin.* (28), 99–100. doi:10.3969/j.issn.1006-3765.2016.01.042

Liu, L. L. (2018). Effect of shenfu injection combined with simvastatin on cardiac function indexes in patients with acute myocardial infarction combined with diabetes mellitus. *J. Pract. Diabetology (Chin.)* 14, 23–24.

Liu, L. L., and Tu, X. X. (2016). Observation on the effect of using shenmai injection before percutaneous coronary intervention in patients with acute myocardial infarction. *J. New Chin. Med. Chin.* 48, 24–26. doi:10.13457/j.cnki.jncm.2016.10.010

Liu, S. K., Liu, Y., and Wang, Y. Y. (2004). Study of effect of Shen Mai injection on acute myocardial infarction. *China J. Mod. Med. Chin.*, 108–109. doi:10.3969/j.issn.1005-8982.2004.05.035

Long, S. E. (2007). Clinical observation on 32 cases of acute myocardial infarction combined with heart failure treated with the aid of shenmai injection. *Guizhou Med. J. Chin.*, 1009–1010. doi:10.3969/j.issn.1000-744X.2007.11.025

Long, Z., Liu, W., Zhao, Z., Tong, S., Wang, L., Zhou, M., et al. (2022). Case fatality rate of patients with acute myocardial infarction in 253 chest pain centers - China, 2019-2020. *China CDC Wkly.* 4, 518–521. doi:10.46234/ccdcw2022.026

Lopaschuk, G. D., and Jaswal, J. S. (2010). Energy metabolic phenotype of the cardiomyocyte during development, differentiation, and postnatal maturation. *J. Cardiovasc Pharmacol.* 56, 130–140. doi:10.1097/FJC.0b013e3181e74a14

Lu, D. X., and Yao, W. Y. (2022). Analysis of the effect of Shengwei injection combined with dobutamine injection in the treatment of heart failure after acute myocardial infarction. *Proc. Clin. Med. (Chin.)* 31, 504–507. doi:10.16047/j.cnki.cn14-1300/r.2022.07.018

Lu, F. P., Su, N., Zheng, Z. M., Zhu, M. M., Shen, Y. J., Shi, H. F., et al. (2018). Shengmai Injection combined with conventional treatment for acute myocardial infarction: a systematic review and Meta-analysis. *Chin. Tradit. Herb. Drugs. (Chin.)* 49, 1201–1210. doi:10.7501/j.issn.0253-2670.2018.05.032

Lu, J. M. (2011). Application of shengmai injection and urokinase in acute myocardial infarction with thrombolytic therapy. *Natl. Med. Front. China (Chin.)* 6, 32–37. doi:10.3969/j.issn.1673-5552.2011.08.0018

Lu, M., Jiang, Y. Z., Zhang, X. H., Zhang, B. M., and Fu, S. P. (2005). Protective effects of Shengmai injection on myocardial ischemic reperfusion injury. *J. Jilin Univ. Med. Ed. Chin.* 3, 446–448. doi:10.3969/j.issn.1671-587X.2005.03.038

Lu, S. Q., and Xiang, C. Q. (2023). Protective effect of Shenfu injection based on mitochondrial target on myocardial injury. *China Med. Pharm. Chin.* 13, 51–54. doi:10.3969/j.issn.2095-0616.2023.06.014

Lu, Y., Li, S., Wu, H., Bian, Z., Xu, J., Gu, C., et al. (2015). Beneficial effects of astragaloside IV against angiotensin II-induced mitochondrial dysfunction in rat vascular smooth muscle cells. *Int. J. Mol. Med.* 36, 1223–1232. doi:10.3892/ijmm.2015.2345

Lu, Y. H. (2009). Clinical observation on the effect of urokinase combined with shengmai injection on left ventricular function in patients with acute myocardial infarction. *J. Clin. Exp. Med. Chin.* 8, 86–87. doi:10.3969/j.issn.1671-4695.2009.02.049

Luan, G. X., Zhao, X. L., and Zheng, X. (2022). Levosimendan combined with Shengmai injection for the treatment of pump failure in 55 patients with acute myocardial infarction. *Chin. J. Prim. Med. Pharm. Chin.* 29, 23–27. doi:10.3760/cma.j.issn.1008-6706.2022.01.006

Luo, S. (2016). Clinical study on the treatment of acute myocardial infarction by shenmai injection together with conventional therapy of western medicine. Asia-Pacific Tradit. *Med. Chin.* 12, 150–151. doi:10.11954/ytctyy.201618074

Ma, X. G., Wang, W. Q., and Zhang, J. L. (2019). Clinical efficacy of shenfu injection in the treatment of acute myocardial infarction combined with heart failure. *Gansu Med. J. Chin.* 38, 916–917.

Ma, X. S., Wang, Y. N., Peng, B., Cui, J., Wang, H. C., and Dong, Z. H. (2022). Effect of shenfu injection on serum sST2 in patients with acute myocardial infarction. *J. Emerg. Trad. Chin. Med. Chin.* 31, 2187–2190. doi:10.3969/j.issn.1004-745X.2022.12.030

McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Bohm, M., et al. (2021). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* 42 (42), 3599–3726. doi:10.1093/eurheartj/ehab368

Meng, F. S. (2014). Clinical observation on the treatment of acute extensive anterior wall myocardial infarction combined with left heart failure by shenfu injection. *J. Emerg. Trad. Chin. Med. Chin.* 23, 2002–2031. doi:10.3969/j.issn.1004-745X.2014.11.015

Mensah, G. A., Fuster, V., Murray, C. J. L., and Roth, G. A. (2023). Global burden of cardiovascular diseases and risks, 1990-2022. *J. Am. Coll. Cardiol.* 82, 2350–2473. doi:10.1016/j.jacc.2023.11.007

Mi, Z. Y., Li, Y. X., and Zhang, D. B. (2009). Observation on the efficacy of Astragalus injection in the treatment of acute myocardial infarction complicated with cardiogenic shock. *J. Emerg. Trad. Chin. Med. Chin.* 18, 1621–1647. doi:10.3969/j.issn.1004-745X.2009.10.032

Mo, C. R., and Zhao, K. M. (2002). Adjuvant treatment of acute myocardial infarction with heart failure by shenfu injection in 36 cases. *Chin. J. Integr. Med. Chin.*, 812. doi:10.7661/CJIM.2002.11.812

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., et al. (2015). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst. Rev.* 4, 1. doi:10.1186/2046-4053-4-1

Nasution, S. A., Alwi, I., Subekti, I., Yamin, M., Suhendro, S., Harimurti, K., et al. (2020). The role of acute hyperglycemia on the risk of malignant arrhythmia in acute myocardial infarction patients: a study of myocardial damage, ion channel changes and inflammatory factors. *Acta Med. Indones.* 52, 102–110.

National Center For ADR Monitoring C (2024). National adverse drug reaction surveillance annual report (2023). *Chin. J. Viral Dis. Chin.* 14, 204–210. doi:10.16505/j.2095-0136.2024.3002

National Center for Cardiovascular Diseases (2024). China DI. Report on cardiovascular health and diseases in China 2023: an updated summary. *Chin. Cardiocirc. J. Chin.* 39, 625–660. doi:10.3969/j.issn.1000-3614.2024.07.001

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Int. J. Surg.* 88, 105906. doi:10.1016/j.ijsu.2021.105906

Pei, J. N., Liu, J., Liang, Z. F., Wang, X. L., Li, W., and Guo, P. (2019). Clinical efficacy of combined Chinese and Western medicine in the treatment of acute anterior wall ST-segment elevation myocardial infarction. *Med. Inf. Chin.* 32, 166–167. doi:10.3969/j.issn.1006-1959.2019.08.052

Peng, G. P., and Li, C. Y. (2019). Thinking and analysis on the safety of traditional Chinese medicine injection. *J. Nanjing Univ. Tradit. Chin. Med. Chin.* 35, 744–751. doi:10.14148/j.issn.1672-0482.2019.0744

Piccini, J. P., Schulte, P. J., Pieper, K. S., Mehta, R. H., White, H. D., Van de Werf, F., et al. (2011). Antiarrhythmic drug therapy for sustained ventricular arrhythmias complicating acute myocardial infarction. *Crit. Care Med.* 39, 78–83. doi:10.1097/CCM.0b013e3181fd6ad7

Qi, Y. W., Wu, Z. R., and Feng, Z. Y. (2015a). Clinical observation on 60 cases of acute myocardial infarction treated with shenmai injection. *Guid. J. Tradit. Chin. Med. Pharmacol. Chin.* 21, 93–95. doi:10.13862/j.cnki.cn43-1446/r.2015.06.033

Qi, Y. W., Wu, Z. R., Ma, Z. G., Feng, Z. Y., and Liu, Y. X. (2015b). Treatment of acute myocardial infarction of ST-segment elevation type by shenmai combined with ritonril and its effect on ventricular function and plasma brain natriuretic peptide level. *Shaanxi J. Tradit. Chin. Med. Chin.* 36, 562–564. doi:10.3969/j.issn.1000-7369.2015.05.021

Qi, Y. W., Wu, Z. R., Ma, Z. G., Feng, Z. Y., Liu, Y. X., and Liu, B. L. (2015c). Action mechanism of adjuvant therapy of shenmai injection in treating acute ST-segment elevation myocardial infarction. *Chin. J. Exp. Tradit. Med. Formulae Chin.* 21, 195–198. doi:10.13422/j.cnki.syfjx.2015100195

Qin, G. Q. (2021). Clinical observation of left ximengdan combined with shenmai injection in the treatment of acute myocardial infarction with cardiogenic shock. *Chin. Health Care (Chin.)* 39, 83–85.

Qu, Y. Z. (2007). Effect of shenmai injection on Q-T dispersion in patients with acute myocardial infarction. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.*, 916–917. doi:10.3969/j.issn.1008-8849.2007.07.037

Roger, V. L., Weston, S. A., Gerber, Y., Killian, J. M., Dunlay, S. M., Jaffe, A. S., et al. (2010). Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation* 121, 863–869. doi:10.1161/CIRCULATIONAHA.109.897249

Shen, Y. X., Gao, H., and Ruan, G. A. (2006). Observation on the efficacy of shenfu injection in the treatment of acute myocardial infarction. *J. Qiqihar Univ. Med. Chin.*, 1038–1039. doi:10.3969/j.issn.1002-1256.2006.09.009

Shi, B. Z., Yang, M. H., Dong, Y., Dong, X., Wang, L., Li, Y. T., et al. (2018). Effect and mechanism study of Shenmai injection in treating acute ST-elevation myocardial infarction with cardiogenic shock. *Chin. J. Hosp. Pharm. Chin.* 38, 2459–2463. doi:10.13286/j.cnki.chinhosppharmacyj.2018.23.16

Shi, J., and Li, S. F. (2016). Clinical study on the adjuvant treatment of acute myocardial infarction with shenmai injection. *Chin. J. Clin. Pharmacol. (Chin.)* 32, 2222–2224. doi:10.13699/j.cnki.1001-6821.2016.24.003

Shi, L., and Lin, L. (2019). The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. *Med. Baltim.* 98, e15987. doi:10.1097/MD.0000000000015987

Song, C. J. (2018). Effect of Shengmai injection combined with routine treatment on cardiogenic shock after AMI and its influence on cardiac function, serum cTnI, cTnI-mRNA, CaM and urine volume. *Clin. Res. Pract. (Chin.)* 3, 108–110. doi:10.19347/j.cnki.2096-1413.201806052

Spatz, E. S., Wang, Y., Beckman, A. L., Wu, X., Lu, Y., Du, X., et al. (2018). Traditional Chinese medicine for acute myocardial infarction in western medicine hospitals in China. *Circ. Cardiovasc Qual. Outcomes* 11, e004190. doi:10.1161/CIRCOUTCOMES.117.004190

Sterne, J., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 366, l4898. doi:10.1136/bmj.l4898

Su, N., Lu, F. P., Zhu, M. M., Zheng, Z. M., Shi, H. F., and Shen, Y. J. (2017). Meta-analysis of Astragalus injection in the treatment of myocardial infarction. *Lishizhen Med. Mater. Medica Res. Chin.* 28, 3009–3013.

Sun, L. (2019). Shenmai injection as an adjunct in the treatment of acute myocardial infarction. *Chin. Pract. Med. Chin.* 14, 102–104. doi:10.14163/j.cnki.11-5547/r.2019.36.054

Suzuki, T., Kataoka, Y., Shiozawa, M., Morris, K., Kiyoshige, E., Nishimura, K., et al. (2023). Heart-brain team approach of acute myocardial infarction complicating acute stroke: characteristics of guideline-recommended coronary revascularization and antithrombotic therapy and cardiovascular and bleeding outcomes. *J. Am. Heart Assoc.* 12, e027156. doi:10.1161/JAHA.122.027156

Tang, F. N. (2019). Effect of treatment with Shengmai Injection combined with tirofiban on vascular endothelial and fibrinolytic function in patients with acute myocardial infarction. *Med. J. Commun. Chin.* 33, 48–49. doi:10.19767/j.cnki.32-1412.2019.01.017

Thiele, H., Akin, I., Sandri, M., Fuernau, G., de Waha, S., Meyer-Saraei, R., et al. (2017). PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N. Engl. J. Med.* 377, 2419–2432. doi:10.1056/NEJMoa1710261

Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Alonso, A., Beaton, A. Z., Bittencourt, M. S., et al. (2022). Heart disease and stroke statistics-2022 update: a report from the American heart association. *Circulation* 145, e153–e639. doi:10.1161/CIR.0000000000001052

Wang, A., Song, Q., Li, Y., Fang, H., Ma, X. J., Li, Y. X., et al. (2024a). Effect of traditional Chinese medicine on metabolism disturbance in ischemic heart diseases. *J. Ethnopharmacol.* 329, 118143. doi:10.1016/j.jep.2024.118143

Wang, A. J., Sun, L., Li, M., Li, J., Lu, S. Q., and Zhang, F. B. (2021a). Study on the efficacy and mechanism of shenmai injection combined with western drugs in patients with acute myocardial infarction. *Prog. Mod. Biomed. Chin.* 21, 100–103. doi:10.13241/j.cnki.pmb.2021.01.021

Wang, C. L., and Qing, L. J. (2017). Clinical observation on the treatment of combined pump failure after PCI for acute myocardial infarction by shenfu injection combined with dopamine continuous sedation. *J. Guangxi Univ. Chin. Med. Chin.* 20, 7–09. doi:10.3969/j.issn.2095-4441.2017.02.003

Wang, G. H. (2019). Effects of shenmai injection on acute myocardial infarction and serum hs-CRP and PCT levels. *Clin. Res. Chin.* 27, 123–124.

Wang, G. Y., Yang, H. X., Wang, X. H., Ma, Y., Mei, X. Y., and Wu, H. X. (2023). Research approaches and methods of basic theory of traditional Chinese medicine. *China J. Tradit. Chin. Med. Pharm. Chin.* 38, 691–694.

Wang, H., Liu, J. S., and Xu, S. X. (2017). Myocardial and microvascular protection by shenmai injection after percutaneous coronary intervention in patients with acute myocardial infarction. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.* 26, 1201–1203. doi:10.3969/j.issn.1008-8849.2017.11.019

Wang, H. Y., Zhang, F. C., Zhang, L. M., Li, T. T., and Zhang, M. L. (2018a). Effect of recombinant human brain natriuretic peptide combined with Shenfu injection in the treatment of acute myocardial infarction complicated with acute heart failure. *J. Bengbu Med. Coll. Chin.* 43, 59–64. doi:10.13898/j.cnki.issn.1000-2200.2018.01.018

Wang, J. (2016). Effects of shenmai injection combined with rehabilitation training on cardiac function and left ventricular remodeling in patients with acute myocardial infarction and its mechanism. *J. Tradit. Chin. Med. Univ. Hunan Chin.* 36, 498–499.

Wang, J., Lin, F., Zeng, M., Liu, M., Zheng, M., Ren, Y., et al. (2024b). Intraoperative blood pressure and cardiac complications after aneurysmal subarachnoid hemorrhage: a retrospective cohort study. *Int. J. Surg.* 110, 965–973. doi:10.1097/JS9.0000000000000928

Wang, J., Wang, T., Yang, B., Chen, Y., Gao, P., Wang, Y., et al. (2024c). Impact of acute silent ischemic lesions on clinical outcomes of carotid revascularization. *Int. J. Surg.* 110, 974–983. doi:10.1097/JS9.0000000000000925

Wang, J. B., and Huang, Y. T. (2017). Clinical effect of urokinase thrombolysis combined with Shenmai injection in the treatment of acute anterior wall infarction. *J. Logist. Univ. Pap. Med. Sci. Chin.* 26, 584–586. doi:10.16548/j.2095-3720.2017.07.009

Wang, L. M., Gao, C. J., Xie, L. C., and Gao, B. (2019a). Clinical study on the treatment of acute myocardial infarction with heart failure by Shengmai Injection combined with

lyophilized recombinant human brain natriuretic peptide. Chin. *J. Integr. Med. Cardio/ Cerebrovasc. Dis. (Chin.)* 17, 3553–3556. doi:10.12102/j.issn.1672-1349.2019.22.026

Wang, Q., Yang, X., Song, Y., Sun, X., Li, W., Zhang, L., et al. (2021c). Astragaloside IV-targeting miRNA-1 attenuates lipopolysaccharide-induced cardiac dysfunction in rats through inhibition of apoptosis and autophagy. *Life Sci.* 275, 119414. doi:10.1016/j.lfs.2021.119414

Wang, R. L., Wang, H. Q., Fan, X. H., Duan, M. X., Li, H. Y., and Wang, S. F. (2020). Analysis of chemical constituents in shenmai injection by LC-Q-TOF-MS and LC-IT-MS. *Chin. J. Chin. Mater. Med. Chin.* 45, 555–564. doi:10.19540/j.cnki.cjcmm.20191002.308

Wang, S., Ye, L., and Wang, L. (2019c). Protective mechanism of shenmai on myocardial ischemia-reperfusion through the energy metabolism pathway. *Am. J. Transl. Res.* 11, 4046–4062.

Wang, S. M., Yang, L. F., and Wang, L. H. (2022). Traditional Chinese medicine enhances myocardial metabolism during heart failure. *Biomed. Pharmacother.* 146, 112538. doi:10.1016/j.biopha.2021.112538

Wang, X., Miao, H., Yan, Y., Guo, R., Gong, W., He, Y., et al. (2021b). Effect of shenfu injection on reperfusion injury in patients undergoing primary percutaneous coronary intervention for st segment elevation myocardial infarction: a pilot randomized clinical trial. *Front. Cardiovasc Med.* 8, 736526. doi:10.3389/fcvm.2021.736526

Wang, X., Wang, Y., Feng, X., Lu, Y., Zhang, Y., Wang, W., et al. (2016). Systematic review and meta-analysis of randomized controlled trials on Wenxin Keli. *Drug Des. Devel Ther.* 10, 3725–3736. doi:10.2147/DDDT.S112333

Wang, X., Wu, Y., Shen, L., Guo, Z. Q., Wang, X. F., Cui, X. Y., et al. (2010). Clinical study of prevention and treatment for reperfusion injury with Shengmai injection after acute myocardial infarction PCI. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.* 19, 3553–3554. doi:10.3969/j.issn.1008-8849.2010.28.002

Wang, X. F. (2008). Clinical study on the prevention and treatment of reperfusion injury after acute myocardial infarction intervention with Shengmai injection. Bachelor's degree. Beijing (China): Beijing University of Chinese Medicine.

Wang, X. Y., Liu, D. J., and Yin, Q. L. (2019b). Efficacy of shenmai injection in acute myocardial infarction and its effect on BNP, cTnT and cardiac function of patients. *J. Med. Theory Pract. (Chin.)* 32, 3443–3444. doi:10.19381/j.issn.1001-7585.2019.21.016

Wang, Y., Zhao, Y., Jiang, W., Zhao, X., Fan, G., Zhang, H., et al. (2018b). iTRAQ-based proteomic analysis reveals recovery of impaired mitochondrial function in ischemic myocardium by shenmai formula. *J. Proteome Res.* 17, 794–803. doi:10.1021/acs.jproteome.7b00450

Wang, Y. T. (2018). Recent efficacy and safety of recombinant human brain natriuretic peptide combined with shenfu injection in the treatment of acute myocardial infarction with heart failure. *World J. Integr. Tradit. West. Med. Chin.* 13, 108–111. doi:10.13935/j.cnki.sjzx.180130

Wang, Z. (2017). Exploration of the clinical value of Shengmai injection combined with alteplase in the treatment of acute myocardial infarction. *J. Med. Theory Pract. Chin.* 30, 193–194. doi:10.19381/j.issn.1001-7585.2017.02.015

Wang, Z., Ju, J. Q., and Li, Y. L. (2015). Systematic evaluation of the effect of shenmai injection on acute myocardial infarction morbidity and mortality and sequential analysis of the trial. *Chin. J. Exp. Tradit. Med. Formulae Chin.* 21, 189–193. doi:10.13422/j.cnki.syfjx.2015190189

Wei, D. X., and Liu, M. (2001). Treatment of acute myocardial infarction with intravenous thrombolysis plus intravenous shenmai injection. *Chin. J. Inf. Tradit. Chin. Med. Chin.*, 45–46.

Wei, J. J., Li, B., Zhu, M. J., Wang, Y. X., and Yu, R. (2021). Meta-analysis and trial sequential analysis of Shenmai Injection in the treatment of heart failure after acute myocardial infarction. *Chin. J. Hosp. Pharm. Chin.* 41, 2082–2090. doi:10.13286/j.1001-5213.2021.20.08

Wen, B. C. (2014). The efficacy of shenfu injections in combination with r-TPA intravenous thrombolysis in the treatment of acute myocardial infarction. *Int. Med. Health Guid. News Chin.* 20, 1738–1740. doi:10.3760/cma.j.issn.1007-1245.2014.12.033

Wu, M. X., and Li, Y. X. (1988). A case of ventricular arrhythmia and neck edema caused by intravenous danshen injection. *J. Henan Univ. Chin.* 356.

Wu, R. M., Jiang, B., Li, H., Bang, W. Z., Bao, W. L., Li, H. D., et al. (2020). A network pharmacology approach to discover action mechanisms of Yangxinshi Tablet for improving energy metabolism in chronic ischemic heart failure. *J. Ethnopharmacol.* 246, 112227. doi:10.1016/j.jep.2019.112227

Wu, Y. F., Chen, J. Q., and Liang, H. T. (2022). Effect of shenmai injection combined with ritongli in the treatment of acute myocardial infarction and its effect on patients' cardiac function and serum inflammatory factor. *J. N. Pharm. Chin.* 19, 64–66. doi:10.3969/j.issn.1672-8351.2022.05.020

Wu, Z. R., Qi, Y. W., and Li, H. Q. (2016). Effect of shenmai injection combined with ritongli on serum IL-6, TNF-α, and CRP in patients with acute ST-segment elevation myocardial infarction. *Shaanxi J. Tradit. Chin. Med. Chin.* 37, 29–30. doi:10.3969/j.issn.1000-7369.2016.01.015

Xian, W. (2019). Influence of recombinant human BNP combined Astragalus injection on heart function and serum levels of inflammatory factors in AMI patients with post-PCI heart failure. *Chin. J. Cardiovasc. Rehabilit. Med. Chin.* 28, 424–428. doi:10.3969/j.issn.1008-0074.2019.04.09

Xie, H. (2018). Effect of shenmai injection with thrombolytic therapy on AMI: impact on ventricular function, level of CRP, BNP, and IL -6. *World J. Integr. Tradit. West. Med. Inf. Tradit. Chin. Med. Chin.* 35, 94–97. doi:10.19656/j.cnki.1002-2406.180027

Xu, K. (2022). Clinical efficacy of Sheng Vein Injection after emergency PCI in patients with acute myocardial infarction. Bachelor's degree. Qingdao (China): Qingdao University.

Xu, X. J. (2018). Clinical effect of shenmai injection combined with clopidogrel in the treatment of acute myocardial infarction and the effect on cardiac function. *J. Guangxi Med. Univ. Chin.* 35, 255–257. doi:10.16190/j.cnki.45-1211/r.2018.02.031

Xuan, J. J., Gao, C. X., Guan, H. M., Jie, J. H., Chen, Y. S., Luo, M. H., et al. (2015). Long-term clinical efficacy of shenmai injection in the treatment of patients with heart failure after acute myocardial infarction. *Chin. Tradit. Pat. Med. Chin.* 37, 465–467. doi:10.3969/j.issn.1001-1528.2015.02.054

Yan, H., Hu, Z. Q., and Xu, G. (2017). Effect of shenfu injection on left ventricular remodeling and cardiac function in patients with early acute myocardial infarction. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.* 26, 52–54. doi:10.3969/j.issn.1008-8849.2017.01.017

Yan, J., Cheng, M. Y., Duan, Y., Wang, Z. R., Feng, H., and Xie, B. (2018). A clinical study on shenmai injection combined with batroxobin in the treatment of acute myocardial infarction. *Prog. Mod. Biomed. Chin.* 18, 4294–4297. doi:10.13241/j.cnki.pmb.2018.22.021

Yan, P. (2018). Protective effect on myocardial injury after thrombolytic therapy of acute ST-segment elevation myocardial infarction assisted by shenmai injection. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.* 27, 2788–2791.

Yang, F. F., Xing, Y. B., Guo, H. Y., Peng, F., Qiu, Y. F., Yuan, M., et al. (2017b). The intervention effect of Shenmai injection on endothelial dysfunction and apoptosis factors in non-ST elevation acute myocardial infarction. *Zhejiang J. Tradit. Chin. Med. Chin.* 5, 68–69. doi:10.3969/j.issn.0411-8421.2017.01.049

Yang, H. Y., Liu, M. L., Luo, P., Yao, X. S., and Zhou, H. (2022). Network pharmacology provides a systematic approach to understanding the treatment of ischemic heart diseases with traditional Chinese medicine. *Phytomedicine* 104, 154268. doi:10.1016/j.phymed.2022.154268

Yang, J. W., Hong, J. N., Fang, J., Xue, F., Ceng, X. P., and Jin, W. X. (2017a). Effect of shenmai injection combined with revascularization on cardiac function in patients with acute myocardial infarction complicated with heart failure. *Mod. Diagn. and Treat. (Chin.)* 28, 3346–3347. doi:10.3969/j.issn.1001-8174.2017.18.008

Yang, M. N., and Wang, P. P. (2021). Effect of Shenmai injection combined with levocarnitine on cardiac function and myocardial microcirculation in patients with ischemic cardiomyopathy and heart failure. *Clin. Res. Pract. Chin.* 6, 140–142. doi:10.19347/j.cnki.2096-1413.202115047

Yang, S. Q. (2014). Effect of shenfu injection on ultrasound cardiogram in patients of acute myocardial infarction combined with pump failure. *Chin. J. Postgrad. Med. Chin.* 37, 56–58. doi:10.3760/cma.j.issn.1673-4904.2014.19.020

Yang, X. Z., Zheng, Y., Guo, S. Q., Li, J. J., and Shang, S. Z. (2014). Clinical observation on intracoronary injection with shenmai injection and western medicine for No-reflow after percutaneous coronary intervention in patients with acute myocardial infarction. *J. Tradit. Chin. Med. Chin.* 55, 854–857. doi:10.13288/j.11-2166/r.2014.10.013

Yang, Y., Li, X., Chen, G., Xian, Y., Zhang, H., Wu, Y., et al. (2023). Traditional Chinese medicine compound (Tongxinluo) and clinical outcomes of patients with acute myocardial infarction: the CTS-AMI randomized clinical trial. *JAMA* 330, 1534–1545. doi:10.1001/jama.2023.19524

Yang, Z. Q., and Cai, L. L. (2016). Effects of Sheng Mai Injection on blood rheology and cardiac pump function in patients with myocardial infarction complicated with cardiac shock. *J. Clin. Emerg. Chin.* 17, 948–951. doi:10.13201/j.issn.1009-5918.2016.12.015

Ye, D. J. (2010). Effect of Shen Mai injection to prognosis and hemorheology on acute myocardial infarction. *Nei Mong. J. Tradit. Chin. Med. Chin.* 29, 1–02. doi:10.16040/j.cnki.cn15-1101.2010.16.023

You, S., and Wang, Y. M. (2019). Effects of Shenfu injection on hemorheology and neuroendocrine hormones in the treatment of acute myocardial infarction with acute heart failure. *Acta Med. Sin. Chin.* 32, 53–57. doi:10.19296/j.cnki.1008-2409.2019-01-015

Yu, H., Hu, Q., Sun, J., Feng, R., Zhang, S., Zhang, J. X., et al. (2019a). Analysis of chemical constituents in Astragalus injection based on ultra performance liquid chromatography-quadrupole-time of flight mass spectrometry. *World Chin. Med. Chin.* 14, 809–817. doi:10.3969/j.issn.1673-7202.2019.04.005

Yu, H. B., Yu, X. W., and Wu, N. B. (2010). Adjuvant therapeutic effect of shenmai injection in non-ST-segment elevation acute myocardial infarction. *Clin. J. Tradit. Chin. Med. Chin.* 22, 133–134. doi:10.16448/j.cjtcm.2010.02.035

Yu, S., Guo, Y. Y., Cao, J. W., and Zhai, X. F. (2023). Analysis of adverse reaction characteristics of Huoxue Huayu traditional Chinese medicine injection based on literature research. *Chin. J. Clin. Ration. Drug Use Chin.* 16, 9–13. doi:10.15887/j.cnki.13-1389/r.2023.10.003

Yu, X. P., Li, P. S., and Chen, K. Q. (2021). Exploration of the efficacy of shenmai injection combined with beta-blockers in the treatment of acute myocardial infarction and the effect on the QTd degree of electrocardiography. *Knowl. Cardiovasc. Dis. Prev Treat. (Chin.)* 11, 20–22. doi:10.3969/j.issn.1672-3015(x).2021.04.007

Yu, Y., Spatz, E. S., Tan, Q., Liu, S., Lu, Y., Masoudi, F. A., et al. (2019b). Traditional Chinese medicine use in the treatment of acute heart failure in western medicine hospitals in China: analysis from the China PEACE retrospective heart failure study. *J. Am. Heart Assoc.* 8, e012776. doi:10.1161/JAHA.119.012776

Yuan, X. H. (2009). Therapeutic efficacy of intravenous thrombolysis combined with shenmai injection in the treatment of acute myocardial infarction. *Chin. Mod. Med. Chin.* 16, 56–59. doi:10.3969/j.issn.1674-4721.2009.10.034

Zang, Y., Wan, J., Zhang, Z., Huang, S., Liu, X., and Zhang, W. (2020). An updated role of astragaloside IV in heart failure. *Biomed. Pharmacother.* 126, 110012. doi:10.1016/j.biopha.2020.110012

Zeng, Y. L. (2005). Adjuvant treatment of acute myocardial infarction with heart failure in 54 cases with shenfu injection. *Chin. Pract. J. Rural. Dr. Chin.*, 31–32. doi:10.3969/j.issn.1672-7185.2005.01.019

Zhan, D. S., and Cui, X. Y. (2023). Effect of Shenmai Injection combined with Ticagrelor in patients with acute myocardial infarction. *Chin. Mod. Med. Chin.* 30, 118–121. doi:10.3969/j.issn.1674-4721.2023.32.030

Zhan, S., Fan, X., Zhang, F., Wang, Y., Kang, L., and Li, Z. (2016). Correction: a proteomic study of Shengmai injection's mechanism on preventing cardiac ischemia-reperfusion injury via energy metabolism modulation. *Mol. Biosyst.* 12, 674–677. doi:10.1039/c5mb90052b

Zhan, Z. A., Yuan, H., Sun, H., Liu, S. T., Zhang, S., Jiang, S., et al. (2024). Effect of shenfu injection of anti-myocardial ischemia-reperfusion injury via modulating HIF-1α/BNIP3 pathway-mediated mitophagy. *Chin. J. Integr. Med. Chin.* 44, 1086–1093.

Zhang, C., and Niu, S. M. (2018). Analysis and discussion of the adverse drug reactions induced by traditional Chinese medicine injections in 86 cases of patients. *Shanghai Med. and Pharm. J. (Chin.)* 39, 41–43. doi:10.3969/j.issn.1006-1533.2018.13.014

Zhang, D., and Jia, X. F. (2019). Clinical study on the adjuvant treatment of acute myocardial infarction with shenmai injection. *Chin. J. Integr. Med. Cardio/Cerebrovasc. Dis. (Chin.)* 17, 1890–1894. doi:10.12102/j.issn.1672-1349.2019.12.037

Zhang, D. L., Yin, L., Jiang, F., Guo, F., Hao, W. H., Yang, H. J., et al. (2018a). Clinical study on the treatment of acute myocardial infarction combined with cardiogenic shock in the elderly with shenmai injection combined with levosimendan. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.* 27, 1453–1457. doi:10.3969/j.issn.1008-8849.2018.13

Zhang, D. M., Sun, D. X., Sun, C. L., Du, L. L., Yao, K. J., and Liu, Y. (2018b). Effects of pressurized rapid intravenous infusion of Shenfu on hemodynamics in patients with acute inferior myocardial infarction. *J. Hebei Med. Univ. Chin.* 39, 882–886. doi:10.3969/j.issn.1007-3205.2018.08.004

Zhang, H., Zhao, Y. H., Xia, Z. X., Du, H. L., Gao, Y., Xue, D., et al. (2018c). Metabolic profiles revealed anti-ischemia-reperfusion injury of Yangxinshi tablet in Rats. *J. Ethnopharmacol.* 214, 124–133. doi:10.1016/j.jep.2017.09.003

Zhang, H. X. (2011). The efficacy of shenfu injection in the treatment of heart failure after acute myocardial infarction. *Chin. J. Ethnomed. Ethnopharm. Chin.* 20, 75. doi:10.3969/j.issn.1007-8517.2011.05.055

Zhang, L., Wang, W., and Xie, Y. M. (2023). Effect of Shenfu Injection on polysaccharide inclusion in patients with acute myocardial infarction complicated by hypotension. *Drug Eval. Res. Chin.* 46, 2408–2414. doi:10.7501/j.issn.1674-6376.2023.11.017

Zhang, M., Chen, K., and Yang, Q. Q. (2011). Effect of shenmai injection on malignant cardiac events and morbidity and mortality in patients with acute massive myocardial infarction. *Shandong Med. J. Chin.* 51, 92–93. doi:10.3969/j.issn.1002-266X.2011.03.056

Zhang, M. L., Zhang, L. T., Qiu, X. F., and Zhou, A. F. (2001). On the relationship between mitochondria and qi in Chinese medicine. *Chin. J. Basic Med. Tradit. Chin. Med. Chin.*, 60–61. doi:10.3969/j.issn.1006-3250.2001.04.024

Zhang, W. J., Cao, Y., Zhang, Y., Ge, Y., Wang, S., Kang, C. Z., et al. (2021). Current status and prospects of implementing GAP in Chinese medicine injection materials. *Chin. J. Chin. Mater. Med. Chin.* 46, 5166–5172. doi:10.19540/j.cnki.cjcmm.20210528.601

Zhang, Y. H., Cheng, R. L., Shang, Y. D., Qu, X. Y., Wang, T. T., Lv, X. Y., et al. (2019). Clinical observation on the treatment of acute myocardial infarction combined with heart failure by shenfu injection. *J. Emerg. Trad. Chin. Med. Chin.* 28, 317–319. doi:10.3969/j.issn.1004-745X.2019.02.037

Zhang, Z. L. (2017). Clinical study on the treatment of acute anterior wall myocardial infarction by intravenous thrombolysis with shenmai injection combined with urokinase. Asia-Pacific Tradit. *Med. Chin.* 13, 124–125. doi:10.11954/ytctyy.201710055

Zhao, C. H. (2020). Analysis of the effects of shenmai injection combined with clopidogrel on cardiac function and prognosis in patients with acute myocardial infarction. *Chin. Remedies and Clin. (Chin.)* 20, 566–568. doi:10.11655/zgywylc2020.04.032

Zhao, J., Zhao, Q., and Wu, T. G. (2016a). Evaluation of the efficacy of recombinant human brain natriuretic peptide combined with shenfu in the treatment of acute myocardial infarction with pump failure. *Mod. J. Integr. Tradit. Chin. West. Med. Chin.* 25, 1413–1416. doi:10.3969/j.issn.1008-8849.2016.13.016

Zhao, L. F., and Sun, F. J. (2021). Effect of coronary artery injection of tirofiban combined with sensitized wheat injection on cardiac function after PCI in patients with acute STEMI. *Chin. J. Integr. Med. Cardio/Cerebrovasc. Dis. (Chin.)* 19, 4337–4339. doi:10.12102/j.issn.1672-1349.2021.24.028

Zhao, X. L., Li, J. Y., and Wang, Y. (1995). A case of polymorphic ventricular tachycardia induced by shengmai injection. *Chin. J. Cardiol. Chin.* 295.

Zhao, X. P., Chen, J., and Guo, S. A. (2005). Research on repurfusion injury after thrombolysis in vein of acute myocardial infarction treated by shenmai injection. *J. Pract. Tradit. Chin. Med. Chin.*, 195–196. doi:10.3969/j.issn.1004-2814.2005.04.001

Zhao, Y., Zhang, Y. G., Wang, H. B., Ren, S. H., Cao, Q. M., Jiang, C. Y., et al. (2016b). One hundred and five cases of related heart failure due to acute myocardial infarction treated with ginseng and Radix ophiopogonis injection. Henan tradit. *Chin. Med. Chin.* 36, 1730–1732. doi:10.16367/j.issn.1003-5028.2016.10.0700

Zheng, Q., Wang, X. Y., Liu, J., Peng, C., Xiong, L., Zhu, Y. N., et al. (2022). Identification of the chemical constituents of shenfu injection and the anti-inflammatory activity of its acetylenic compounds. *China Pharm. Chin.* 33, 1931–1936. doi:10.6039/j.issn.1001-0408.2022.16.03

Zheng, Y. (2016). Clinical effect analysis of shenmai injection in the treatment of patients with heart failure after acute myocardial infarction. *Chin. J. Mod. Drug Appl. Chin.* 10, 171–172. doi:10.14164/j.cnki.cn11-5581/r.2016.08.132

Zhou, J. Y., Liu, Y. C., and Guo, D. C. (2019). Effect of Astragalus injection on the improvement of cardiac function and vascular endothelial function in patients with acute myocardial infarction. *Chin. J. Pharm. Biotechnol. Chin.* 26, 236–239. doi:10.19526/j.cnki.1005-8915.20190310

Zhou, R. S. (2017). Evaluation of the effect and safety of shenmai injection combined with thrombolytic drugs in the treatment of acute ST-segment elevation myocardial infarction. J. China Prescr. *Drug (Chin.)* 15, 77–78.

Zhou, S. J. (2024). The effect of sensitized wheat injection combined with tegretol in patients with acute myocardial infarction. *Pract. Clin. J. Integr. Tradit. Chin. West. Med. (Chin.)* 24, 95–97. doi:10.13638/j.issn.1671-4040.2024.02.028

Zhu, C. Z., Wang, X. H., Liu, X., Xue, J. H., Zhao, L., Song, Y. F., et al. (2019). The efficacy of shenfu injection combined with aspirin and clopidogrel in the treatment of acute myocardial infarction. *Eval. Anal. Drug-Use Hosp. China (Chin)* 19, 950–952. doi:10.14009/j.issn.1672-2124.2019.08.015

Zhu, G. J. (2006). Clinical study on the myocardial protective effect of ginseng and auxiliary injection on patients with acute myocardial infarction. *Chin. Med. Theory Pract. (Chin.)* 16, 827–828.

Zhu, X. H., Ye, H. F., and Yang, L. (2020). Effect of shenfu injection on myocardial TIMI flow grading during PCI in patients with acute myocardial infarction and major adverse cardiac events in the immediate postoperative period. *Chin. J. Integr. Med. Cardio/Cerebrovasc. Dis. (Chin.)* 18, 2107–2111. doi:10.12102/j.issn.1672-1349.2020.13.023

Zhu, Y. H., Shen, X. X., Han, Q. Q., and Zhao, J. (2018). Meta-analysis of the clinical efficacy of shenfu injection in the treatment of myocardial infarction with heart failure. Chin. J. Evid.-Bases Cardiovasc. *Med. Chin.* 10, 402–406. doi:10.3969/j.issn.1674-4055.2018.04.04

Zhuo, D. Q., Min, L., Zhang, D. Y., and Ren, W. Q. (2018). Observation of the hemodynamic intervention effect of Shenfu injection on patients with acute myocardial infarction and cardiogenic shock. *Chin. J. Tradit. Med. Sci. Technol. Chin.* 25, 381–382.

Zong, X. L., Du, A. F., and Zhao, L. M. (2014). Clinical analysis of ginseng injection with urokinase thrombolysis therapy in anterior wall acute myocardial infarction. *Hainan Med. J. Chin.* 25, 2822–2824. doi:10.3969/j.issn.1003-6350.2014.19.1112

Zou, J. F. (2014). Clinical efficacy of shenmai injection and atorvastatin in the treatment of acute myocardial infarction. *Med. Forum (Chin.)* 18, 2495–2496.

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 09 April 2025
DOI 10.3389/fphar.2025.1510657

OPEN ACCESS

EDITED BY
Michael Heinrich,
University College London, United Kingdom

REVIEWED BY
Guang Chen,
The University of Hong Kong, Hong Kong SAR, China
Yuxiang Fei,
China Pharmaceutical University, China
Yuting Huang,
Tianjin University of Traditional Chinese Medicine, China

*CORRESPONDENCE
Qun Gao,
gaoqun_1990@126.com
Qian Lin,
linqian62@126.com

RECEIVED 13 October 2024
ACCEPTED 28 March 2025
PUBLISHED 09 April 2025

CITATION
Mao T, Jiang K, Pang Y, Pan Y, Jia W, Gao Q and Lin Q (2025) Hydroxysafflor yellow A for ischemic heart diseases: a systematic review and meta-analysis of animal experiments. *Front. Pharmacol.* 16:1510657. doi: 10.3389/fphar.2025.1510657

Hydroxysafflor yellow A for ischemic heart diseases: a systematic review and meta-analysis of animal experiments

Tianshi Mao[1], Kaixin Jiang[1], Yanting Pang[1], Yi Pan[1], Wenhao Jia[2], Qun Gao[1]* and Qian Lin[1,3]*

[1]Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, [2]Department of Cardiology, Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing, China, [3]Dongfang Hospital, Beijing University of Chinese Medicine, Beijing, China

Background: Hydroxysafflor yellow A (HSYA) possesses a variety of pharmacological activities which has been demonstrated to be effective against ischemic heart disease (IHD). This study aimed to comprehensively examine the efficacy and summarize the potential mechanisms of HSYA against IHD in animal models.

Methods: We conducted electronic searches for preclinical studies on PubMed, Embase, Web of Science, Cochrane Library, CNKI, SinoMed, Wanfang, and Chinese VIP databases from inception to 31 January 2024. The CAMARADES checklist was chosen to assess the quality of evidence. STATA 14.0 software was utilized to analyze the data. The underlying mechanisms were categorized and summarized.

Results: Twenty-eight studies involving 686 rodents were included and the mean score of methodology quality was 5.04 (range from 4 to 7). Meta-analysis observed that HSYA could decrease myocardial infarction size (SMD: −2.82, 95%CI: −3.56 to −2.08, $p < 0.001$) and reduce the levels of biomarkers of myocardial injury including cTnI (SMD: −3.82, 95%CI: −5.20 to −2.44, $p < 0.001$) and CK-MB (SMD: −2.74, 95%CI: −3.58 to −1.91, $p < 0.001$). HSYA displayed an improvement in cardiac function indicators including LVEF, LVSP, +dp/dt max and -dp/dt max. Furthermore, HSYA was able to reduce the levels of MDA, TNF-α and IL-6, while increasing SOD and NO levels. Mechanistically, the protective effect of HSYA in alleviating myocardial injury after ischemia may be associated with NLRP3 inflammasome, Bcl-2, Bax, caspase-3, eNOS proteins, and TLR/NF-κB, Nrf2/HO-1, JAK/STAT, PI3K/Akt, AMPK/mTOR, VEGFA pathways.

Conclusion: This study demonstrates that HSYA exerts cardioprotective effects in decreasing infarct size, reducing myocardial enzymes and improving cardiac function, which may be mediated by anti-inflammatory, antioxidant, anti-apoptotic, regulation of autophagy, improvement of microcirculation and promotion of angiogenesis. However, the absence of safety assessment, lack of animal models of co-morbidities, and inconsistency between timing of administration and clinical practice are limitations of preclinical studies.

Systematic Review Registration: clinicaltrials.gov, Identifier, CRD42023460790.

KEYWORDS

hydroxysafflor yellow A, myocardial ischemia, myocardial infarction, myocardial ischemia/reperfusion injury, meta-analysis

1 Introduction

Cardiovascular disease (CVD) remains a formidable threat to global public health. Despite considerable advancements in the treatment of CVD over the past 30 years, there is still an increasing trend in both incidence and mortality worldwide (Mensah et al., 2019). In 2020, the United States reported 127.9 million prevalent cases of CVD among adults, whereas there was a higher number of 330 million cases in China (Tsao et al., 2023; WCOTROCHADIC, 2023). Ischemic heart disease (IHD) is responsible for 49.2% of all CVD deaths and is also the leading cause of heart failure, accounting for 38.1%, which places a heavy burden on human health and medical care costs (Roth et al., 2020; Joseph et al., 2023). IHD comprises a range of myocardial ischemic diseases such as myocardial ischemia (IS), myocardial infarction (MI), and myocardial ischemia/reperfusion injury (MIRI) (Dong et al., 2023). In general, irreversible cardiomyocyte damage and death resulting from insufficient blood-oxygen supply are typical characteristics of IHD (Schirone et al., 2022). Therefore, several cardioprotective interventions aimed at ameliorating cardiac function by reducing cardiomyocyte injury and death have been implemented (Heusch, 2020).

As one of the oldest and most established medical systems in the world, traditional Chinese medicine (TCM) has been used and developed for more than 2,500 years. Currently, TCM plays an indispensable role in clinical treatment. According to the theory of TCM, IHD belongs to the category of "chest impediment disease", and "blood stasis pattern" is the key pathogenesis. Based on pattern differentiation and treatment, "activating blood" and "resolving stasis" are the basic treatment principles of such disease. In the Compendium of Materia Medica (Ming Dynasty, ~500 years ago), *Carthamus tinctorius* L. [Compositae; Carthami flos] is described as being able to "invigorate the blood circulation" (Cheng et al., 2024) and also becomes one of the frequently utilized botanical drugs for blood stasis disorders, suggesting its potential applications against IHD. The principal active product derived from safflower is called hydroxysafflor yellow A (HSYA), which serves as the designated marker metabolite utilized to measure the medicinal benefits of safflower in the 2020 edition of the *People's Republic of China Pharmacopoeia* (Zhao et al., 2020). As reported, HSYA possesses a variety of pharmacological properties including antithrombotic, anti-inflammatory, antioxidant, anti-apoptotic, cardio-cerebral and even liver protection effects (Xue et al., 2021; Bai et al., 2020). For example, HSYA inhibits inflammation by regulating nod-like receptor protein-3 (NLRP3) inflammasome and suppressing nuclear factor kappa-B (NF-κB) signal pathway (Han et al., 2016; Ye et al., 2020). HSYA can also promote angiogenesis in the ischemic myocardium (Zou et al., 2018). Despite the facts that the therapeutic role and molecular mechanisms of HSYA for IHD have been partially elucidated, it is still difficult to transfer these findings from animals into humans. Certain scholars contend that a preclinical meta-analysis or systematic review is essential for improving the reproducibility and applicability of animal research (Spanagel, 2022). However, to the best of our knowledge, no review has systematically examined the effects of HSYA for IHD in animal models. Therefore, this systematic review aimed to investigate the therapeutic effects of HSYA for IHD and summarize the potential mechanisms, forming a chain of preclinical evidence and hoping to provide some ideas and research orientation for future preclinical research.

2 Materials and methods

2.1 Protocol

We have registered the protocol in the PROSPERO (CRD42023460790) and the status is "ongoing" now. Besides, the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 statement and PRISMA-ATCM reporting guidelines was strictly followed in this study (Page et al., 2021; Zhao et al., 2022).

2.2 Search strategies

We did electronic searches across eight databases: PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, SinoMed, Wanfang, and Chinese VIP, from their inception up to 31 January 2024. The search entries were formulated as: ("hydroxysafflor yellow A" OR "HSYA") AND ("myocardial ischemia" OR "myocardial infarction" OR "myocardial ischemia-reperfusion" OR "myocardial I/R").

2.3 Inclusion criteria

The following prespecified inclusion criteria were stated: 1) The literature type was animal studies; 2) The research subjects were rats or mice, and the experimental animal models were IS, MI, or MIRI; 3) The intervention group received any dose of HSYA as monotherapy; 4) The control group was given a vehicle or no treatment; 5) The primary outcomes were myocardial infarct size (MIS), the serum level of cardiac troponin I (cTnI), creatine kinase myocardial band (CK-MB), CK, and lactic dehydrogenase (LDH). The secondary outcomes were left ventricular ejection fraction (LVEF), left ventricular systolic pressure (LVSP), left ventricular end dilated pressure (LVEDP), maximal left ventricular pressure rising rate (+dp/dt max) or maximal left ventricular pressure decreasing rate (-dp/dt max), the fibrosis of whole myocardium, the serum levels of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), malondialdehyde (MDA), superoxide dismutase (SOD), 6-

keto-prostaglandin F1α (6-keto-PGF1α), or nitric oxide (NO), the endothelial nitric oxide synthase (eNOS) activity in myocardium, the protein expression of B-cell lymphroma-2 (Bcl-2), Bcl-2-associated X protein (Bax), cleaved caspase-3 or light chain 3 (LC3), the mRNA level of nuclear factor erythroid 2-related factor 2 (Nrf2) or vascular endothelial growth factor A (VEGFA), and the apoptosis rate of cardiomyocytes.

2.4 Exclusion criteria

The following were preset criteria for exclusion: 1) Not *in vivo* studies: clinical trials, reviews, letter, meeting abstracts, *in vitro* studies; 2) Not rats or mice models with IS, MI and MIRI; 3) HSYA was not the only intervention; 4) The control group received any drugs treatment; 5) No one of the outcome indicators; 6) Studies with repeated publication of data; 7) Studies not available in full text.

2.5 Data extraction

This task was completed by two researchers independently, and the third researcher was responsible for resolving disagreements. The specifics of data extraction comprised: 1) General details: the first author's name and publication year; 2) Animal information: species, gender, weight, and sample sizes; 3) Animal model: modeling methods and the anesthesia methods for model induction; 4) Intervention group: the dosage, administration method and time; 6) Control group: the vehicle name; 7) Outcome indicators.

We obtained data only from the highest dose group and final time point if the medication was administered at different doses or outcome indicators were recorded at multiple time nodes. The online tool WebPlotDigitizer was used to calculate the mean and standard deviation (SD) if the data was depicted graphically.

2.6 Risk of bias and quality assessment

To evaluate the risk of bias and methodological quality of enrolled studies, the grading scale of CAMARADES 10-item with minor modifications was employed (Macleod et al., 2004). The modifications are as follows: (F): use of anesthetic without significant intrinsic cardioprotective activity; (I): compliance with animal welfare regulations (including three or more of the following points: preoperative anaesthesia, postoperative analgesia, nutrition, disinfection, environment temperature, environment humidity, circadian rhythm, and euthanasia). Two individuals evaluated all enrolled literature independently.

2.7 Statistical analysis

Meta-analysis was conducted with the use of STATA 14.0 software. All outcome indicators belong to continuous variable type data and were shown as the standardized mean difference (SMD) along with a 95% confidence interval (95% CI). The statistical significance between the medication and control groups was set at $p < 0.05$. The effects model was selected depending on heterogeneity measures by Q test and I^2 statistics. A fixed effects model was applied to merge the effect size when the included studies had better homogeneity with $I^2 \leq 50\%$ and $p > 0.1$. Otherwise, the random effects model was adopted ($I^2 > 50\%$ and $p < 0.1$). Meanwhile, we performed meta-regression and subgroup analyses to explore the probable reasons for heterogeneity. To assess the credibility of the pooled results, we further carried out the sensitivity analysis. When more than 10 studies were included, Egger's test with $p < 0.05$ was denoted by a significant publication bias.

3 Results

3.1 Research selection

Initially, a total of 332 records were retrieved electronically. Then, 163 duplicate articles were excluded and there were 169 articles left. Next, 52 literature consisting of 39 reviews, 12 meeting abstracts and 1 letter were excluded after screening their titles and abstracts. Subsequently, 89 papers that met the exclusion criteria were excluded by skimming the whole text. Finally, our meta-analysis comprised 28 studies (Wang et al., 2007; Huang et al., 2009; Jin et al., 2009; Wang, 2009; Wang et al., 2009; Fu et al., 2011; Liu et al., 2011; Sun, 2012; Zhang et al., 2012; Guan et al., 2013; Dong et al., 2014; Xu et al., 2014; Chen, 2015; Hu et al., 2015; Liu et al., 2015; Zhou et al., 2015; Hu et al., 2016; Wei et al., 2016; Wei et al., 2017; Ni et al., 2018; Su et al., 2018; Zou et al., 2018; Zhou et al., 2019; Ye et al., 2020; Zhang and Zhang, 2020; He, 2022; Ge et al., 2023; Yu and Qu, 2023). Figure 1 displays the flowchart of literature selection.

3.2 Research quality

The quality scores of studies included in the meta-analysis ranged from 4 to 7, with an average of 5.04. Twenty-five studies underwent peer review. Only nine articles definitely mentioned temperature control, and two articles failed to describe the random allocation. Despite all studies employed appropriate animal models, blinded induction of model and blinded assessment of outcome were not mentioned in any of the studies. With the exception of one, all articles described the use of anesthetic without significant intrinsic cardioprotective activity. Each study provided information on the number of animals used, nonetheless, it is a pity that none of them calculated the sample size. Sixteen articles abided by the compliance with animal welfare regulations and ten literature declared potential conflict of interests. The methodological quality of each study is presented in Figure 2.

3.3 Research characteristics

Twenty-eight articles were included for meta-analysis, with 11 articles being English and the other 17 articles being Chinese publications. The detailed characteristics of the 28 articles are given in Table 1.

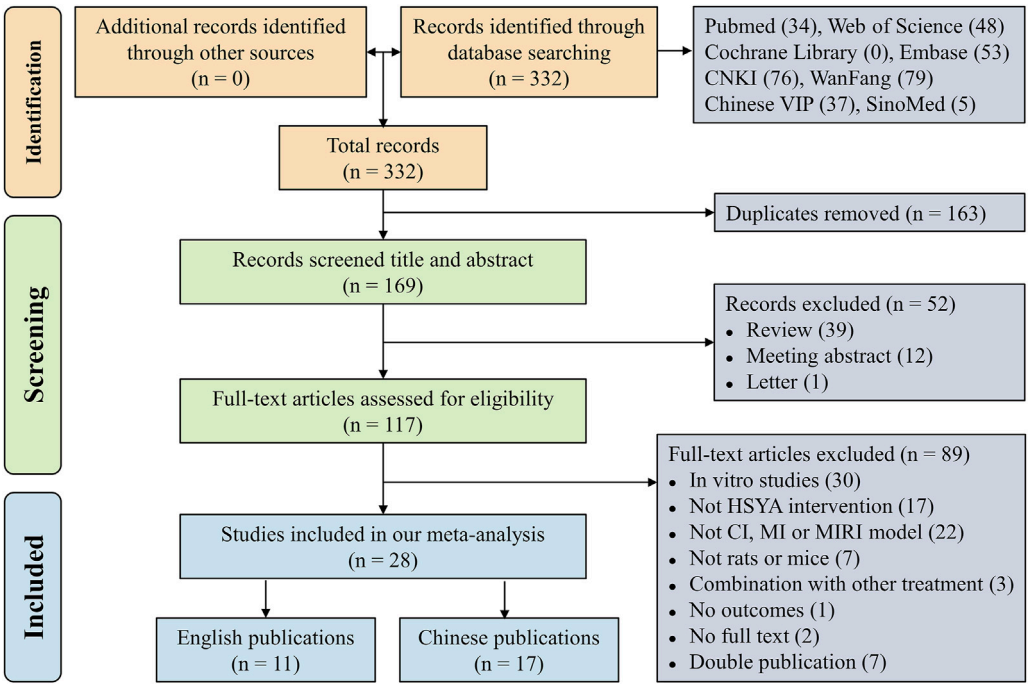


FIGURE 1
Flow diagram of the present systematic review and meta-analysis.

Study ID	A	B	C	D	E	F	G	H	I	J	Total
Wang T (2007)	√		√			√	√				4
Huang X (2009)	√	√				√	√		√		5
Jin M (2009)	√		√			√	√				4
Wang T (2009)	√		√			√	√		√	√	6
Wang HM (2009)	√		√			√	√				4
Liu JG (2011)	√	√				√	√		√		5
Fu JH (2011)	√		√			√	√				4
Sun YQ (2012)		√	√				√		√	√	5
Zhang JJ (2012)	√		√			√	√				4
Guan Y (2013)	√		√			√	√				4
Dong WB (2014)	√		√			√	√				4
Xu AB (2014)	√		√			√	√				4
Zhou MX (2015)	√		√			√	√				4
Chen MC (2015)		√	√			√	√		√	√	6
Hu TX (2015)	√	√	√			√	√		√		6
Liu YG (2015)	√		√			√	√				4
Hu TX (2016)	√		√			√	√		√		5
Wei G (2016)	√		√			√	√		√		5
Wei G (2017)	√	√	√			√	√		√	√	7
Ni B (2018)	√		√			√	√		√	√	6
Zou J (2018)	√		√			√	√		√	√	6
Su N (2018)	√	√	√			√	√		√		6
Zhou DL (2019)	√		√			√	√		√	√	6
Ye JX (2020)	√	√	√			√	√		√	√	7
Zhang Y (2020)	√		√			√	√				4
He W (2022)		√	√			√	√		√	√	6
Ge CW (2023)	√		√			√	√		√	√	6
Yu H (2023)	√		√			√	√				4

FIGURE 2
Risk of bias and quality assessment scores of included studies. Note: **(A)** peer review publication; **(B)** control of temperature; **(C)** random allocation to treatment or control; **(D)** blinded induction of model; **(E)** blinded assessment of outcome; **(F)** use of anesthetic without significant intrinsic cardioprotective activity; **(G)** appropriate animal model; **(H)** sample size calculation; **(I)** compliance with animal welfare regulations (including three or more of the following points: preoperative anesthesia, postoperative analgesia, nutrition, disinfection, environment temperature, environment humidity, circadian rhythm, and euthanasia); **(J)** statement of potential conflict of interests.

TABLE 1 Basic characteristics of included studies.

Study ID	Species (I/C)	Sex	Weight (g)	Model method	Anesthesia	Dosage (way)	Vehicle	Duration	Outcome
Wang et al. (2007)	Wister rats (10/10)	Male	250–300	LAD ligation	Urethanum	20 mg/kg iv	Saline	1d	(1), (3), (4), (15), (18)
Huang et al. (2009)	SD rats (7/7)	Male	200–240	LAD ligation	Sodium pentobarbital	77.3 mg/kg oral	Saline	0.5d	(1)
Jin et al. (2009)	Wister rats (8/8)	Male	200–250	ISO	Urethanum	240 mg/kg ip	Saline	3d	(20)
Wang et al. (2009)	SD rats (8/8)	Male	260–280	LAD ligation	Chloralose	8 mg/kg iv	NM	3d	(1), (3), (15), (16)
Wang, (2009)	SD rats (8/8)	Male	230–270	LAD ligation	Urethanum	20 mg/kg ip	Saline	4d	(15)
Liu et al. (2011)	SD rats (10/10)	Male	180–200	Ischemia 40 min, then reperfusion 120 min	Urethanum	17.87 g/kg iv	Saline	0.5d	(1), (3), (18)
Fu et al. (2011)	Wister rats (12/12)	Male	180–220	LAD ligation	Chloral hydrate	40 mg/kg ip	Saline	0.5d	(1), (3), (13), (14)
Sun, (2012)	SD rats (8/8)	Male	250–300	Ischemia 30 min, then reperfusion 24 h	NM	10 mg/kg iv	Saline	1d	(2), (4), (13), (14) (16), (20), (21), (22) (23), (24)
Zhang et al. (2012)	Wister rats (12/12)	Male, female	280–330	Ischemia 30 min, then reperfusion 120 min	Urethanum	16 mg/kg iv	Saline	0.5d	(1), (3), (18)
Guan et al. (2013)	SD rats (6/6)	NM	250–300	Ischemia 30 min, then reperfusion 3 h	Sodium pentobarbital	0.2 mg/kg iv	Saline	0.5d	(1), (3), (5), (7), (8), (9) (10), (11), (13), (14)
Dong et al. (2014)	SD rats (10/10)	Male, female	180–200	LAD ligation	Sodium pentobarbital	40 mg/kg iv	NM	3d	(1), (3), (4)
Xu et al. (2014)	SD rats (10/10)	Male, female	180–220	Ischemia 30 min, then reperfusion 3 h	Sodium pentobarbital	5 mg/kg iv	Saline	0.5d	(1), (3), (5), (7), (8), (9) (10), (11), (12)
Zhou et al. (2015)	Wister rats (31/31)	Male	80–120	LAD ligation	3.5% chloral hydrate	40 mg/kg ip	Saline	0.5d	(1)
Chen, (2015)	SD rats (6/6)	Male	230–270	ISO injection	10% chloral hydrate	100 mg/kg ig	Saline	14d	(20)
Hu et al. (2015)	SD rats (6/6)	Male	220–260	Ischemia 30 min, then reperfusion 180 min	Sodium pentobarbital	0.05 mg/kg iv	Saline	0.5d	(1), (3), (4), (5)
Liu et al. (2015)	SD rats (8/8)	Male	250–300	Ischemia 40 min, then reperfusion 4 h	Urethanum	16 mg/kg iv	Saline	0.5d	(1), (3), (4), (18)
Hu et al. (2016)	SD rats (10/10)	Male	230–270	Ischemia 30min, then reperfusion 180min	Sodium pentobarbital	70 mg/kg iv	NM	0.5d	(1), (3), (5), (13), (14)
Wei et al. (2016)	SD rats (12/12)	Male	220–260	LAD ligation	10% chloral hydrate	0.1 mg/kg iv	Saline	7d	(1), (6), (7), (8), (9) (10)
Wei et al. (2017)	C57BL/6 mice (40/40)	Male	25–30	LAD ligation	Sodium pentobarbital	60 mg/kg iv	Saline	28d	(6), (25)
Ni et al. (2018)	SD rats (10/10)	Male	275–300	LAD ligation	Isoflurane	5 mg/kg ip	NM	28d	(17)
Zou et al. (2018)	C57BL/6 mice (20/20)	Male	20–25	LAD ligation	Isoflurane	25 mg/kg ip	Saline	14d	(1), (7), (8), (9), (10) (19), (25)

(Continued on following page)

TABLE 1 (*Continued*) Basic characteristics of included studies.

Study ID	Species (I/C)	Sex	Weight (g)	Model method	Anesthesia	Dosage (way)	Vehicle	Duration	Outcome
Su et al. (2018)	C57BL/6 mice (10/10)	Male, female	18–22	LAD ligation	Isoflurane	10 mg/kg ip	DMSO	7d	(1), (11), (12), (21) (22)
Zhou et al. (2019)	SD rats (10/10)	Male	230–270	Ischemia 30min, then reperfusion 2 h	Sodium pentobarbital	5 mg/kg ip	Saline	0.5d	(1), (4), (5), (12) (13), (14), (20) (21), (22), (23)
Ye et al. (2020)	SD rats (15/15)	Male	260–300	Ischemia 30min, then reperfusion 24 h	Sodium pentobarbital	16 mg/kg iv	NM	0.5d	(1), (3), (4), (11), (20) (21), (22), (23), (24)
Zhang and Zhang (2020)	SD rats (10/10)	Male	180–200	Ischemia 30 min, then reperfusion 120 min	10% chloral hydrate	20 mg/kg ig	Saline	14d	(7), (8), (11), (12)
He, (2022)	C57BL/6 mice (16/16)	Male	18–22	LAD ligation	Isoflurane	10 mg/kg ip	DMSO	7d	(1), (3), (5), (11), (12) (15), (17)
Ge et al. (2023)	C57BL/6 mice (10/10)	Male	21–22	Ischemia 30min, then reperfusion 120min	Sodium pentobarbital	20 mg/kg ip	NM	14d	(1), (2), (4), (5), (19)
Yu and Qu (2023)	SD rats (20/20)	Male	NM	Ischemia 30min, then reperfusion 120min	Sodium pentobarbital	20 mg/kg ig	Saline	14d	(1), (2), (4), (5), (6) (13), (14), (21), (22)

Note: (1) MIS, myocardial infarct size; (2) CK, creatine kinase; (3) CK-MB, creatine kinase myocardial band; (4) LDH, lactic dehydrogenase; (5) cTnI, cardiac troponin I; (6) LVEF, left ventricular ejection fraction; (7) LVSP, left ventricular systolic pressure; (8) LVEDP, left ventricular end dilated pressure; (9) +dp/dt max; (10) -dp/dt max; (11) TNF-α, tumor necrosis factor-α; (12) IL-6, interleukin 6; (13) MDA, malondialdehyde; (14) SOD, superoxide dismutase; (15) NO, nitric oxide; (16) eNOS, endothelial nitric oxide synthase; (17) Nrf2, nuclear factor erythroid 2-related factor 2; (18) 6-keto-PGF1α, 6-keto-prostaglandin F1α; (19) fibrosis of myocardium; (20) apoptosis index; (21) Bax, Bcl-2-associated X protein; (22) Bcl-2, B-cell lymphroma-2; (23) cleaved caspase-3; (24) LC3II/LC3I, light chain 3II/light chain 3I; (25) VEGFA, vascular endothelial growth factor A; LAD: left anterior descending; NM: not mentioned; I: intervention group; C: control group; iv: intravenous; ip: intraperitoneal injection; ig: intragastric administration.

There were 686 included animals in total, of which 50.73% were Sprague-Dawley rats (348/686), 21.28% were Wister rats (146/686), and 27.99% were C57BL/6J mice (192/686). In terms of sex, the proportion of male and female animals were 92.13% (632/686) and 6.12% (42/686), respectively, while the left 1.75% (12/686) of animals were not mentioned sex. Regarding the methods of animal models establishment, 13 studies used only left anterior descending (LAD) ligation, 2 studies conducted by isoprenaline (ISO) injection, and 13 studies used the reperfusion after LAD ligation. To induce anesthesia, 11 studies used sodium pentobarbital, six studies used urethane, four studies used isoflurane, five studies utilized chloral hydrate, one study utilized chloralose, and the residual one study did not report the anesthetic. All studies were divided into three dose groups (low dose group: dosage ≤20 mg/kg/d, medium dose group: 20 mg/kg/d < dosage ≤40 mg/kg/d, high dose group: dosage >40 mg/kg/d) according to the dosage of HSYA, with 18 studies at low dose, four studies at medium dose, and six studies at high dose. The basic information about HSYA in each study are presented in Supplementary Table S1.

3.4 Primary outcome indicators

3.4.1 Myocardial infarct size (MIS)

Meta-analysis of twenty-one studies proclaimed that HSYA had a significant effect on decreasing MIS in the animal models of IS, MI, and MIRI (n = 335, SMD: −2.82, 95% CI: −3.56 to −2.08, $p < 0.001$), with a high heterogeneity ($I^2 = 80.6\%$, $p < 0.001$) (Figure 3A). To identify the potential reason of heterogeneity, the meta-regression analyses for dosage of HSYA and treatment duration were performed (Figures 4A, B). The results revealed that the treatment duration was the major cause of heterogeneity for MIS ($p = 0.002$) (Table 2).

3.4.2 Myocardial enzymes

Myocardial enzymes are released after cardiomyocyte injury, and their levels are positively correlated with the degree of myocardial ischemia and injury.

3.4.2.1 cTnI level

Eight articles detected the serum cTnI level, while an elevated heterogeneity was observed ($I^2 = 81.8\%$, $p < 0.001$). The pooled results showed that compared with control, the medication group experienced a noticeable decrease in serum cTnI level (n = 142, SMD: −3.82, 95% CI: −5.20 to −2.44, $p < 0.001$) (Figure 3B).

3.4.2.2 CK-MB level

A total of thirteen articles with an obvious heterogeneity ($I^2 = 79.5\%$, $p < 0.001$) used the serum level of CK-MB as an outcome index. The meta-analysis results pointed to a significant reduction in CK-MB level with HSYA treatment (n = 226, SMD: −2.74, 95% CI: −3.58 to −1.91, $p < 0.001$) compared with the control group

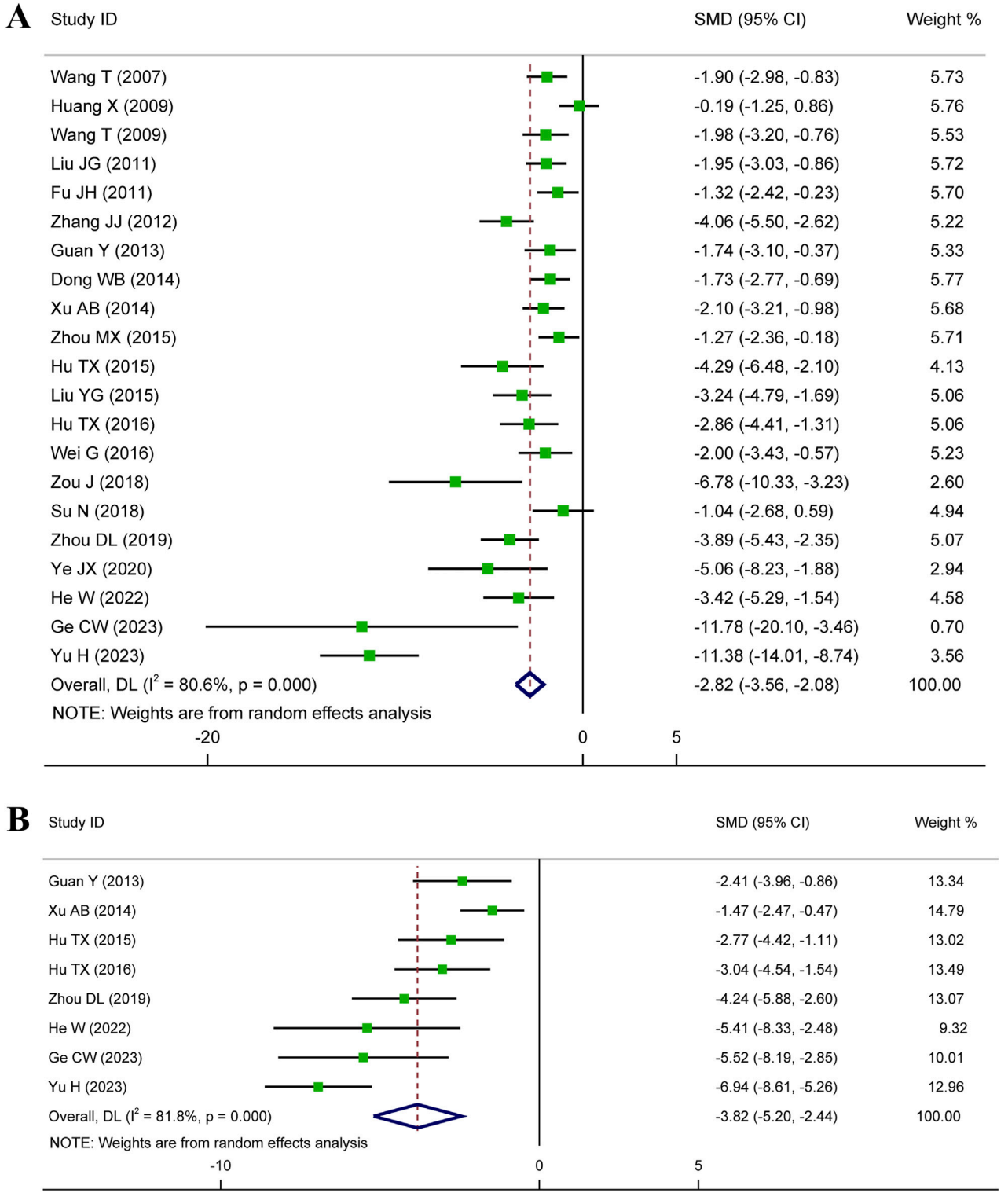


FIGURE 3
Forest plot presenting SMD and 95%CI for the effect of HSYA on MIS **(A)** and cTnI **(B)**.

(Figure 5A). According to the results of meta-regression analysis shown in Figures 4C, D; Table 2, we found that the dosage of HSYA and duration were not the major factors of heterogeneity for CK-MB level.

3.4.2.3 CK level

Overall three articles reported the serum level of CK, and a fixed effects model was employed due to low heterogeneity ($I^2 = 0.0\%$, $p = 0.443$). Compared to the control group, HSYA exhibited a notable

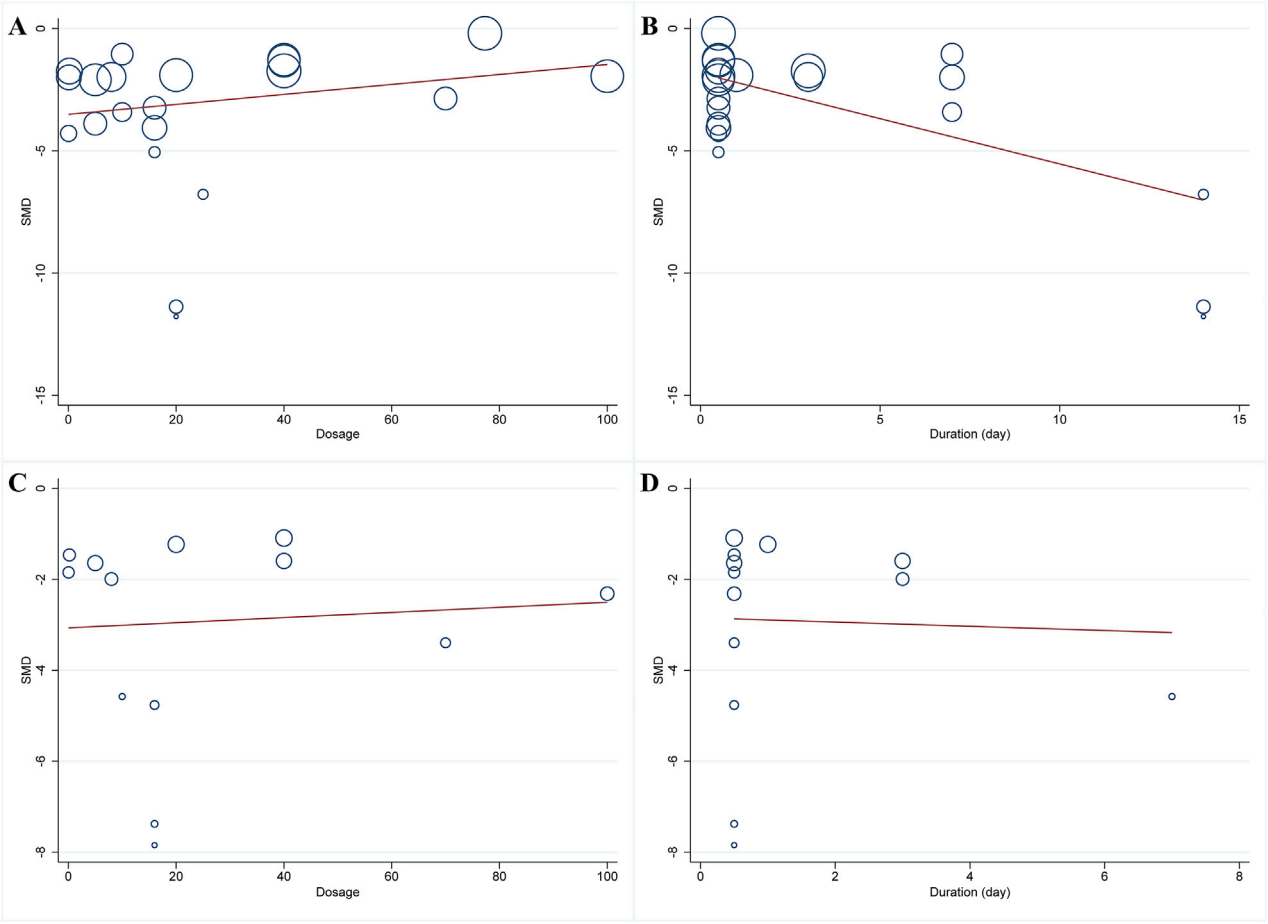


FIGURE 4
Meta-regression plots of MIS and CK-MB. **(A)** dosage and MIS; **(B)** treatment duration and MIS; **(C)** dosage and CK-MB; **(D)** treatment duration and CK-MB.

impact on decreasing serum CK level (n = 68, SMD: −4.81, 95% CI: −5.79 to −3.84, $p < 0.001$) (Figure 5B).

3.4.2.4 LDH level

Nine articles were analyzed using a random effects model (I^2 = 86.3%, $p < 0.001$). We could observe that the serum levels of LDH were significantly decreased in HSYA group (n = 176, SMD: −4.10, 95% CI: −5.54 to −2.67, $p < 0.001$) (Figure 5C).

3.5 Secondary outcome indicators

3.5.1 Cardiac function

To confirm the impact of HSYA therapy on cardiac function in MI, IS, and MIRI animal models, the related indices such as LVEF, LVSP, LVEDP, and ±dp/dt max were examined. Among these indicators, LVEF serves as an indicator of cardiac contractility. Meanwhile, LVSP, LVEDP, and ±dp/dt max represent the hemodynamic state and cardiac compliance of ventricle. Three research for LVEF, five for LVSP or LVEDP, and four studies for ± dp/dt max were brought into our meta-analysis. Figure 6 showed that HSYA treatment yielded remarkable improvements in LVEF (n = 62, SMD: 4.45, 95% CI: 3.48 to 5.43, $p < 0.001$; I^2 = 45.6%, $p = 0.159$), LVSP (n = 74, SMD: 2.03, 95% CI: 1.44 to 2.62, $p < 0.001$; I^2 = 35.3%, $p = 0.186$), LVEDP (n = 74, SMD: −2.21, 95% CI: −3.45 to −0.97, $p < 0.001$; I^2 = 74.4%, $p = 0.004$), +dp/dt max (n = 54, SMD: 1.72, 95% CI: 1.07 to 2.37, $p < 0.001$; I^2 = 7.6%, $p = 0.355$), and -dp/dt max (n = 54, SMD: 1.88, 95% CI: 1.20 to 2.55, $p < 0.001$; I^2 = 36.7%, $p = 0.192$). To summarize, HSYA treatment prominently improved cardiac dysfunction caused by myocardial injury. Specifically, HSYA enhanced myocardial contractility, consequently leading to an improvement in cardiac systolic function. It also improved cardiac hemodynamics and ventricular compliance, thereby contributing to the improvement of cardiac diastolic function.

3.5.2 Inflammatory cytokines

Inflammation is the main factor of myocardial ischemic injury, and TNF-α and IL-6 are important mediators of inflammatory response. We analyzed data from six studies for TNF-α and five studies for IL-6. The pooled effects demonstrated that HSYA importantly reduced the levels of TNF-α (n = 80, SMD: −4.68, 95% CI: −6.40 to −2.95, $p < 0.001$; I^2 = 70.2%, $p = 0.005$) and IL-6 (n = 76, SMD: −3.98, 95% CI: −5.96 to −1.99, $p < 0.001$; I^2 = 81.9%,

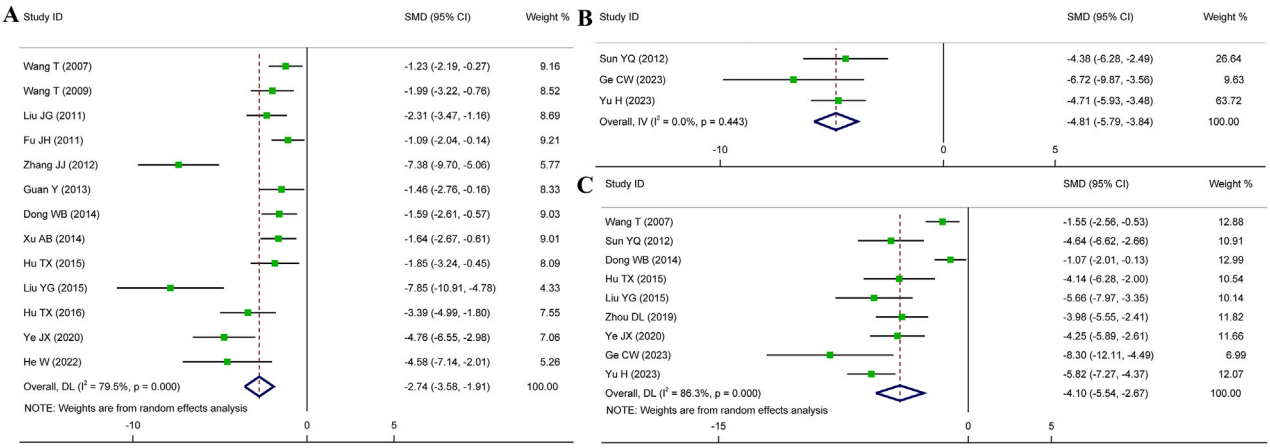


FIGURE 5
Forest plot presenting SMD and 95%CI for the effect of HSYA on the levels of CK-MB **(A)**, CK **(B)**, and LDH **(C)**.

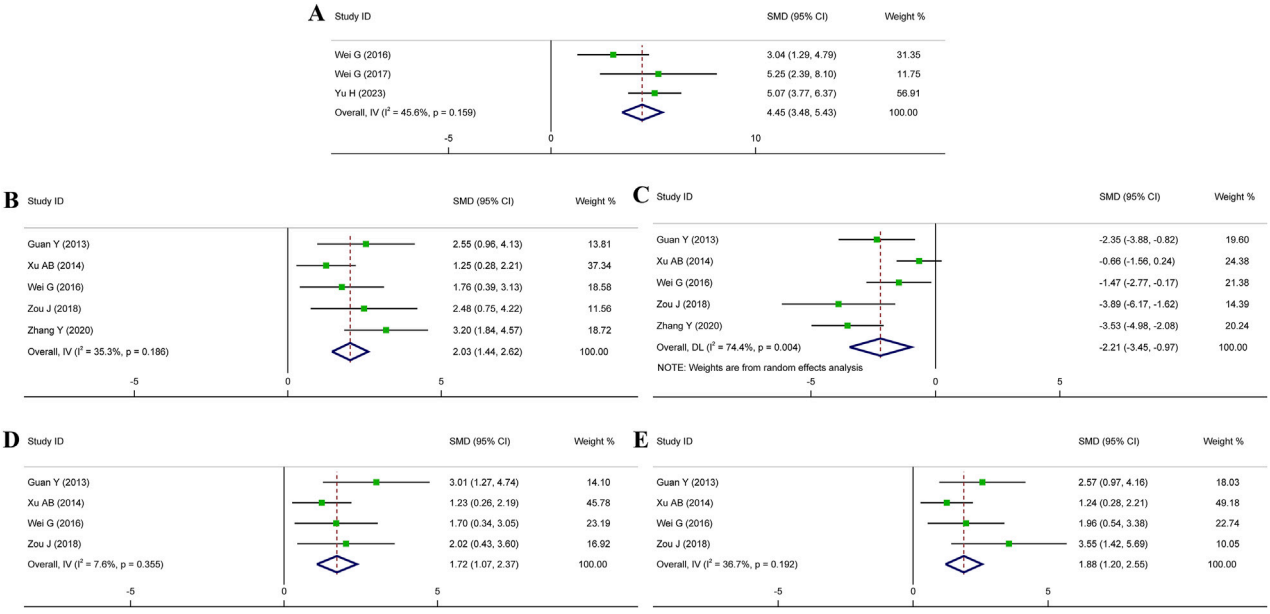


FIGURE 6
Forest plot presenting SMD and 95%CI for the effects of HSYA on cardiac function. **(A)** LVEF; **(B)** LVSP; **(C)** LVEDP; **(D)** +dp/dt max; **(E)** -dp/dt max.

TABLE 2 Meta-regression analysis.

Outcome	Factor	Coefficient (β)	Adj R^2	95% CI	*p*-value
MIS	Dosage	0.0204	1.64%	−0.0200, 0.0608	0.304
	Duration	−0.3705	41.48%	−0.5923, −0.1488	**0.002**
CK-MB	Dosage	0.0056	−15.05%	−0.0414, 0.0527	0.797
	Duration	−0.0464	−12.36%	−0.0844, 0.7513	0.900

Abbreviations: MIS, myocardial infarct size; CK-MB, creatine kinase myocardial band.

$p < 0.001$) in comparison to control group (Supplementary Figure S1). Our findings exhibited a significant therapeutic effect for anti-inflammation of HSYA in animal models.

3.5.3 Oxidative stress indicators

To determine the relationship between HSYA treatment and oxidative stress levels, we used the following five indicators: the serum levels of MDA, SOD and NO, the protein eNOS activity, and the mRNA level of Nrf2 in myocardium. MDA and SOD are good indicators for evaluating oxidative stress, and Nrf2 is an important regulatory factor for antioxidant activity. The pooled estimates displayed that compared to control group, HSYA treatment could decrease MDA level (n = 124, SMD: −3.23, 95% CI: −4.39 to −2.06, $p < 0.001$; $I^2 = 76.1\%$, $p = 0.001$), enhance SOD activity (n = 124, SMD: 2.73, 95% CI: 1.61 to 3.85, $p < 0.001$; $I^2 = 78.4\%$, $p < 0.001$) and increase NO level (n = 62, SMD: 1.77, 95% CI: 1.15 to 2.39], $p < 0.001$; $I^2 = 49.5\%$, $p = 0.114$). HSYA also showed a definite action on increasing eNOS activity (n = 32, SMD: 4.41, 95% CI: 1.27 to 7.55, $p = 0.006$; $I^2 = 79.0\%$, $p = 0.029$) and Nrf2 mRNA level (n = 26, SMD: 8.01, 95% CI: 5.52 to 10.50, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.734$) (Supplementary Figure S2). Hence, it is confirmed that HSYA could alleviate oxidative stress levels in animal models of IHD.

3.5.4 Platelet aggregation indicator

6-keto-PGF1α is a factor of platelet aggregation that reflects the blood circulation of myocardial. The reduced level gives rise to platelet aggregation and disorder of blood circulation, thereby exacerbating the extent of myocardial ischemia. A total of four studies reported the serum level of 6-keto-PGF1α as an outcome indicator and a random effects model was applied. According to the meta-analysis, HSYA increased serum level of 6-keto-PGF1α (n = 80, SMD: 2.51, 95% CI: 0.57 to 4.45, $p = 0.011$) compared to control and exhibited the inhibitory effect on platelet aggregation (Supplementary Figure S3A).

3.5.5 Fibrosis of myocardium

Two studies applied Masson staining to detect the degree of myocardial injury and fibrosis. A fixed effects model was employed and the pooled results suggested that HYSA treatment alleviated myocardial injury and delayed the fibrosis progression (n = 16, SMD: −5.39, 95% CI: −7.77 to −3.00, $p < 0.001$) (Supplementary Figure S3B).

3.5.6 Autophagy indicator

Two studies used the ratio of LC3II/LC3I as the outcome index and were analyzed by random effects model in this meta-analysis. The pooled results found no obviously statistical difference of HSYA on LC-3II/LC-3I ratio (n = 22, SMD: −15.02, 95% CI: −54.41 to 24.38, $p = 0.455$) in animal models of myocardial injury (Supplementary Figure S3C).

3.5.7 Angiogenesis indicator

Two studies utilized VEGFA mRNA expression to evaluate the role of HSYA in angiogenic. The homogeneity between two studies was positive and the fixed effects model was utilized. The mRNA expression of VEGFA was significantly higher in HSYA group than in the control group (n = 20, SMD: 11.33, 95% CI: 7.30 to 15.36, $p < 0.001$), which suggests that HSYA is beneficial to the promotion of angiogenesis after myocardial injury in animal models (Supplementary Figure S3D).

3.5.8 Apoptosis indicators

To investigate the correlation between HSYA treatment and cell apoptosis, we focused on some indicators of myocardial apoptosis. Five articles reported myocardial apoptosis rate by TUNEL assay, five articles provided data on Bax protein and Bcl-2 protein, as well as three articles on cleaved caspase-3. Results from eligible studies demonstrated that HSYA alleviated myocardial apoptosis (n = 70, SMD: −3.09, 95% CI: −4.55 to −1.64, $p < 0.001$; $I^2 = 69.6\%$, $p = 0.011$), inhibited the activation of caspase-3 (n = 28, SMD: −9.94, 95% CI: −19.40 to −0.48, $p = 0.039$; $I^2 = 90.1\%$, $p < 0.001$), reduced the Bax expression (n = 88, SMD: −5.28, 95% CI: −8.52 to −2.03, $p = 0.001$; $I^2 = 91.0\%$, $p < 0.001$) and increased Bcl-2 expression (n = 88, SMD: 6.42, 95% CI: 4.46 to 8.39, $p < 0.001$; $I^2 = 57.9\%$, $p = 0.050$) (Supplementary Figure S4). Taken together, HSYA could mitigate cardiomyocyte apoptosis *in vivo* of myocardial injury.

3.6 Subgroup analyses

Based on the potential factors (dosage, treatment duration, and stage of administration) that may contribute to heterogeneity, the subgroup analyses of MIS, cTnI, and CK-MB were conducted. In addition, considering that there were different methods of MIS calculation, subgroup analysis of MIS was also performed accordingly: area at infarction/area at risk (AAI/AAR), area at risk/left ventricle area (AAR/LVA), and area at risk/total myocardial area (AAR/TMA).

As presented in Table 3, the treatment duration was the major cause of heterogeneity for MIS, but the methods of MIS were not. It is consistent with the results of the meta-regression analysis. For CK-MB, the *p*-value of heterogeneity between groups was less than 0.01, indicating that the dosage of HSYA was the main source of heterogeneity. Similarly, the stage of administration may be the major source of heterogeneity for cTnI.

3.7 Publication bias and sensitivity analyses

For the primary outcome indicators MIS and CK-MB, the output results of publication bias using Egger's test indicated the presence of publication bias (MIS: $t = -4.85$, $p < 0.001$; CK-MB: $t = -7.85$, $p < 0.001$) (Supplementary Figure S5).

Owing to the existence of heterogeneity and publication bias, we completed the sensitivity analyses using the leave-one-out method to assess the robustness of MIS, CK-MB, and cTnI. The results of sensitivity analyses showed that the overall effect size was not significantly changed, which implied that our findings of this study were relatively stable and reliable (Figure 7).

4 Discussion

4.1 Summary of evidence

Up to now, this is the first preclinical meta-analysis and systemic review to examine the effect of IHD following HSYA treatment *in vivo*. A previous study (Zhao et al., 2020) systematically summarized the basic data for related research of HSYA, including

TABLE 3 Subgroup analysis.

Outcome	Number of studies	SMD	95% CI	*p*-value	Heterogeneity	
					I^2	*p*
MIS						
Overall	21	−2.82	−3.56, −2.08	<0.001	80.6%	<0.001
Subgroup by (Duration), Heterogeneity between groups: $p < 0.001$						
≤7 days	18	−2.22	−2.73, −1.70	<0.001	60.9%	<0.001
>7 days	3	−9.65	−13.16, −6.13	<0.001	54.3%	0.112
Subgroup by (Methods of MIS), Heterogeneity between groups: $p = 0.103$						
AAI/AAR	5	−3.09	−4.01, −2.17	<0.001	34.5%	0.191
AAR/LVA	8	−2.21	−2.79, −1.63	<0.001	38.3%	0.124
AAR/TMA	8	−3.96	−5.90, −1.96	<0.001	91.1%	<0.001
CK-MB						
Overall	13	−2.74	−3.58, −1.91	<0.001	79.5%	<0.001
Subgroup by (Dosage), Heterogeneity between groups: $p = 0.009$						
≤20 mg/kg	9	−3.26	−4.50, −2.01	<0.001	83.9%	<0.001
20 ~ ≤ 40 mg/kg	2	−2.71	−3.73, −1.69	<0.001	13.1%	0.283
>40 mg/kg	2	−1.32	−2.02, −0.63	<0.001	0.0%	0.478
cTnI						
Overall	8	−3.82	−5.20, −2.44	<0.001	81.8%	<0.001
Subgroup by (Stage of administration), Heterogeneity between groups: $p < 0.001$						
Therapeutic administration	4	−2.24	−3.01, −1.47	<0.001	20.0%	0.290
Prophylactic administration	4	−5.54	−6.91, −4.16	<0.001	40.9%	0.166

Abbreviations: MIS, myocardial infarct size; AAI, area at infarction; AAR, area at risk; LVA, left ventricle area; TMA, total myocardial area; CK-MB, creatine kinase myocardial band; cTnI, cardiac troponin I.

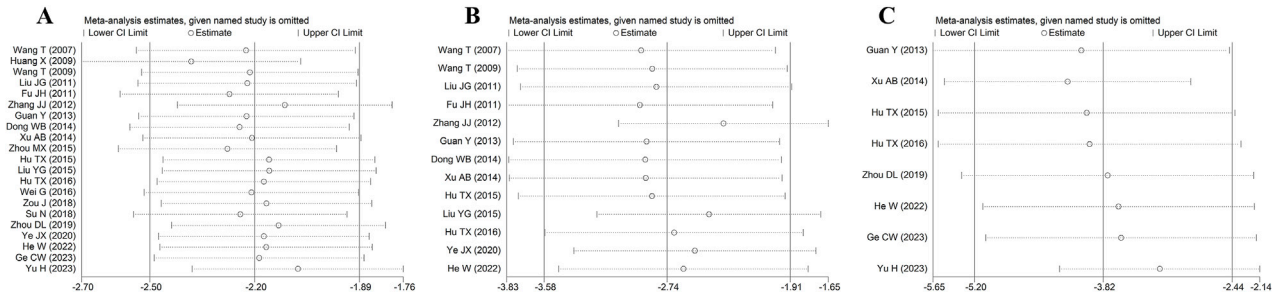


FIGURE 7
Sensitivity analysis of MIS **(A)**, CK-MB **(B)**, and cTnI **(C)**.

pharmacological effects and molecular mechanism. But it focused more on reporting the methods of acquisition, extraction and detection, as well as pharmacokinetics. Moreover, regarding the cardioprotective effects of HSYA, it only summarized oxidative stress and inflammation related signaling pathways. In our review, we provided evidence about the efficacy of HSYA against IHD through meta-analysis and updated a more comprehensive review of pharmacological mechanisms.

Our findings found that HSYA is devoted to reducing MIS, serum myocardial enzymes and troponin, enhancing cardiac function, decreasing serum inflammatory cytokines, and ameliorating myocardial apoptosis and fibrosis. In brief, HSYA

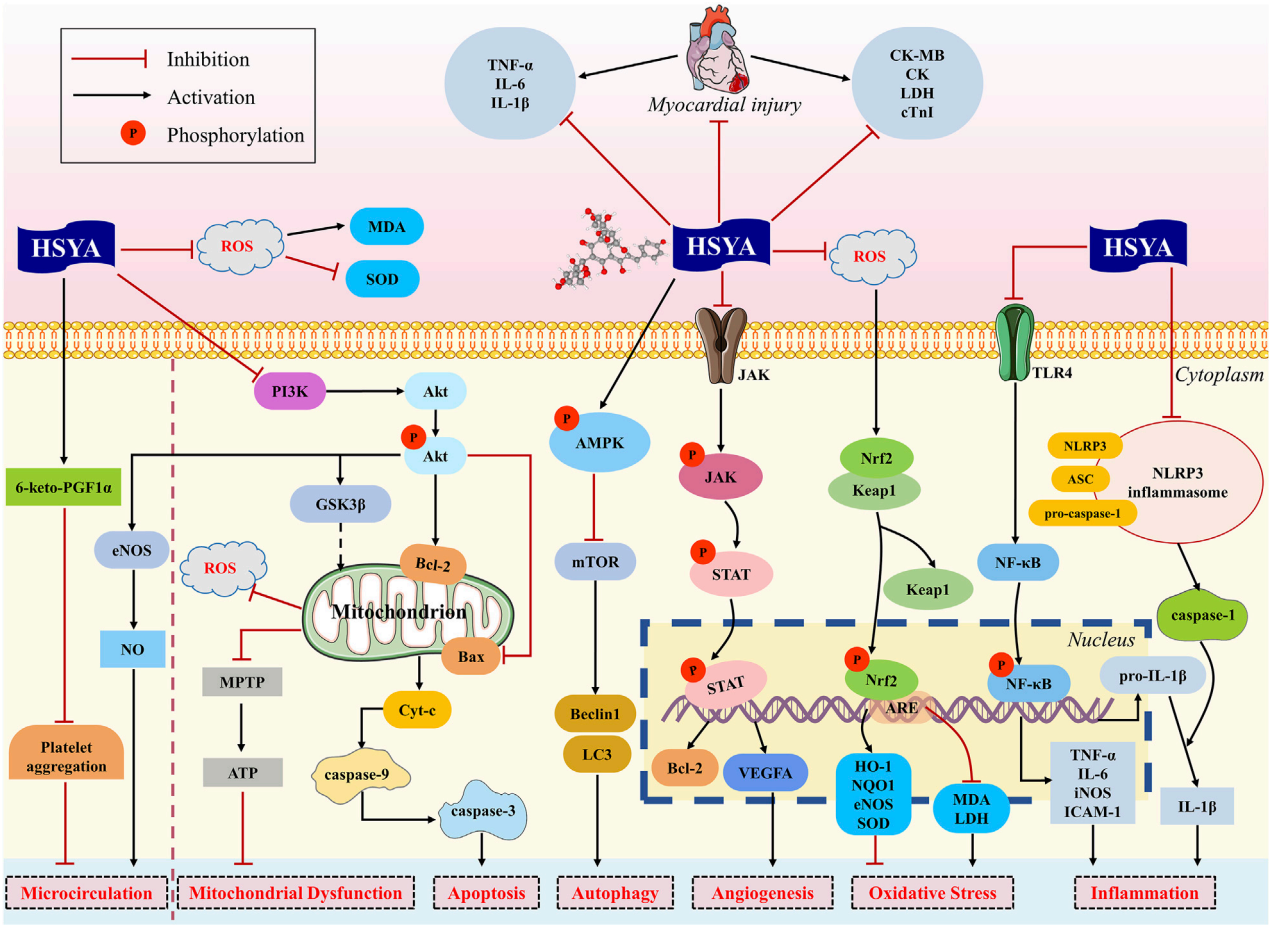


FIGURE 8
Potential cardioprotective mechanisms of HSYA against myocardial ischemia.

exerts potential cardioprotective action against myocardial ischemic injury mainly through anti-inflammatory, antioxidant, anti-apoptotic, regulation of autophagy, improvement of microcirculation and mitochondrial dysfunction, and promotion of angiogenesis (Figure 8).

4.2 Molecular mechanisms of HSYA for myocardial ischemia

4.2.1 Effects on inflammation

During the process of myocardial ischemia, inflammatory cells infiltrate the infarct region and promote the release of inflammatory mediators. The inflammatory responses localized at the myocardium are triggered, which is considered to be the primary factor responsible for myocardial damage and aggravated cardiac dysfunction (Ong et al., 2018).

The toll-like receptor 4 (TLR4)/NF-κB signal pathway contributes an important part in inflammation. TLR4, as a pattern recognition receptor located on the cell membrane, participates in the inflammatory response actively (Wei et al., 2023). In case of myocardial injury, TLR4 activation triggers the downstream signaling p-NF-κB, bringing about the secretion of proinflammatory cytokines such as TNF-α, IL-6, IL-1β, and inducible nitric oxide synthase (iNOS) (Moghimpour Bijani et al., 2012). This inflammatory cascade worsens myocardial damage and is likely to induce an enlargement of infarct size. It was reported that HSYA attenuated TLR4 overexpression and NF-κB activation, contributing to the downregulation of TNF-α, IL-6 and IL-1β, and the upregulation of anti-inflammatory cytokine IL-10, which in turn inhibits the inflammatory response of cardiomyocytes (Guan et al., 2013; Han et al., 2016).

Moreover, recent preclinical studies of MI and MIRI have identified that NLRP3 inflammasome is also closely connected to heart inflammation, infarct size, and cardiac function (Toldo et al., 2016). NLRP3 inflammasome is composed of three components: NLRP3 protein, apoptosis-associated speck-like (ASC) protein, and pro-caspase-1 (Abderrazak et al., 2015). Ischemia can trigger NLRP3 activation, which contributes to the production and release of IL-1β (Xu et al., 2020; Dai et al., 2023). HSYA effectively suppressed NLRP3 inflammasome activation in rats with MIRI, resulting in decreased IL-1β release and infarction size (Ye et al., 2020).

4.2.2 Effects on oxidative stress

Excessive production of reactive oxygen species (ROS) is the main pathophysiological factor implicated in the progression of MI

and MIRI (Peoples et al., 2019). During myocardial ischemia, the amount of ROS increases and antioxidant systems are impaired. The redox transcription factor Nrf2 is essential to the regulation of cellular redox homeostasis, thereby exhibiting the effect of antioxidant stress. Keap1 is a vital element for the regulation of Nrf2. Under normal conditions, Nrf2 is bound to Keap1, which promotes the proteasomal degradation of Nrf2 by way of ubiquitination, keeping Nrf2 maintain a low level in the cytoplasm. But in oxidative stress conditions, Nrf2 dissociates from its complex pair and translocates to the nucleus. Once Nrf2 is transported to the nucleus, it always binds to the sequence known as the antioxidant response element (ARE), boosting the transcription of Nrf2-regulated genes (Loboda et al., 2016; Geertsema et al., 2023). Two downstream targets of Nrf2, heme oxygenase-1 (HO-1) and NAD(P)H-quinone oxidoreductase 1 (NQO1) are believed to possess a protective effect on oxidative stress. HSYA has been shown to reduce oxidative stress damage in mice which is achieved by inhibiting the level of Keap1 mRNA and enhancing the level of Nrf2 and HO-1 (He, 2022). As well, HSYA also exerts antioxidant and anti-hypertrophic effects in rats with MI by activating Nrf2/HO-1 signaling pathway (Ni et al., 2018).

4.2.3 Effects on apoptosis and mitochondrial dysfunction

Apoptosis is recognized to involve in the progression of myocardial ischemia (Singh et al., 2019). Cardiomyocyte apoptosis begins shortly following the onset of MI and appears to be enhanced apparently during reperfusion, leading to the stasis of myocardium, the enlargement of infarct area, and the insufficiency of cardiac function (Zhao et al., 2003).

The overproduction of ROS is the major apoptotic stimulus signal. Subsequently, the apoptotic cascade is initiated, which involves the loss of mitochondrial membrane potential, the opening of mitochondrial permeability transition pore (MPTP), and the release of cytochrome-C (Cyt-C) (Heusch, 2020). Cyt-C can combine with apoptotic protease activating factor-1 (Apaf-1), causing the sequential activation of caspase-3, which is subsequently processed into cleaved caspase-3. The activated and cleaved caspase-3 is regarded as an indicator of the intensity of apoptosis (Sahoo et al., 2023). Bcl-2 and Bax are crucial mitochondrial membrane proteins and serve as the integral regulators of apoptosis, which are responsible for maintaining mitochondrial membrane integrity and the balance of apoptosis (Czabotar and Garcia-Saez, 2023; Senichkin et al., 2020). Bcl-2 can block Cyt-C release and regulate MPTP opening to inhibit apoptosis, whereas Bax performs the opposite effect. HSYA was found to reduce Cyt-C release, increase the expression level of Bcl-2, and decrease the expression of Bax and caspase-3 *in vivo*, thereby inhibiting cardiomyocyte apoptosis (Sun, 2012; Zhou et al., 2019; Ye et al., 2020).

Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signal pathway is essential for cell apoptosis and ischemia injury (Pang et al., 2023). JAK2 could be activated by ROS and then STAT1 is phosphorylated by JAK2. Previous research identified that STAT1 could modulate MPTP opening and enhance the expression of pro-apoptotic genes such as p53, Fas, and Fas ligand (FasL) (Krämer et al., 2006). HSYA decreased JAK2 and STAT1 activity, inhibited the expression of Bax, Fas, and FasL, improved antioxidant capacity, and reduced apoptosis in IR-induced models. It was suggested that HSYA is effective in ameliorating myocardial injury by inhibiting apoptosis, which is partially mediated by JAK2/STAT1 pathway (Zhou et al., 2019).

Mitochondrial dysfunction is among the pathophysiological mechanisms involved in MIRI. During acute ischemia, the overproduction of ROS causes an overload of mitochondrial Ca^{2+}, which promotes the opening of MPTP, leading to impaired adenosine triphosphate (ATP) synthesis and mitochondrial swelling (Halestrap et al., 2004). Therefore, the formation and opening of MPTP are the major causes of mitochondrial dysfunction and cardiomyocyte apoptosis (Deng and Zhou, 2023). HSYA has been shown to prevent myocardial injury through inhibiting the opening of MPTP in isolated rat hearts (Liu et al., 2008). Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/glycogen synthase kinase three beta (GSK3β) signaling pathway has been claimed to benefit mitochondrial and myocardial damage (Zhang et al., 2018). GSK3β, as the key downstream molecule of PI3K/Akt pathway, has been proven to regulate MPTP opening. It has been reported that HSYA increases levels of p-Akt and GSK3β in H/R-induced H9c2 cells, which inhibits cardiomyocyte apoptosis, prevents MPTP opening, and restores mitochondrial ATP synthesis (Min and Wei, 2017).

4.2.4 Effects on microcirculation

During the progression of MI and MIRI, partly coronary microvascular cells also may experience irreversible damage except for cardiomyocyte death, leading to microcirculation dysfunction (Heusch, 2019). Platelet aggregation is a major factor in microcirculation disturbance. 6-keto-PGF1α is a derivative of prostaglandin I_2 (PGI_2), which is an important active substance that inhibits platelet aggregation. Studies found that 6-keto-PGF1α decreased in rats with MI and MIRI, while HSYA could increase the level of 6-keto-PGF1α (Wang et al., 2007; Liu et al., 2011; Zhang et al., 2012). Additionally, as a natural inorganic compound to protect against platelet aggregation, NO is produced in vascular endothelium by eNOS (Lundberg and Weitzberg, 2022). It was discovered that HSYA could attenuate the decrease of eNOS activity caused by acute myocardial ischemia and consequently enhance NO content in MI rats (Wang et al., 2009). This cardioprotective effect is claimed to be relevant to the promotion of the PI3K/Akt/eNOS pathway after HSYA treatment in MIRI rats (Sun, 2012).

4.2.5 Other effects

Angiogenesis is an essential process in the recovery of blood flow in ischemic myocardial tissue. It helps to establish collateral circulation and further promotes myocardial regeneration (Ware and Simons, 1997). Currently, plenty of evidence has reported the proangiogenic effect of HSYA by using various ischemic models. In MI mice, HSYA has performance in promoting myocardial neovascularization and recovering heart function, which might be attributed to the activation of HO-1/VEGF/SDF-1 cascade pathway (Wei et al., 2017). Furthermore, HSYA could upregulate VEGFA expression to promote angiogenesis in ischemic myocardium, thereby ameliorating ischemia-induced cardiac dysfunction and myocardial injury (Zou et al., 2018).

Autophagy is a major regulator of cardiac homeostasis in response to various stressful conditions, thereby reducing myocardial injury and protecting cardiac function (Sciarretta

et al., 2018). The mammalian target of rapamycin (mTOR) is a well-known inhibitor of autophagy, whereas AMP-activated protein kinase (AMPK), the upstream of mTOR, is the positive regulator. It was found that HSYA could increase p-AMPK level and decrease mTOR level to stimulate cardiomyocyte autophagy in MIRI rats. Moreover, the autophagy-related proteins were observed, with Beclin one and LC3II showing an increasing trend while LC3I decreased in rats receiving HSYA (Ye et al., 2020). However, the specific mechanisms of HSYA regulating autophagy are not well understood and require further experiments.

4.3 Limitations

Firstly, nearly 50% of the studies had a quality score of less than five points, indicating an overall low quality of all included studies. Low methodological quality indeed affects the credibility of the results.

Secondly, most outcome measures in this study exhibited high heterogeneity, which could be attributed to a few factors such as animal species, drug dosage, modeling methods, and measurement errors. However, we further performed meta-regression, subgroup analysis, and sensitivity analysis, and the results validated the effectiveness and reliability of HSYA for treating myocardial ischemia.

Thirdly, it was found a significant publication bias for MIS and CK-MB. Those studies not with positive results are rarely published, especially animal experiments. Thus, the efficacy of HSYA may be overestimated. We controlled for publication bias by using as many database sources as possible, but we could not collect all the relevant literature.

Lastly, none of the preclinical studies reported the assessment of safety, which makes us fail to provide evidence of safety through meta-analysis.

4.4 Future prospects

Despite HSYA has been investigated the diverse pharmacological activities, it is well known for being a pan-assay interference compound (PAINS) if tested *in vitro*. PAINS are molecules that have been observed to show activity in multiple types of assays by interfering with the assay readout rather than through specific compound/target interactions, which are often viewed as highly promiscuous players that produce false positive results (Magalhães et al., 2021).

PAINS always exhibit some known typical behaviors: redox reactivity, aggregation, membrane disruption, and fluorescence interference (Nelson et al., 2017). *In vitro*, PAINS may interfere with oxidative stress-related detection by scavenging free radicals (redox reactivity); PAINS could lead to false results through nonspecific bind to antibodies in some biochemical assays (aggregation); color or fluorescence properties of PAINS may produce an effect on fluorescence signal (fluorescence interference). *In vitro* experiments are usually performed under simplified conditions that lack the complexities of environment *in vivo*, such as inability to be reduced by hepatic metabolic enzymes that may interfere with the assay in prototype form. Additionally, the concentrations of PAINS were used ranging from μM to mM levels, which significantly exceed the physiological concentrations observed *in vivo*, thereby greatly increasing the probability of nonspecific reactions (Bolz et al., 2021). It is obvious that the *in vitro* interference properties of HSYA may offer many traps of investigations.

However, PAINS have relatively little interference with the *in vivo* experiments. Firstly, HSYA undergoes hydroxylation and glucuronidation under the action of hepatic enzymes (Zhao et al., 2020). The metabolites decrease the nonspecific reactivity on oxidative stress detection. Furthermore, *in vivo* experiments rely on a comprehensive phenotype to assess efficacy of PAINS, rather than a single biochemical test. For instance, MIS, the primary outcome of this meta-analysis, was assessed by TTC staining and was not directly interfere by redox properties of PAINS. Cardiac function parameters (LVEF, +dp/dt max, etc.) were also not affected by the activity of single or multiple targets. Taken together, the integration of evidence from animal research may further enhance confidence in our results. But this does not mean that PAINS will not have interference effects at all *in vivo* experiments, and future research need to further ensure the reliability of results through conducting pharmacokinetic studies and looking for biophysical orthogonal methods for support of target engagement (e.g., surface plasmon resonance, cellular thermal shift assay) (Dahlin et al., 2015).

Moreover, the further preclinical research should adopt more rigorous experimental design such as blinded implementation and sample size calculation. Safety assessment should also be one of the concerns for each research. In addition, how to resolve the inconsistency between the timing of administration and clinical practice remains a key issue for future research.

5 Conclusion

In summary, our review findings indicate that HSYA exerts cardioprotective benefits in decreasing myocardial infarct size, reducing myocardial enzymes, and improving cardiac function in animal models of IS, MI, and MIRI. Specifically, the potential effects of HSYA in alleviating myocardial injury after ischemia mainly include attenuating inflammation, oxidative stress, cardiac myocyte apoptosis, and fibrosis of myocardium, improving microcirculation, and promoting angiogenesis. The underlying mechanisms may be associated with NLRP3 inflammasome, Bcl-2, Bax, caspase-3, eNOS proteins, and TLR/NF-κB, Nrf2/HO-1, JAK/STAT, PI3K/Akt, AMPK/mTOR, VEGFA pathways. However, none of included studies reported the safety endpoint and used animals with co-morbidities such as hyperlipidemia and hypertension, which is the typical situation in human for IHD. Moreover, the timing of administration of HSYA does not align with clinical practice. Safety assessment, standardized experimental design and comorbid animal models may strengthen the preclinical evidence base. Therefore, stronger evidence is required to better convert these finding to clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

TM: Data curation, Methodology, Visualization, Writing – original draft, Writing – review and editing. KJ: Data curation, Visualization, Writing – original draft, Writing – review and editing. YaP: Data curation, Methodology, Writing – review and editing. YiP: Visualization, Writing – review and editing. WJ: Visualization, Writing – review and editing. QG: Project administration, Supervision, Writing – review and editing. QL: Funding acquisition, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Administration of Traditional Chinese Medicine High-level TCM Key discipline Project (grant number: zyyzdxk-2023253) and Chinese Medicine inheritance and innovation "thousand million" Talents Project (Qi Huang Project 2021) Qi Huang Scholars.

Acknowledgments

We wish to thank the reviewers and also the authors of all references.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1510657/full#supplementary-material

References

Abderrazak, A., Syrovets, T., Couchie, D., EL Hadri, K., Friguet, B., Simmet, T., et al. (2015). NLRP3 inflammasome: from a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases. *Redox Biol.* 4, 296–307. doi:10.1016/j.redox.2015.01.008

Bai, X., Wang, W., Fu, R., Yue, S., Gao, H., Chen, Y., et al. (2020). Therapeutic potential of hydroxysafflor yellow A on cardio-cerebrovascular diseases. *Front. Pharmacol.* 11, 01265. doi:10.3389/fphar.2020.01265

Bolz, S. N., Adasme, M. F., and Schroeder, M. (2021). Toward an understanding of pan-assay interference compounds and promiscuity: a structural perspective on binding modes. *J. Chem. Inf. Model* 61, 2248–2262. doi:10.1021/acs.jcim.0c01227

Chen, M. C. (2015). *Anti-oxidative effects and mechanisms of combinating hydroxy safflower yellow A and acetyl-11-keto-beta-boswellic acid against myocardial injury*. Xincheng, China. The Fourth Military Medical University.

Cheng, H., Yang, C., Ge, P., Liu, Y., Zafar, M. M., Hu, B., et al. (2024). Genetic diversity, clinical uses, and phytochemical and pharmacological properties of safflower (Carthamus tinctorius L.): an important medicinal plant. *Front. Pharmacol.* 15, 1374680. doi:10.3389/fphar.2024.1374680

Czabotar, P. E., and Garcia-Saez, A. J. (2023). Mechanisms of BCL-2 family proteins in mitochondrial apoptosis. *Nat. Rev. Mol. Cell Biol.* 24, 732–748. doi:10.1038/s41580-023-00629-4

Dahlin, J. L., Nissink, J. W. M., Strasser, J. M., Francis, S., Higgins, L., Zhou, H., et al. (2015). PAINS in the assay: chemical mechanisms of assay interference and promiscuous enzymatic inhibition observed during a sulfhydryl-scavenging HTS. *J. Med. Chem.* 58, 2091–2113. doi:10.1021/jm5019093

Dai, Y., Zhou, J., and Shi, C. (2023). Inflammasome: structure, biological functions, and therapeutic targets. *MedComm* 4, e391. doi:10.1002/mco2.391

Deng, R. M., and Zhou, J. (2023). The role of PI3K/AKT signaling pathway in myocardial ischemia-reperfusion injury. *Int. Immunopharmacol.* 123, 110714. doi:10.1016/j.intimp.2023.110714

Dong, W. B., Ye, X. D., Cheng, M., Wang, J. Q., and Zheng, G. L. (2014). Protective effect of hydroxy safflower yellow A on myocardial ischemia. *China J. Chin. Pharmacol. Ther.* 19, 1001–1005.

Dong, L., Shen, Z., Chi, H., Wang, Y., Shi, Z., Fang, H., et al. (2023). Research progress of Chinese medicine in the treatment of myocardial ischemia-reperfusion injury. *Am. J. Chin. Med.* 51, 1–17. doi:10.1142/S0192415X23500015

Fu, J. H., Zhang, Q., Fan, C. Z., and Liu, J. G. (2011). Protective effect of intravenous infusion injection of safflor yellow and hydroxyl safflor yellow A on acute myocardial ischemia injury in rats. *Int. J. Trad. Chin. Med.* 33, 692–694. doi:10.3760/cma.j.issn.1673-4246.2011.08.007

Ge, C., Peng, Y., Li, J., Wang, L., Zhu, X., Wang, N., et al. (2023). Hydroxysafflor yellow A alleviates acute myocardial ischemia/reperfusion injury in mice by inhibiting ferroptosis via the activation of the HIF-1α/SLC7A11/GPX4 signaling pathway. *Nutrients* 15, 3411. doi:10.3390/nu15153411

Geertsema, S., Bourgonje, A. R., Fagundes, R. R., Gacesa, R., Weersma, R. K., VAN Goor, H., et al. (2023). The NRF2/Keap1 pathway as a therapeutic target in inflammatory bowel disease. *Trends Mol. Med.* 29, 830–842. doi:10.1016/j.molmed.2023.07.008

Guan, Y., Yin, Y., Zhu, Y. R., Guo, C., Wei, G., Duan, J. L., et al. (2013). Dissection of mechanisms of a Chinese medicinal formula: danhong injection therapy for myocardial ischemia/reperfusion injury *in vivo* and *in vitro*. *Evid-based Complement. Altern. Med.* 2013, 972370. doi:10.1155/2013/972370

Halestrap, A. P., Clarke, S. J., and Javadov, S. A. (2004). Mitochondrial permeability transition pore opening during myocardial reperfusion--a target for cardioprotection. *Cardiovasc Res.* 61, 372–385. doi:10.1016/S0008-6363(03)00533-9

Han, D., Wei, J., Zhang, R., Ma, W., Shen, C., Feng, Y., et al. (2016). Hydroxysafflor yellow A alleviates myocardial ischemia/reperfusion in hyperlipidemic animals through the suppression of TLR4 signaling. *Sci. Rep.* 6, 35319. doi:10.1038/srep35319

Heusch, G. (2019). Coronary microvascular obstruction: the new frontier in cardioprotection. *Basic Res. Cardiol.* 114, 45. doi:10.1007/s00395-019-0756-8

Heusch, G. (2020). Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat. Rev. Cardiol.* 17, 773–789. doi:10.1038/s41569-020-0403-y

He, W. (2022). *Effect and mechanism of hydroxysafflor yellow A on myocardial ischemic injury through Nrf2/Keap1/NF-κB signal pathway. Master Nanjing, China*. Nanjing University of Traditional Chinese Medicine.

Hu, T. X., Wen, A. D., Zhu, Y. R., Yue, G., and Zhao, R. H. (2015). Protective effect of danshensu and hydrosaffloryellow A for using alone or in combination on myocardial Ischemic-reperfusion injury in rats. *Mod. Chin. Med.* 17, 15–19. doi:10.13313/j.issn.1673-4890.2015.1.004

Huang, X., Qin, F., Zhang, H. M., Xiao, H. B., Wang, L. X., Zhang, X. Y., et al. (2009). Cardioprotection by Guanxin II in rats with acute myocardial infarction is related to its three compounds. *J. Ethnopharmacol.* 121, 268–273. doi:10.1016/j.jep.2008.10.029

Hu, T., Wei, G., XI, M., Yan, J., Wu, X., Wang, Y., et al. (2016). Synergistic cardioprotective effects of Danshensu and hydroxysafflor yellow A against myocardial ischemia-reperfusion injury are mediated through the Akt/Nrf2/HO-1 pathway. *Int. J. Mol. Med.* 38, 83–94. doi:10.3892/ijmm.2016.2584

Jin, M., Dong, N. N., Wu, W., Li, J. R., Zang, B. X., and Tung, J. (2009). Inhibition of hydroxysafflor yellow A against rat cardiomyocyte apoptosis. *Chin. Tradit. Herb. Drugs* 40, 924–930. doi:10.1155/2021/6643615

Joseph, P., Roy, A., Lonn, E., StöRK, S., Floras, J., Mielniczuk, L., et al. (2023). Global variations in heart failure etiology, management, and outcomes. *JAMA* 329, 1650–1661. doi:10.1001/jama.2023.5942

KräMER, O. H., Baus, D., Knauer, S. K., Stein, S., JäGER, E., Stauber, R. H., et al. (2006). Acetylation of Stat1 modulates NF-kappaB activity. *Genes Dev.* 20, 473–485. doi:10.1101/gad.364306

Liu, Y. G., Li, F. J., and Tang, F. (2015). Protective effect of hydroxysaffloryellow A on rats with myocardial ischemia and reperfusion injury. *Pharma Clin Chin Materia Med.* 31, 71–74. doi:10.13412/j.cnki.zyyl.2015.01.023

Liu, Y. N., Zhou, Z. M., and Chen, P. (2008). Evidence that hydroxysafflor yellow A protects the heart against ischaemia-reperfusion injury by inhibiting mitochondrial permeability transition pore opening. *Clin. Exp. Pharmacol. Physiol.* 35, 211–216. doi:10.1111/j.1440-1681.2007.04814.x

Liu, J., Zhang, D., Li, J., Feng, J., Yang, X., Shi, D., et al. (2011). Effects of Salvia miltiorrhiza and Carthamus tinctorius aqueous extracts and compatibility on rat myocardial ischemic reperfusion injury. *Zhongguo Zhongyao Zazhi* 36, 189–194. doi:10.4268/cjcmm20110222

Loboda, A., Damulewicz, M., Pyza, E., Jozkowicz, A., and Dulak, J. (2016). Role of Nrf2/HO-1 system in development, oxidative stress response and diseases: an evolutionarily conserved mechanism. *Cell Mol. Life Sci.* 73, 3221–3247. doi:10.1007/s00018-016-2223-0

Lundberg, J. O., and Weitzberg, E. (2022). Nitric oxide signaling in health and disease. *Cell* 185, 2853–2878. doi:10.1016/j.cell.2022.06.010

Macleod, M. R., O'Collins, T., Howells, D. W., and Donnan, G. A. (2004). Pooling of animal experimental data reveals influence of study design and publication bias. *Stroke* 35, 1203–1208. doi:10.1161/01.STR.0000125719.25853.20

MagalhãES, P. R., Reis, P. B. P. S., Vila-ViçOSA, D., Machuqueiro, M., and Victor, B. L. (2021). Identification of pan-assay INterference compoundS (PAINS) using an MD-based protocol. *Methods Mol. Biol.* 2315, 263–271. doi:10.1007/978-1-0716-1468-6_15

Mensah, G. A., Roth, G. A., and Fuster, V. (2019). The global burden of cardiovascular diseases and risk factors: 2020 and beyond. *J. Am. Coll. Cardiol.* 74, 2529–2532. doi:10.1016/j.jacc.2019.10.009

Min, J., and Wei, C. (2017). Hydroxysafflor yellow A cardioprotection in ischemia-reperfusion (I/R) injury mainly via Akt/hexokinase II independent of ERK/GSK-3β pathway. *Biomed. Pharmacother.* 87, 419–426. doi:10.1016/j.biopha.2016.12.113

Moghimpour Bijani, F., Vallejo, J. G., and Rezaei, N. (2012). Toll-like receptor signaling pathways in cardiovascular diseases: challenges and opportunities. *Int. Rev. Immunol.* 31, 379–395. doi:10.3109/08830185.2012.706761

Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., and Walters, M. A. (2017). The essential medicinal chemistry of curcumin. *J. Med. Chem.* 60, 1620–1637. doi:10.1021/acs.jmedchem.6b00975

Ni, B., Zhou, D., Jing, Y., and Liu, S. (2018). Hydroxysafflor yellow A protects against angiotensin II-induced hypertrophy. *Mol. Med. Rep.* 18, 3649–3656. doi:10.3892/mmr.2018.9399

Ong, S.-B., HernáNDEZ-ReséNDIZ, S., Crespo-Avilan, G. E., Mukhametshina, R. T., Kwek, X.-Y., Cabrera-Fuentes, H. A., et al. (2018). Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities. *Pharmacol. Ther.* 186, 73–87. doi:10.1016/j.pharmthera.2018.01.001

Page, M. J., Mckenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71. doi:10.1136/bmj.n71

Pang, Q., You, L., Meng, X., Li, Y., Deng, T., Li, D., et al. (2023). Regulation of the JAK/STAT signaling pathway: the promising targets for cardiovascular disease. *Biochem. Pharmacol.* 213, 115587. doi:10.1016/j.bcp.2023.115587

Peoples, J. N., Saraf, A., Ghazal, N., Pham, T. T., and Kwong, J. Q. (2019). Mitochondrial dysfunction and oxidative stress in heart disease. *Exp. Mol. Med.* 51, 1–13. doi:10.1038/s12276-019-0355-7

Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G., Ammirati, E., Baddour, L. M., et al. (2020). Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J. Am. Coll. Cardiol.* 76, 2982–3021. doi:10.1016/j.jacc.2020.11.010

Sahoo, G., Samal, D., Khandayataray, P., and Murthy, M. K. (2023). A review on caspases: key regulators of biological activities and apoptosis. *Mol. Neurobiol.* 60, 5805–5837. doi:10.1007/s12035-023-03433-5

Schirone, L., Forte, M., D'Ambrosio, L., Valenti, V., Vecchio, D., Schiavon, S., et al. (2022). An overview of the molecular mechanisms associated with myocardial ischemic injury: state of the art and translational perspectives. *Cells* 11, 1165. doi:10.3390/cells11071165

Sciarretta, S., Maejima, Y., Zablocki, D., and Sadoshima, J. (2018). The role of autophagy in the heart. *Annu. Rev. Physiol.* 80, 1–26. doi:10.1146/annurev-physiol-021317-121427

Senichkin, V. V., Pervushin, N. V., Zuev, A. P., Zhivotovsky, B., and Kopeina, G. S. (2020). Targeting bcl-2 family proteins: what, where, when? *Biochem. (Mosc).* 85, 1210–1226. doi:10.1134/S0006297920100090

Singh, R., Letai, A., and Sarosiek, K. (2019). Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. *Nat. Rev. Mol. Cell Biol.* 20, 175–193. doi:10.1038/s41580-018-0089-8

Spanagel, R. (2022). Ten points to improve reproducibility and translation of animal research. *Front. Behav. Neurosci.* 16, 869511. doi:10.3389/fnbeh.2022.869511

Su, N., Lu, F. P., Zhu, M. M., Zheng, Z. H., Shen, Y. J., Liu, T. Y., et al. (2018). Protective effect of astragaloside IV combined with hydroxysafflor yellow A on mice with myocardial infarction. *Chin. J. Exp. Tradit. Med. Form.* 24, 98–103.

Sun, Y. Q. (2012). *The effect of HSYA on anti-myocardial ischemia-reperfusion injury by regulating mitochondrion*. Doctor: JiLin University.

Toldo, S., Marchetti, C., Mauro, A. G., Chojnacki, J., Mezzaroma, E., Carbone, S., et al. (2016). Inhibition of the NLRP3 inflammasome limits the inflammatory injury following myocardial ischemia-reperfusion in the mouse. *Int. J. Cardiol.* 209, 215–220. doi:10.1016/j.ijcard.2016.02.043

Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Anderson, C. A. M., Arora, P., Avery, C. L., et al. (2023). Heart disease and stroke statistics-2023 update: a report from the American heart association. *Circulation* 147, e93–e621. doi:10.1161/CIR.0000000000001123

Wang, H. M. (2009). Effects of hydroxysafflor yellow A on FFA, NO and iNOS in rats of myocardial infarction. *Qilu Pharma Aff.* 28, 625–627.

Wang, T., Fu, F. H., Han, B., Li, G. S., Zhang, L. M., and Liu, K. (2009). Hydroxysafflor yellow A reduces myocardial infarction size after coronary artery ligation in rats. *Pharm. Biol.* 47, 458–462. doi:10.1080/13880200902822612

Wang, T., Fu, F. H., Han, B., Zhu, M., Li, G. S., and Liu, K. (2007). Protection and mechanisms of hydroxysafflor yellow A on experimental myocardial infarction in rats. *Chin. Tradit. Herb. Drugs* 38, 1853–1856.

Ware, J. A., and Simons, M. (1997). Angiogenesis in ischemic heart disease. *Nat. Med.* 3, 158–164. doi:10.1038/nm0297-158

WCOTROCHADIC (2023). Report on cardiovascular health and diseases in China 2022: an updated summary. *Biomed. Environ. Sci.* 36, 669–701. doi:10.3967/bes2023.106

Wei, G., Duan, J. L., Yin, Y., Wang, Y. H., and Wen, A. D. (2016). Effect of danshensu and hydroxysafflower yellow A on promoting angiogenesis and preventing myocardial infarction in rats. *Lishizhen Med. Mater Med. Res.* 27, 2576–2578.

Wei, G., Yin, Y., Duan, J., Guo, C., Zhu, Y., Wang, Y., et al. (2017). Hydroxysafflor yellow A promotes neovascularization and cardiac function recovery through HO-1/VEGF-A/SDF-1α cascade. *Biomed. Pharmacother.* 88, 409–420. doi:10.1016/j.biopha.2017.01.074

Wei, J., Zhang, Y., Li, H., Wang, F., and Yao, S. (2023). Toll-like receptor 4: a potential therapeutic target for multiple human diseases. *Biomed. Pharmacother.* 166, 115338. doi:10.1016/j.biopha.2023.115338

Xu, A. B., Liu, J. G., Zhang, J., and Li, J. X. (2014). Hydroxysafflor yellow A for ameliorating injury of myocardial ischemia/reperfusion in SD rats. *Chin. J. Evid. Based Cardiovasc Med.* 6, 733–736.

Xu, L. J., Chen, R. C., Ma, X. Y., Zhu, Y., Sun, G. B., and Sun, X. B. (2020). Scutellarin protects against myocardial ischemia-reperfusion injury by suppressing NLRP3 inflammasome activation. *Phytomedicine* 68, 153169. doi:10.1016/j.phymed.2020.153169

Xue, X., Deng, Y., Wang, J., Zhou, M., Liao, L., Wang, C., et al. (2021). Hydroxysafflor yellow A, a natural compound from Carthamus tinctorius L with good effect of alleviating atherosclerosis. *Phytomedicine* 91, 153694. doi:10.1016/j.phymed.2021.153694

Ye, J., Lu, S., Wang, M., Ge, W., Liu, H., Qi, Y., et al. (2020). Hydroxysafflor yellow A protects against myocardial ischemia/reperfusion injury via suppressing NLRP3 inflammasome and activating autophagy, *Front. Pharmacol.* 11, 1170. doi:10.3389/fphar.2020.01170

Yu, H., and Qu, L. (2023). Protective effect of hydroxysafflor yellow A on myocardial ischemia/reperfusion injury in rats based on p38MAPK/SERCA2α pathway. *Cell Mol. Immunol.* 39, 1395–1401+1408.

Zhang, J. J., Zhang, Z. Y., and Wang, N. (2012). Effect and mechanism of action of hydroxysafflor yellow A on myocardial ischemia-reperfusion injury in rats. *Chin. Hosp. Pharm. J.* 32, 1526–1530. doi:10.13286/j.cnki.chinhosppharmacyj.2012.19.006

Zhang, R., Li, G., Zhang, Q., Tang, Q., Huang, J., Hu, C., et al. (2018). Hirsutine induces mPTP-dependent apoptosis through ROCK1/PTEN/PI3K/GSK3β pathway in human lung cancer cells. *Cell Death Dis.* 9, 598. doi:10.1038/s41419-018-0641-7

Zhang, Y., and Zhang, Y. (2020). Effects of hydroxysafflor yellow A on inflammatory factors and NF-κB in rats with myocardial ischemia-reperfusion injury. *Chin J Inte Med Cardio/Cere Dis.* 18, 2603–2607.

Zhao, Z. Q., Morris, C. D., Budde, J. M., Wang, N. P., Muraki, S., Sun, H. Y., et al. (2003). Inhibition of myocardial apoptosis reduces infarct size and improves regional contractile dysfunction during reperfusion. *Cardiovasc Res.* 59, 132–142. doi:10.1016/s0008-6363(03)00344-4

Zhao, B., Hu, K., Zeng, X., Kwong, J. S. W., Li, B., Chen, H., et al. (2022). Development of a reporting guideline for systematic reviews of animal experiments in the field of traditional Chinese medicine. *J. Evid. Based Med.* 15, 152–167. doi:10.1111/jebm.12480

Zhao, F., Wang, P., Jiao, Y., Zhang, X., Chen, D., and Xu, H. (2020). Hydroxysafflor yellow A: a systematical review on botanical resources, physicochemical properties, drug delivery system, pharmacokinetics, and pharmacological effects. *Front. Pharmacol.* 11, 579332. doi:10.3389/fphar.2020.579332

Zhou, M. X., Fu, J. H., Zhang, Q., and Wang, J. Q. (2015). Effect of hydroxy safflower yellow A on myocardial apoptosis after acute myocardial infarction in rats. *Genet. Mol. Res.* 14, 3133–3141. doi:10.4238/2015.April.10.24

Zhou, D., Ding, T., Ni, B., Jing, Y., and Liu, S. (2019). Hydroxysafflor Yellow A mitigated myocardial ischemia/reperfusion injury by inhibiting the activation of the JAK2/STAT1 pathway. *Int. J. Mol. Med.* 44, 405–416. doi:10.3892/ijmm.2019.4230

Zou, J., Wang, N., Liu, M., Bai, Y., Wang, H., Liu, K., et al. (2018). Nucleolin mediated pro-angiogenic role of Hydroxysafflor Yellow A in ischaemic cardiac dysfunction: post-transcriptional regulation of VEGF-A and MMP-9. *J. Cell. Mol. Med.* 22, 2692–2705. doi:10.1111/jcmm.13552

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 29 May 2025
DOI 10.3389/fphar.2025.1529478

OPEN ACCESS

EDITED BY
Chen Huei Leo,
National University of Singapore, Singapore

REVIEWED BY
Guang Chen,
The University of Hong Kong, Hong Kong, SAR China
Yuxiang Fei,
China Pharmaceutical University, China

*CORRESPONDENCE
Min Yang,
yangmin@ahmu.edu.cn
Yue Liu,
liuyueheart@hotmail.com

RECEIVED 17 November 2024
ACCEPTED 19 May 2025
PUBLISHED 29 May 2025

CITATION
Shi W, Xu Y, Wei J, Zhang X, Zhu S, Guo H, Huang Q, Qi C, Hua T, Liu Y and Yang M (2025) Plant-derived secondary metabolites and nanotechnology: innovative strategies and emerging challenges in myocardial ischemia-reperfusion injury therapy.
Front. Pharmacol. 16:1529478.
doi: 10.3389/fphar.2025.1529478

Plant-derived secondary metabolites and nanotechnology: innovative strategies and emerging challenges in myocardial ischemia-reperfusion injury therapy

Wei Shi[1,2], Yang Xu[1,2], Jian Wei[1,2], Xiaoyu Zhang[1,2], Shuaijie Zhu[1,2], Heng Guo[1,2], Qihui Huang[1,2], Chuyao Qi[1,2,3,4], Tianfeng Hua[1,2], Yue Liu[3,4]* and Min Yang[1,2]*

[1]The Second Department of Critical Care Medicine, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China, [2]Laboratory of Cardiopulmonary Resuscitation and Critical Care, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China, [3]National Clinical Research Center for TCM Cardiology, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing, China, [4]Key Laboratory of Disease and Syndrome Integration Prevention and Treatment of Vascular Aging, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Beijing, China

Therapy for acute myocardial infarction often causes myocardial ischemia-reperfusion injury (MIRI), which is characterized by oxidative stress, inflammation, and apoptosis. Traditional therapies have shown poor effectiveness because of their low absorption and inappropriate targeting. Recently, nanotechnology has emerged as a promising treatment option for MIRI. Nanocarriers, such as liposomes, polymers, inorganic nanoparticles, and hybrid nanoparticles, make therapies more effective by making drugs more stable, improving targeting accuracy and lowering side effects. Plant-derived secondary metabolites and nanoparticles, specifically those containing *Panax notoginseng* saponins and flavonoids, have been shown to work together as a therapeutic approach. These nanoparticles have antioxidant, anti-inflammatory, and anti-apoptotic properties that significantly reduce myocardial injury after reperfusion. Targeting specificity and safety limit clinical translation, even with significant technological developments in these areas. Herein, we review current studies on nanocarriers and plant-derived secondary metabolite nanoparticles for MIRI treatment, as well as potential future clinical applications and limitations.

KEYWORDS

nanoparticles, myocardial ischemia-reperfusion injury, plant-derived secondary metabolites, nanocarriers, targeting strategies

1 Introduction

The incidence of ischemic heart disease, a leading cause of death and disability worldwide, has been rapidly increasing as people age and adopt unhealthy lifestyles. Public health services have been substantially affected by this trend (Safiri et al., 2022). Major symptoms of ischemic heart disease, acute myocardial infarction, are often treated with reperfusion treatments, such as percutaneous coronary intervention and coronary

artery bypass grafting, which attempt to restore blood flow to the ischemic myocardium. Although reperfusion significantly reduces myocardial necrosis, it may also aggravate myocardial ischemia-reperfusion injury (MIRI), thereby compromising the patient's prognosis (Schäfer et al., 2022). Often leading to arrhythmia and heart failure, MIRI is characterized by a range of pathogenic mechanisms, including oxidative stress, inflammation, and apoptosis (Welt et al., 2024).

Current clinical intervention strategies for MIRI face multidimensional technical challenges (Liu et al., 2023). Existing therapeutic approaches primarily include pharmacological treatments, ischemic conditioning, and physical interventions; however, their clinical efficacy remains significantly constrained. In the pharmacological domain, conventional agents such as antioxidants and calcium channel blockers suffer from limitations in targeted delivery efficiency and suboptimal pharmacokinetics, characterized by rapid systemic clearance, insufficient myocardial tissue accumulation, and adverse effects (e.g., immunosuppression associated with cyclosporine A) (Upadhaya et al., 2017). For non-pharmacological strategies, ischemic conditioning demonstrates procedural simplicity but exhibits substantial heterogeneity in clinical outcomes across randomized controlled trials (Pei et al., 2014; Donato et al., 2017) Hypothermia therapy, as a physical intervention, faces critical technical challenges in translational medicine, particularly in precise temperature control and rewarming management (Voronkov et al., 2024). Notably, although certain botanical drugs show therapeutic potential, their clinical reproducibility is hindered by compositional complexity, undefined molecular targets, and non-standardized preparation protocols, leading to inconsistent pharmacokinetic profiles (Xu et al., 2021).

Recent advances in nanodelivery systems based on plant-derived secondary metabolites (PDSMs) offer innovative avenues to overcome MIRI treatment limitations. Through rational structural design and functional modification of nanocarriers, these systems effectively address the drawbacks of conventional drug delivery, significantly enhancing targeting efficiency and biostability (Wei et al., 2022). Research priorities focus on bioactive secondary metabolites with well-characterized pharmacological properties, including baicalein (flavonoid from *Scutellaria baicalensis* Georgi), notoginsenoside R1 (triterpenoid saponin from *Panax notoginseng* (Burk.) F.H. Chen), and curcumin (polyphenol from *Curcuma longa* L.). While these compounds exhibit anti-inflammatory and antioxidant activities, their inherent low solubility and nonspecific biodistribution limit therapeutic efficacy. Current studies demonstrate that polydopamine-modified nanocarriers encapsulating baicalein activate the Nrf2-ARE pathway, markedly suppressing reactive oxygen species (ROS) accumulation in myocardial tissues (Chen et al., 2024). Mesoporous silica nanoparticles conjugated with CD11b antibody (MSN-NGR1-CD11b) enhance cardiac repair by suppressing reactive oxygen species (ROS) accumulation through activation of AKT/MAPK signaling pathways in myocardial infarction (Li H. et al., 2022). Similarly, curcumin nanoparticles significantly reduce oxidative stress markers and elevate antioxidant capacity in diabetic rats with acute myocardial injury, further supporting the efficacy of nanotechnological approaches in mitigating ROS-mediated myocardial damage (Boarescu et al., 2019b).

This work reviews recent advancements in the treatment of MIRI using PDSM nanoparticles. By focusing on their potential to enhance therapeutic efficacy, improve targeting precision, and reduce side effects, we evaluate current research and explore the clinical feasibility of PDSM nanoparticles. Additionally, we propose novel approaches for cardiovascular disease treatment.

2 Methods

A systematic literature search was conducted across multiple electronic databases (PubMed, Web of Science, Scopus, ScienceDirect, Embase) to identify studies published up to November 2024. Inclusion criteria encompassed *in vitro* and *in vivo* investigations evaluating the therapeutic effects of botanical drugs/PDSMs combined with nanotechnology for MIRI. The search strategy employed the following Boolean operators and keywords in titles/abstracts/keywords (nano OR nanoparticle* OR nanocarrier OR "drug delivery" OR nanophytochemical* OR nanophytomedicine* OR liposome* OR polymer* OR inorganic*) AND ("traditional Chinese medicine" OR TCM OR "Chinese herbal medicine" OR plant* OR "phytochemical extract" OR "herbal drug*" OR "botanical drug*" OR "medicinal plants" OR "plant-derived secondary metabolites") AND ("myocardial ischemia-reperfusion injury" OR MIRI OR "cardiac ischemia-reperfusion injury" OR "acute myocardial infarction")*. Non-English publications and studies lacking experimental validation were excluded to ensure methodological rigor.

3 Targeting strategies of nanoparticles

Nanotechnology demonstrates enhanced drug delivery efficiency and therapeutic efficacy in MIRI through multimodal targeting approaches. Passive targeting capitalizes on the enhanced permeability and retention (EPR) effect to promote nanoparticle accumulation in ischemic myocardium, thereby reducing systemic adverse effects (Yao et al., 2015; Li et al., 2020; Lan et al., 2022). Active targeting strategies utilize antibody or peptide-modified nanoparticles to improve cardiomyocyte-specific binding affinity and drug internalization efficiency (Wei et al., 2024). Magnetic guidance systems enable precise spatiotemporal delivery through external magnetic field manipulation (Wei et al., 2024). Stimuli-responsive platforms integrated with biomimetic designs achieve pathology-triggered drug release mechanisms, such as oxidative stress-responsive payload deployment, while maintaining enhanced biocompatibility and targeting specificity (Bae et al., 2016; Wang J. et al., 2023; Wang et al., 2023 Y.; Zhou et al., 2023). Emerging hybrid systems combining passive-active targeting synergies with multidrug co-delivery capabilities present a transformative paradigm for optimizing MIRI intervention (Sun et al., 2012; Yang et al., 2023).

Abbreviations: MIRI, Myocardial ischemia-reperfusion injury; PDSMs, Plant-derived secondary metabolites; EPR, Enhanced Permeability and Retention; ROS, Reactive oxygen species; PEG, Polyethylene glycol; RAGE, Receptor of Advanced Glycation Endproducts; TPP, Triphenylphosphonium; PLGA, Polylactic acid/glycolic acid; NGR1, Notoginsenoside R1.

TABLE 1 Summary of the application and advantages of different types of nanoparticles in MIRI.

Type of nanocarriers	Plant-derived secondary metabolites	Models	Efficacy	Safety	References
Neutrophil membrane-camouflaged MSN	Allicin	*In vitro*: Rat cardiac microvascular endothelial cells (CMECs) hypoxia-reoxygenation (H/R) injury model *In vivo*: Wistar rat MIRI model	Improved cardiac function, reduced myocardial infarct size, inhibition of ferroptosis, enhanced microvascular function, antioxidant and anti-inflammatory effects	Hemolysis rate <5% (at 100 μg/mL); no pathological damage in major organs; no significant toxicity to CMECs	Li et al. (2024)
Neutrophil decoys	18β-Glycyrrhetinic acid	Mouse MIRI model	Suppressed oxidative stress, reduced myocardial infarct size, improved cardiac function, blocked HMGB1-mediated inflammatory cascade	No hemolysis or coagulation abnormalities; no pathological damage in major organs; no significant toxicity to cardiomyocytes or ECs	Han et al. (2024)
PLGA-PEG nanoparticles	Orientin, Vitexin, Quercetin	*In vitro*: H9c2 cardiomyocyte H/R injury model *In vivo*: SD rat isoproterenol (ISO)-induced acute myocardial ischemia model	Improved cardiac function, reduced myocardial injury, regulated oxidative stress, anti-inflammatory effects	Hemolysis rate <5% (at 100 μg/mL); no pathological damage in major organs; no significant toxicity to H9c2 cells	Jing et al. (2024)
PLGA nanoparticles	Dihydromyricetin	*In vitro*: H_2O_2-induced oxidative stress model in rat H9c2 cardiomyocytes *In vivo*: SD rat pharmacokinetic model	Increased cardiomyocyte survival, reduced oxidative damage, improved bioavailability, optimized pharmacokinetic parameters	No significant cytotoxicity; excellent biocompatibility of PLGA material	Du et al. (2024)
Carbon dots	Curcumae Radix	*In vitro*: H_2O_2-induced oxidative stress model in H9c2 cardiomyocytes *In vivo*: SD rat ISO-induced acute myocardial infarction (AMI) model	Improved cardiac function, reduced myocardial infarct size, restored ATPase activity, significantly lowered blood lipid levels	Low cytotoxicity (H9c2 cell viability >95% at ≤125 μg/mL); no reported cardiac pathological damage	Dong et al. (2024)
Salvia-derived exosome-like nanoparticles	Salvia miltiorrhiza	C57BL/6 mouse MIRI model	Promoted endothelial cell proliferation/migration, enhanced myocardial angiogenesis, improved cardiac function, reduced myocardial fibrosis and inflammation	No histological signs of inflammation or injury in organs; excellent systemic compatibility after intravenous injection	Zhang et al. (2024)
Magnesium Ion-Doped Mesoporous Bioactive Glasses	Gallic Acid	C57BL/6 mouse MIRI model	ROS scavenging, reduced cardiomyocyte apoptosis, promoted angiogenesis, suppressed inflammation, improved cardiac function	No significant toxicity to HL-1 cardiomyocytes or HUVECs at ≤100 μg/mL; good hemocompatibility; no hemolysis or organ damage	Yu et al. (2024)
PEG-modified cationic liposomes	Apigenin	*In vitro*: ISO-treated H9C2 cells simulating myocardial ischemic injury *In vivo*: SD rat ISO-induced myocardial ischemic injury model	Reduced cardiomyocyte oxidative stress, decreased inflammatory factor secretion, inhibited apoptosis, reduced infarct size, improved ECG abnormalities	No significant cytotoxicity; excellent blood compatibility; no organ toxicity	Liu et al. (2024)
PEG-PPS self-assembled nanomicelles	Tilianin	H9c2 cardiomyocyte H/R injury model	Reduced inflammatory factors and oxidative stress, inhibited apoptosis	No significant toxicity to H9c2 cardiomyocytes at ≤5 μg/mL	Wang et al. (2018)

4 Application of nanocarriers in MIRI

Nanotechnology offers innovative therapeutic strategies for MIRI by enabling precision drug delivery, enhancing pharmaceutical stability, and improving bioavailability. The integration of PDSMs' inherent bioactivities with functionalized nanocarrier designs synergistically modulates oxidative stress, inflammatory responses, and apoptotic pathways, thereby overcoming the limitations of conventional treatment modalities. The following sections review several common nanocarriers applied in MIRI intervention, detailing their structural configurations and therapeutic mechanisms (Table 1; Figure 1).

Synthetic nanocarriers enable efficient drug loading and controlled release through material engineering design, primarily

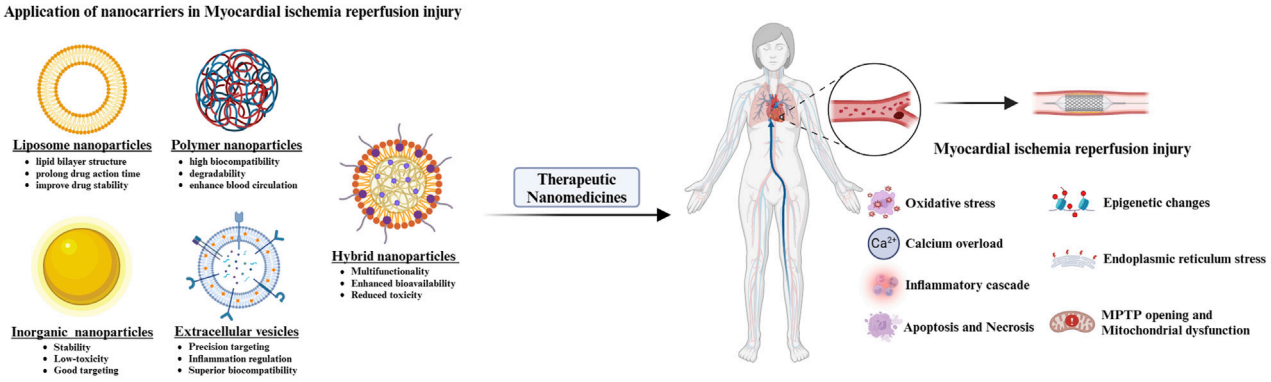


FIGURE 1
Application of nanocarriers in MIRI.

including polymer-based nanocarriers (e.g., poly (lactic-co-glycolic acid), PLGA), inorganic nanocarriers, and lipid-based systems. Du et al. engineered PLGA nanoparticles incorporating dihydromyricetin (DMY, a flavonoid metabolite derived from *Ampelopsis grossedentata* (Hand.-Mazz.) W.T. Wang), which demonstrated enhanced oral bioavailability. These DMY-PLGA nanoparticles attenuated oxidative damage by activating the PGC1α/PPARα pathway (Du et al., 2024). Jing et al. formulated nanoparticles (OVQ-NPs) containing bioactive flavonoids (hyperoside, vitexin, quercetin) from *Polygonum orientale* L., which regulated oxidative stress and inflammatory pathways through sustained-release properties, effectively reducing myocardial enzyme levels and suppressing apoptosis (Jing et al., 2024). Yu et al. designed magnesium-doped mesoporous bioactive glass nanoparticles (MgNPs/GA) loaded with gallic acid (GA, a polyphenolic metabolite from *Rhus chinensis* Mill.), achieving dual-phase myocardial protection through early-phase ROS scavenging and late-phase Mg^{2+}-mediated angiogenesis promotion with macrophage M2 polarization (Yu et al., 2024). Carbon dots derived from carbonized *Curcuma longa L.* rhizomes (CRC-CDs) directly enhanced myocardial antioxidant capacity and inhibited apoptosis, demonstrating the innovative potential of nanoscale botanical drug formulations (Dong et al., 2024). Additionally, PEGylated liposomes (P-CLP-A/R) loaded with apigenin (a flavonoid from *Apium graveolens* L.) synergistically modulated the RAGE/NF-κB pathway through targeted delivery, significantly ameliorating ischemic myocardial injury (Liu et al., 2024).

Extracellular vesicles represent biomimetic nanocarriers that enhance drug targeting and biocompatibility by mimicking biological components. Zhang et al. isolated exosome-like nanoparticles from *Salvia miltiorrhiza* Bunge, which promoted endothelial cell migration and myocardial neovascularization through inherent pro-angiogenic activity, offering a non-invasive therapeutic strategy for reperfusion injury (Zhang et al., 2024). These exosomes inherit bioactivity from parent cells while exhibiting cost-effectiveness and high yield, highlighting clinical translation potential. For composite nanocarriers, Li et al. engineered neutrophil membrane-camouflaged mesoporous silica nanoparticles (AL@MSNs@NM) that leveraged natural neutrophil interactions with inflamed myocardial microvascular endothelial cells. This system enabled precision delivery of allicin (a sulfur-containing compound from *Allium sativum* L.), inhibiting ferroptosis and upregulating PECAM-1 expression to improve cardiac function and reduce infarct size (Li et al., 2024). Similarly, Han et al. developed neutrophil degranulosomes (NDs) loaded with 18β-glycyrrhetinic acid (GA, a triterpenoid saponin from *Glycyrrhiza uralensis* Fisch.), which achieved synchronized mitigation of oxidative stress and inflammation via H_2O_2-responsive release, effectively attenuating myocardial fibrosis and remodeling (Han et al., 2024). These hybrid systems overcome limitations of single-component carriers by integrating biological membrane functionality with synthetic material-controlled release properties.

5 Plant-derived secondary metabolite nanoparticles in MIRI

The increasing recognition of PDSMs in the treatment of MIRI has highlighted the significant therapeutic potential of botanical drug extracts, which possess strong anti-inflammatory, antioxidant, anti-apoptotic, and cardiovascular-protective properties (Dong et al., 2023). Thus, PDSMs are promising therapeutic approaches for the treatment of MIRI. Concurrently, the rapid advancement of nanotechnology has opened new avenues for research and clinical applications of PDSMs, particularly in two key areas.

Processing drugs into nanoscale suspensions or co-crystals markedly increases their surface areas. This approach enhances the solubility of these drugs and improves their chemical stability. For example, studies have demonstrated that converting curcumin and quercetin into nanodispersions significantly boosts their bioavailability and pharmacological efficacy. This nanoprocessing technology effectively addresses the inadequate absorption of PDSMs by the body (Gao et al., 2010; Li H. et al., 2021).

Nanoparticles are often used for the targeted delivery of PDSMs. Unlike synthetic drugs, PDSMs often non-selectively affect multiple organ systems. However, these natural chemicals present significant therapeutic challenges, including low absorption rates, poor chemical stability, limited permeability, and risk of liver and

TABLE 2 Mechanisms and therapeutic advantages of nanocarriers delivering plant-derived secondary metabolites in myocardial ischemia-reperfusion injury.

Extract type	Nanocarrier type	Model	Drug treatment	Effects	References
Panax notoginseng (PNS, total extract)	Core-shell hybrid liposomal vesicles (HLV)	Rat AMI model	PNS (30 mg/kg, po); PNS-HLV (30 mg/kg, po) Duration: Pre-treatment for 10 days	Reduces oxidative stress; Long-term stability (4°C, 12 months); High encapsulation efficiency; Enhanced sustained-release properties	Zhang et al. (2012)
Salvianolic acid B (Sal B, monomer) + *Panax notoginseng* (PNS, total extract)	RGD-modified lipid-polymer hybrid nanoparticles (RGD-LPNs)	Rat AMI model	Free Sal B (30 mg/kg, iv); Free PNS (30 mg/kg, iv); RGD-S/P-LPNs (Sal B 10 mg/kg, PNS 10 mg/kg, iv) Duration: Pre-treatment for 10 days, observation for 3 days post-surgery	Significantly reduces myocardial infarction area; Improves cardiac drug distribution and prolongs plasma circulation time; Sustained release *in vitro* with no significant cytotoxicity	Qiu et al. (2017)
Notoginsenoside R1 (NGR1, monomer)	Mesoporous silica nanoparticles conjugated with CD11b antibody (MSN-CD11b antibody)	*In vivo*: Mouse myocardial infarction (MI) model *In vitro*: H9c2 cells and primary cardiomyocytes under oxygen-glucose deprivation	NGR1: *In vivo* 40 mg/kg (iv, oral dose equivalent to nano-group); *In vitro* 100 μmol/L (pre-treatment for 30 min) MSN-NGR1-CD11b antibody: 267 ng/kg (iv) Duration: Single dose 24 h post-surgery, observation for 4 weeks	Improves cardiac function, reduces infarction area and collagen deposition; Inhibits cardiomyocyte apoptosis, modulates macrophage phenotypes and inflammatory factors; Promotes angiogenesis via AKT, MAPK, and Hippo signaling pathways	Li et al. (2022a)
Panax japonicus (C.A.Mey.) Hoo & Tseng (Araliaceae) (total extract)	Silver nanoparticles (Ag@ *P.japonicus*)	Wistar rat ISO-induced MI model	Ag@*P. japonicus:* 50, 100 μg/kg Duration: Pre-treatment for 14 days, ISO administration for 2 days	Ameliorates ECG abnormalities, reduces heart/body weight ratio and infarction area; Alleviates myocardial injury and oxidative stress; Inhibits inflammatory cytokines and apoptosis; Regulates PI3K/Akt/mTOR and Keap1/Nrf2/HO-1 pathways	Xu et al. (2024)
Ginsenoside Rg3 (monomer)	ROS-responsive polymeric nanoparticles (PEG-b-PPS)	*In vivo*: SD rat MIRI model *In vitro*: H9c2 cells under H/R	*In vitro*: Rg3 (10 nM) *In vivo*: PEG-b-PPS-Rg3 (0.5 mg Rg3/100 μL, intramyocardial injection) Duration: *In vitro* 24 h; Single dose post-reperfusion, observation for 2 h	*In vitro*: Enhances H9c2 cell viability post-H/R injury, reduces ROS generation and apoptosis; *In vivo*: Reduces myocardial infarction area, improves cardiac function, alleviates myocardial injury; Attenuates oxidative stress, inflammation, and fibrosis (downregulates TGF-β/Smad); Targets FoxO3a to activate anti-apoptotic pathways	Li et al. (2020)
Curcumae Radix Carbonisata (CRC, total extract)	Carbon dots (CDs)	*In vivo*: SD rat ISO-induced MI model *In vitro*: H9c2 cells under H_2O_2 injury	*In vivo*: CRC-CDs (1.75–7 mg/kg/day, po) *In vitro*: CRC-CDs (31.25–125 μg/mL) Duration: *In vivo* pre-treatment for 14 days + ISO induction for 2 days; *In vitro* pre-treatment for 24 h	Ameliorates ECG abnormalities, reduces myocardial infarction area; Alleviates myocardial injury and oxidative stress; Inhibits cardiomyocyte apoptosis; Improves mitochondrial ATPase activity	Dong et al. (2024)
Curcumin (monomer)	Polymeric nanoparticles	Wistar rat ISO-induced MI model	Curcumin (100–200 mg/kg, po); Curcumin nanoparticles (100–200 mg/kg, po) Duration: Pre-treatment	Ameliorates ECG abnormalities; Reduces myocardial injury and oxidative stress; Alleviates cardiomyocyte edema,	Boarescu et al. (2019b)

(Continued on following page)

TABLE 2 (*Continued*) Mechanisms and therapeutic advantages of nanocarriers delivering plant-derived secondary metabolites in myocardial ischemia-reperfusion injury.

Extract type	Nanocarrier type	Model	Drug treatment	Effects	References
			for 15 days, ISO induction for 2 days	inflammatory infiltration, and fibrosis	
Curcumin (monomer)	Polymeric nanoparticles	Streptozotocin (STZ)-induced diabetic + ISO-induced MI rat model	Curcumin (200 mg/kg, po); Curcumin nanoparticles (200 mg/kg, po) Duration: Pre-treatment for 7 days (pre-DM induction) + 15 days (post-DM induction), ISO induction for 2 days	Reduces myocardial injury; Lowers inflammatory cytokines; Improves oxidative stress	Boarescu et al. (2019a)
Curcumin (monomer)	Polylactic acid nanoparticles (CurNisNp)	Guinea pig ISO-induced MI model	CurNisNp (10, 21 mg/kg, po) Duration: Pre-treatment for 7 days, ISO induction for 2 days	Ameliorates ECG abnormalities; Reduces myocardial injury and oxidative stress; Alleviates cardiomyocyte necrosis and inflammatory infiltration	Nabofa et al. (2018)
Puerarin (PUE, monomer)	Ischemic myocardium-targeting peptide (IMTP) and triphenylphosphonium cation (TPP)-co-modified liposomes (PUE@T/I-L)	*In vitro*: H9c2 cells under H/R *In vivo*: C57BL/6 mouse MIRI model	*In vitro*: PUE@T/I-L (20 μM, administered during reoxygenation for 12 h) *In vivo*: PUE@T/I-L (15 mg/kg, iv, 5 min pre-reperfusion) Duration: *In vitro* 12 h; Single dose *In vivo*	*In vitro*: Inhibits mitochondrial permeability transition pore (mPTP) opening, reduces ROS generation, enhances SOD activity, improves cell viability post-H/R injury; *In vivo*: Reduces myocardial infarction area, alleviates myocardial injury; Improves mitochondrial morphology, inhibits apoptosis, targets ischemic myocardium mitochondria	Wang et al. (2024a)
Puerarin (PUE, monomer)	RGD-modified and PEGylated solid lipid nanoparticles (RGD/PEG-PUE-SLN)	SD rat AMI model (left anterior descending coronary artery ligation)	Free PUE (50 mg/kg, iv); RGD/PEG-PUE-SLN (50 mg/kg, iv) Duration: Single dose, observation for 36 h	Prolongs systemic circulation time; Enhances cardiac drug concentration, reduces myocardial infarction area; No significant cytotoxicity *In vitro*; Improves myocardial histopathology *In vivo*	Dong et al. (2017)
Quercetin (monomer)	Mesoporous silica nanoparticles (Q-MSNs)	*In vivo*: SD rat MIRI model *In vitro*: Neonatal SD rat primary cardiomyocytes under H/R	*In vitro*: Free Quercetin (10–40 μM); Q-MSNs (10–40 μM) *In vivo*: Free Quercetin (40 μmol/L, po); Q-MSNs (40 μmol/L, po) Duration: *In vivo* pre-treatment for 10 days; *In vitro* pre-treatment for 24 h	Activates JAK2/STAT3 pathway, inhibits cardiomyocyte apoptosis; Reduces myocardial infarction area, improves ventricular remodeling; Ameliorates oxidative stress; *In vitro*: Enhances cell viability post-H/R injury	Liu et al. (2021a)
Quercetin (monomer)	Poly (lactic-co-glycolic) acid nanoparticles (PLGA-NPs)	*In vitro*: H9c2 cardiomyocytes under H/R	Free Quercetin (1–10 μM); PLGA-Quercetin NPs (1–10 μM) Duration: 24 h pre-treatment	Inhibits mitochondrial superoxide generation; Enhances cell viability, reduces thiol oxidative damage; Preserves mitochondrial membrane potential and ATP synthesis, maintains mitochondrial respiration	Lozano et al. (2019)
Berberine (BBR, monomer)		SD rat MI model	BBR@PLGA@PLT NPs (0.8 mg BBR/kg, iv;	Reduces M1 macrophages ($CD86^+$) and increases	Zhu et al. (2023a)

(Continued on following page)

TABLE 2 (*Continued*) Mechanisms and therapeutic advantages of nanocarriers delivering plant-derived secondary metabolites in myocardial ischemia-reperfusion injury.

Extract type	Nanocarrier type	Model	Drug treatment	Effects	References
	Platelet membrane-coated PLGA nanoparticles (BBR@PLGA@PLT NPs)		additional doses on days 0, 3, 6 post-MI) Duration: Observation for 3 days (inflammatory markers) to 28 days (cardiac function)	M2 macrophages (CD206+) in infarct zone; Inhibits inflammatory cytokine secretion; Improves cardiac function and scar elasticity at 28 days; Targets infarcted myocardium with minimal liver uptake and organ toxicity	
Berberine (BBR, monomer)	PEGylated liposomes (BB-lip)	*In vivo*: C57BL/6 J mouse MI model *In vitro*: RAW 264.7 macrophages under LPS stimulation	Free BBR (1.5 mg/kg, iv; additional doses on days 0, 3, 6 post-MI) BB-lip (1.5 mg/kg, iv; additional doses on days 0, 3, 6 post-MI) Duration: *In vitro* 2 h pre-treatment +12 h LPS stimulation; *In vivo* observation for 28 days	*In vitro*: Free BBR inhibits IL-6 secretion, BB-lip shows no inhibition due to sustained release; *In vivo*: Preserves LVEF at 28 days, reduces left ventricular end-diastolic/systolic volumes, inhibits fibrosis and inflammatory infiltration; Liposomes target infarct zone, co-localize with macrophages, reduce systemic toxicity	Allijn et al. (2017)
Tanshinone IIA (monomer)	Methoxy polyethylene glycol-polylactic acid-vitamin E succinate nanoparticles (mPEG-PLA-TPGS NPs)	C57BL/6 mouse MI model	Free Tanshinone IIA (1, 10 mg/kg, iv); Tanshinone IIA-NPs (0.5 mL/kg, iv) Duration: Post-surgery administration for 5 consecutive days, observation for 4 weeks	Improves cardiac function; Inhibits myocardial fibrosis; Exerts anti-inflammatory and anti-apoptotic effects via NF-κB pathway inhibition (reduced phosphorylated IκB and nuclear p65)	Mao et al. (2018)

kidney damage. Nanotechnology has distinct benefits in addressing these difficulties, as nanoparticle-based delivery methods may significantly enhance the bioavailability and therapeutic efficiency of PDSMs while reducing side effects. This precise delivery approach addresses long-standing issues in PDSMs treatment and offers new possibilities for the therapeutic use of potent botanical drug medications (Xie et al., 2024).

Nanotechnology has provided new prospects for expanding the study of PDSMs while offering technical support for their clinical application. The integration of several PDSMs with nanotechnology has been successfully implemented in therapeutic investigations targeting MIRI, with outstanding results in the targeted distribution of critical components. These include ginsenoside, puerarin, tanshinone IIA, baicalin, triptolide, and ligustrazine (Kim et al., 2018; Yan et al., 2019; Xu et al., 2020; Mi et al., 2021; Yalikong et al., 2021; Zhu et al., 2021). Nanoparticle delivery technologies significantly increase the targeting precision and therapeutic effectiveness of these drugs while effectively mitigating adverse effects.

The following section introduces several representative PDSMs with nanocarriers that are currently under investigation, along with examples of their applications and mechanisms in the treatment of MIRI (Table 2; Figures 2, 3). The successful implementation of these nanoparticles not only validates the potential of nanotechnology in enhancing the efficacy of botanical drugs but also provides valuable insights into the modernization of botanical drugs and its integration with precision medicine.

5.1 Notoginsenoside

Notoginsenoside R1 (NGR1), a triterpenoid saponin primarily isolated from the dried roots and rhizomes of *Panax notoginseng* (Burk.) F.H.Chen (Araliaceae family, *Panax* genus), demonstrates potent cardioprotective effects against MIRI (Zhu and Wan, 2023). NGR1 suppresses the transforming growth factor-β-activated kinase 1-JNK/p38 signaling pathway, reducing inflammatory cytokine production, considerably reducing infarct size, and enhancing heart function (Zeng et al., 2023). NGR1 reduces apoptosis by regulating critical signaling pathways, including AKT and JAK2, thereby enhancing its cardioprotective effects (Lei et al., 2022; Xu et al., 2022).

Owing to its anti-inflammatory, antioxidant, and anti-apoptotic properties, NGR1 has been extensively investigated. MIRI-related damage is primarily caused by oxidative stress and myocardial cell death. Superoxide dismutase, which lowers ROS generation and shields cardiac cells from oxidative stress (Tong et al., 2019), is an antioxidant enzyme that NGR1 promotes. Moreover, NGR1 helps stabilize mitochondrial membrane potential, thereby lowering mortality and shielding against heart injury (Yan et al., 2021).

Although notoginsenoside has enormous therapeutic potential, its low bioavailability, poor water solubility, and sensitivity to metabolic breakdown restrict its therapeutic uses (Li et al., 2007). To overcome these limitations, researchers have devised mesoporous silica nanoparticle-based delivery systems, including NGR1. This method, together with CD11b antibodies, focuses on

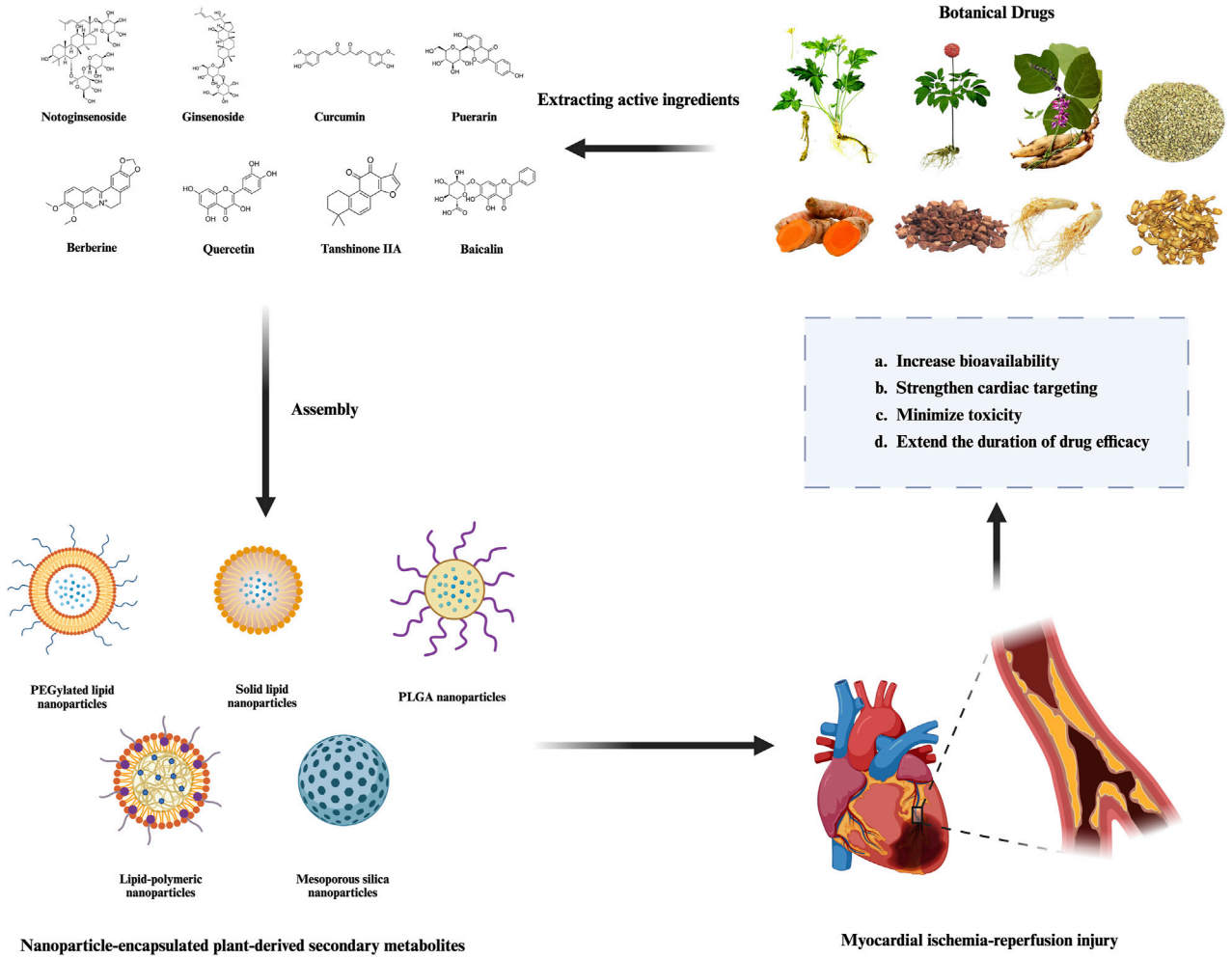


FIGURE 2
Therapeutic advantages of nanoparticle-encapsulated plant-derived secondary metabolites in MIRI.

injured regions after myocardial infarction, thereby increasing the local concentration of NGR1 in the myocardium. This method reduces myocardial reperfusion damage, enhances heart performance, and increases the antioxidant, anti-inflammatory, and anti-apoptotic actions of NGR1. Moreover, the treatment controls energy metabolism and induces angiogenesis (Li H. et al., 2022). However, the long-term biosafety profile of Notoginsenoside R1-loaded mesoporous silica nanoparticles conjugated with CD11b antibody and their potential off-target effects on non-infarcted tissues expressing CD11b remain uncharacterized, necessitating further preclinical validation.

NGR1 was used in a core-shell hybrid liposome nanoparticle system to increase the bioavailability of notoginsenoside. After oral delivery, this method greatly enhanced the pharmacological effects of notoginsenosides, thereby lowering the severity of myocardial infarction, controlling oxidative stress, and increasing myocardial cell survival rates (Zhang et al., 2012). This study proposes a novel approach to enhance the delivery of notoginsenoside. Notably, the current findings are limited by the lack of pharmacokinetic evaluations to delineate the absorption mechanisms of panax notoginsenoside-encapsulated core-shell hybrid liposomal delivery systems and insufficient toxicological monitoring over extended durations, which necessitates further investigation prior to human trials.

Researchers incorporated notoginsenoside and salvianolic acid B into an RGD-modified dual-drug delivery system. This technique greatly improved myocardial targeting, lowered infarction size, and improved heart function (Qiu et al., 2017). With significant consequences for future cardiovascular disease treatments, this dual-drug delivery system epitomizes the benefits of multi-target therapeutic approaches. The limitations of this study include that the experimental findings were primarily derived from a rat model of acute myocardial ischemia, which may not fully replicate the pathophysiological complexity of human cardiovascular disease, potentially restricting the direct clinical translatability of the results.

5.2 Ginsenoside

Ginsenosides, a class of dammarane-type and oleanane-type triterpenoid saponins characteristic of *Panax* genus (Araliaceae) plants, are secondary metabolites predominantly distributed in the

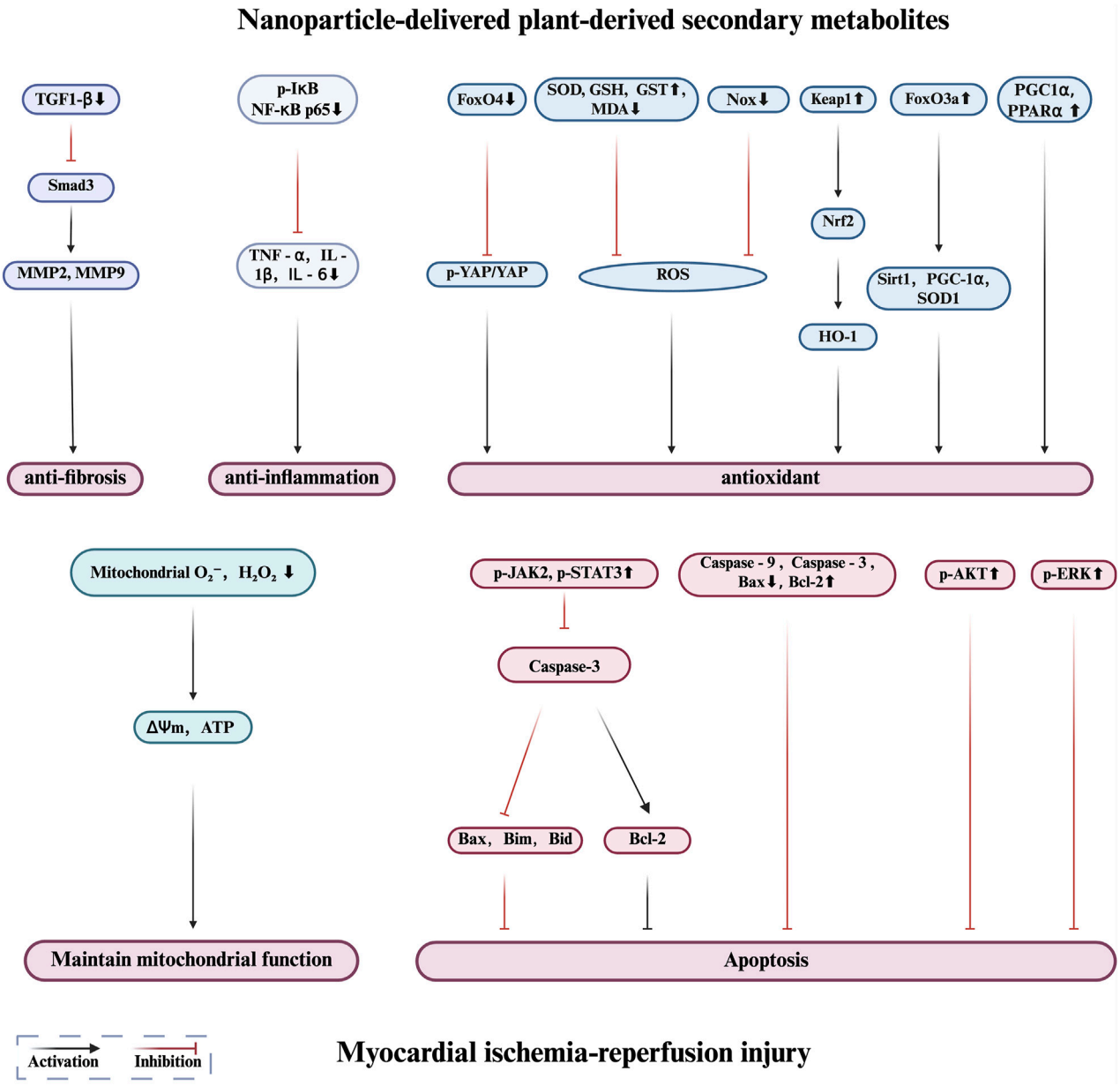


FIGURE 3
Protective mechanisms of nanoparticle-delivered plant-derived secondary metabolites in myocardial ischemia reperfusion injury.

roots and rhizomes of *Panax ginseng* C.A.Mey., *Panax notoginseng* (Burk.) F.H.Chen, and *Panax quinquefolius* L. These bioactive compounds exhibit multi-pharmacological properties including anti-inflammatory, antioxidant, antitumor, and neuroprotective activities. Common ginsenosides, such as Rg1, Rg3, Rb1, and Rc, affect many physiological processes by regulating cellular signaling pathways (Chen, 2020). In addition to their potential in treating neurodegenerative diseases and cancer, ginsenosides have attracted attention for their protective effects on the cardiovascular system (Sarhene et al., 2021).

Qin et al. have demonstrated that ginsenoside Rb1 significantly improved MIRI by reducing myocardial autophagy through the modulation of the PI3K/Akt/mTOR signaling pathway (Qin et al., 2021). Similarly, Wang et al. have reported that ginsenoside Rd alleviates MIRI by reducing inflammation and apoptosis via inhibition of the PI3K/AKT signaling pathway (Wang et al., 2024c). Ye et al. have found that ginsenoside Re protects cardiomyocytes by inhibiting ferroptosis by regulating the miR-144–3p/SLC7A11 signaling pathway (Ye et al., 2023). Furthermore, Xue et al. have found that ginsenoside Rc mitigates MIRI by activating the sirtuin 1 (SIRT1 pathway), thereby reducing mitochondrial oxidative stress and apoptosis (Xue et al., 2023). Li et al. have demonstrated that ginsenoside Rg2 significantly improves MIRI by inhibiting necrosis by modulating the transforming growth factor-β-activated kinase one signaling pathway (Li Y. et al., 2022). Huang et al. have demonstrated that the ginsenoside Rb2 reduces MIRI by inhibiting SF3A2 acetylation and regulating Fscn1 selective splicing (Huang et al., 2023). Another study by Xue et al. has

revealed that ginsenoside Rb2 improves cardiac function by reducing oxidative stress through SIRT1 activation (Xue et al., 2020). Collectively, these studies highlight the diverse cardioprotective mechanisms of ginsenosides against MIRI.

Despite their promising therapeutic effects, the clinical application of ginsenosides is limited owing to their low water solubility and poor bioavailability (Pan et al., 2018). Therefore, improving their bioavailability and pharmacological efficacy has become a major focus of current research. Recently, nanotechnology has been used to enhance the stability, targeting, and circulation time of ginsenoside-based drugs, thereby boosting their clinical efficacy. Nanoparticles not only improve the solubility of hydrophobic ginsenosides, such as Rg3, but also concentrate drug effects at specific disease sites through targeted delivery, thereby minimizing side effects. For example, Xu et al. developed Ag@*P. japonicus* nanoparticles by integrating silver nanoparticles with *Panax* japonicus extract. These nanoparticles reduced myocardial apoptosis and inflammation, enhanced antioxidant enzyme activity (e.g., superoxide dismutase and glutathione peroxidase), decreased infarct size, and improved cardiac function in an isoproterenol-induced myocardial infarction model. This study underscored the potential of nanotechnology in enhancing the efficacy and stability of ginsenosides (Xu et al., 2024). Li et al. investigated a ROS-responsive nanoparticle delivery system for ginsenoside Rg3. By targeting the FoxO3a pathway, Rg3 inhibited oxidative stress, inflammation, and fibrosis, resulting in improved cardiac function after MIRI. Nanotechnology significantly enhanced the bioavailability of Rg3, demonstrating its potential as a delivery strategy for other natural products (Li et al., 2020). Li et al. demonstrated limitations in their study by failing to comprehensively evaluate the long-term biosafety and potential immunogenicity of reactive oxygen species (ROS)-responsive nanoparticles, while the lack of validation in preclinical large animal models further constrained their clinical translatability (Li et al., 2020). Xu et al. did not address the *In vivo* pharmacokinetics or long-term bioaccumulation risks of silver nanoparticles, nor did they systematically analyze dose-dependent toxicity or stability in complex pathological microenvironments, thereby compromising a thorough assessment of therapeutic safety (Xu et al., 2024).

5.3 Curcumin

Curcumin, a diarylheptanoid compound (chemical formula $C_{21}H_{20}O_6$, molecular weight 368.38 Da), is primarily isolated from the dried rhizomes of *C. longa* L (Zingiberaceae). Secondary botanical sources include rhizomes of the congeneric species *Curcuma aromatica* Salisb. And *Curcuma zedoaria* (Berg.) Rosc., albeit with lower extraction yields. In MIRI, curcumin mitigates oxidative stress by scavenging ROS and enhancing antioxidant enzyme activity. It also inhibits the production of pro-inflammatory cytokines such as TNF-α and IL-6, thereby reducing inflammation while suppressing myocardial cell apoptosis by regulating apoptosis-related proteins. Numerous studies have investigated multiple protective mechanisms of curcumin in MIRI, consistently revealing its significant cardioprotective effects.

For example, Wu et al. have demonstrated that curcumin exerts protective effects against myocardial damage by activating the PI3K/Akt/mTOR signaling pathway, providing key insights into its role in cellular signal transduction (Wu et al., 2021). Cui et al. have revealed that curcumin stimulates vascular endothelial cells to secrete fibroblast growth factor 2, thereby reducing hypoxia/reoxygenation damage to myocardial cells and reinforcing the role of curcumin in promoting myocardial repair (Cui J.-K. et al., 2024). Moreover, Cui et al. have revealed that curcumin alleviates myocardial injury by increasing endogenous H_2S levels and regulating m6A RNA modifications, offering deeper insights into its molecular regulatory mechanisms (Cui J. et al., 2024). Zhang et al. have shown that curcumin regulates mitochondrial metabolism and inhibits apoptosis, significantly improving the outcomes of cardiopulmonary resuscitation following cardiac arrest (Zhang et al., 2022).

Nanotechnology has been widely used to enhance the bioavailability and stability of curcumin. Nabofa et al. investigated curcumin-nisin-based polylactic acid nanoparticles (CurNisNp) and found that they effectively prevented isoproterenol-induced myocardial injury by reducing oxidative stress and inflammation (Nabofa et al., 2018). Boarescu et al. used nano-curcumin particles with a PLGA carrier, which significantly improved the absorption rate of curcumin and demonstrated stronger antioxidant and anti-inflammatory effects, particularly by enhancing electrocardiogram readings and protecting cardiac function (Boarescu et al., 2019b). In another study, Boarescu et al. validated the superior performance of nano-curcumin in a diabetic MIRI model, demonstrating that it not only significantly reduced oxidative stress and inflammation but also exhibited excellent cardioprotective effects (Boarescu et al., 2019a). Additionally, Dong et al. studied carbon quantum dot nanoparticles (CRC-CDs) extracted from turmeric, which further reduced cardiac damage in MIRI by enhancing antioxidant enzyme activity and inhibiting myocardial cell apoptosis (Dong et al., 2024).

While existing studies provide valuable insights into nanomaterial-based cardioprotective strategies, several critical limitations persist. Dong et al. focused exclusively on short-term rodent models, neglecting evaluations of chronic toxicity and sustained therapeutic efficacy of carbon dots in clinically relevant myocardial ischemia paradigms, thereby limiting translational validity (Dong et al., 2024). Boarescu et al. omitted pharmacokinetic profiling of nanocurcumin, particularly its long-term bioavailability and metabolic fate, and employed a restricted experimental dose range that may inadequately characterize dose-response relationships (Boarescu et al., 2019b); their subsequent study further constrained generalizability by excluding non-diabetic myocardial infarction models and failing to address nanoparticle stability and tissue distribution dynamics (Boarescu et al., 2019a). Additionally, Nabofa et al. relied solely on guinea pig models, which exhibit marked cardiovascular physiological divergence from humans, while overlooking immunogenicity assessments and chronic safety risks of their composite nanoparticles (Nabofa et al., 2018). Collectively, these limitations highlight gaps in interspecies physiological relevance, comprehensive chronic exposure evaluations, and rigorous pharmacokinetic characterization, necessitating further research to bridge preclinical findings and clinical applicability.

5.4 Puerarin

Puerarin, an isoflavone C-glycoside (chemical formula $C_{21}H_{20}O_9$, molecular weight 416.38 Da), is primarily isolated from the roots of *Pueraria lobata* (Willd.) Ohwi and *Pueraria thomsonii* Benth (Fabaceae family, *Pueraria* genus). This phytochemical demonstrates significant cardioprotective effects within the cardiovascular system, underpinning its widespread clinical application in managing hypertension and coronary artery disease (Zhou et al., 2014). Consequently, it is widely used in the treatment of cardiovascular diseases such as hypertension and coronary artery disease. Numerous studies have demonstrated the beneficial effects of puerarin on MIRI with its protective mechanisms operating at multiple levels (Zhou et al., 2021).

Puerarin regulates miR-21, reducing apoptosis and inhibiting oxidative stress, which enhances antioxidant capacity and significantly improves the survival rate of myocardial cells during MIRI (Xu et al., 2019). It further protects cardiac cells by increasing the long non-coding RNA ANRIL and blocking autophagy (Han et al., 2021). Puerarin inhibits the SIRT1/NF-κB pathway and prevents NLRP3 inflammasome activation, thereby reducing MIRI-induced inflammation (Wang et al., 2020). Puerarin also prevents ferroptosis, a unique type of cell death that reduces cardiac cell damage and provides overall cardioprotection (Ding et al., 2023).

Despite its promising therapeutic potential, its low water solubility and short half-life limit its clinical use (Wang et al., 2022). Nanoparticle carrier technologies have been developed to improve the bioavailability and targeting efficiency of PUR. For example, triphenylphosphonium cation and ischemic myocardium-targeting peptide-modified liposomes (PUE@T/I-L) were designed to target mitochondria, increasing puerarin localization in the myocardium, reducing oxidative stress, protecting myocardial cells from ischemia-reperfusion injury, and decreasing infarct size (Wang et al., 2024a). Moreover, RGD-modified and PEGylated solid lipid nanoparticles significantly prolonged the retention time of puerarin in the body, augmenting its concentration and efficacy in the heart while offering substantial protection against acute myocardial ischemia [148]. These nanoparticle carriers not only promote medication stability and controlled release but also maximize targeted distribution, highlighting the promise of puerarin in the precision treatment of cardiovascular disorders (Dong et al., 2017).

However, the following methodological limitations may constrain their translational relevance: Wang et al. did not validate the long-term biodistribution or organotoxicity of their dual-targeted liposomes in large mammals or advanced preclinical models, potentially undermining clinical translatability (Wang et al., 2024b); Dong et al. omitted systematic evaluation of RGD-modified nanoparticles' targeting stability under dynamic pathological conditions (e.g., fibrosis or chronic inflammation), limiting generalizability of their therapeutic strategy (Dong et al., 2017).

5.5 Quercetin

Quercetin, a flavonol ubiquitously distributed in the plant kingdom (chemical formula $C_{15}H_{10}O_7$, molecular weight 302.24 Da), predominantly occurs in nature as glycosidic forms such as rutin, liberating free quercetin upon acid hydrolysis or enzymatic conversion. Its principal botanical sources include the flower buds (Huaimi) of *Sophora japonica* L (Fabaceae), epidermal tissues of *Allium cepa* L (Amaryllidaceae), and fruit peel of *Malus domestica* Borkh (Rosaceae). Quercetin have demonstrated notable cardioprotective effects in MIRI therapy owing to their strong antioxidant and anti-inflammatory properties (Zhang et al., 2020). Quercetin regulates the main pathways involved in MIRI. To prevent cell death, it scavenges ROS, reduces oxidative stress, quiesces inflammatory responses, and preserves mitochondrial activity. Moreover, it influences signaling channels, including ATP-sensitive potassium channels and the nitric oxide system, which cooperate to minimize cardiac cell damage and necrosis. Many studies have demonstrated the effectiveness of quercetin in reducing cardiac damage caused by MIRI via various molecular pathways. Liu Y et al. have discovered that quercetin greatly reduced myocardial cell death and provided cardiac protection by inducing the NO system and mitochondrial ATP-sensitive potassium channels (Liu Y. et al., 2021). Chang et al. have shown that via a DNA-PKcs-SIRT5-regulated mitochondrial quality control mechanism, quercetin reduces necroptosis and, therefore, enhances heart function (Chang et al., 2024). Furthermore, Li et al. have discovered that quercetin significantly reduced oxidative stress and mitochondrial-mediated death by modulating the extracellular signal-regulated protein kinases one and 2/DRP1 signaling pathway, thereby increasing the resistance of the heart to damage. These results demonstrate the enormous therapeutic potential of quercetin in MIRI (Li F. et al., 2021).

Despite the potential therapeutic effects of quercetin, its clinical use is limited because of its physicochemical properties. Quercetin has poor water solubility and is rapidly metabolized in the body, resulting in low bioavailability and difficulty in maintaining a sufficient drug concentration and duration of action, which restricts its therapeutic effectiveness (Alizadeh and Ebrahimzadeh, 2022). To overcome these challenges, nanotechnology has been used to enhance the drug delivery performance of quercetin.

Nanotechnology has significantly improved the therapeutic efficacy of quercetin. Liu et al. have demonstrated that loading quercetin into mesoporous silica nanoparticles effectively reduced myocardial infarction size and improved cardiac physiological and biochemical functions, particularly in protecting against MIRI by activating the JAK2/STAT3 signaling pathway and inhibiting apoptosis and oxidative stress (Liu C.-J. et al., 2021). Similarly, Lozano et al. encapsulated quercetin in PLGA nanoparticles and found that this nanodelivery system exhibited stronger cardioprotective effects against oxidative stress compared with free quercetin, especially by reducing mitochondrial ROS production, maintaining mitochondrial function and preserving ATP synthesis (Lozano et al., 2019).

Although both studies provide critical evidence for the therapeutic potential of nanoparticle-mediated quercetin delivery, their methodological frameworks exhibit significant limitations. Liu et al. exclusively employed a 10-day prophylactic pretreatment regimen prior to ischemia-reperfusion (IR), failing to evaluate acute therapeutic interventions or clinically relevant post-ischemic treatment windows (e.g., intra-reperfusion or emergency

post-infarction administration), thereby limiting the clinical translatability of their efficacy assessments (Liu C.-J. et al., 2021). Similarly, Lozano et al. relied solely on *in vitro* hypoxia-reoxygenation models using the H9c2 rat cardiomyoblast cell line, omitting validation in primary cardiomyocytes or pathophysiologically complex conditions (e.g., hypertension or metabolic comorbidities), which may overestimate the applicability of their findings to human cardiac pathophysiology (Lozano et al., 2019).

5.6 Berberine

Berberine, an isoquinoline alkaloid (chemical formula $C_{20}H_{18}NO_4^+$, molecular weight 336.36 Da), is predominantly isolated from the rhizomes of *Coptis chinensis* Franch (Ranunculaceae), root bark of *Berberis julianae* Schneid (Berberidaceae), and bark of *Phellodendron amurense* Rupr (Rutaceae). This phytochemical has garnered significant pharmacological attention due to its broad-spectrum bioactivities. These include anti-inflammatory, antioxidant, antibacterial, and metabolic regulatory effects (Song et al., 2020). Berberine's potential in cardiovascular illnesses has recently received considerable attention for its preventive function against MIRI (Feng et al., 2019). Jia et al. showed that berberine greatly reduces myocardial damage by decreasing inflammation and oxidative stress, predominantly via the miR-26b-5p-mediated prostaglandin-endoperoxide synthase 2/MAPK signaling pathway (Jia et al., 2022). Long et al. have discovered that berberine improves cardioprotection by upregulating miR-340-5p and inhibiting high mobility group box 1 (HMGB1)-mediated inflammatory response (Long et al., 2023). Abdulredha et al. have demonstrated the ability of berberine to prevent MIRI by interfering with oxidative stress and inflammatory pathways (Abdulredha et al., 2021). Hu et al. have discovered that berberine decreased myocardial damage by blocking excessive autophagy via the RhoE/adenosine monophosphate-activated protein kinase pathway (Hu et al., 2024). Yang et al. have clarified this process and found that berberine suppressed cardiomyocyte ferroptosis, providing further protection (Yang et al., 2022). Overall, these findings show that berberine has a broad cardioprotective effect against MIRI by modulating inflammation, oxidative stress, autophagy, and ferroptosis.

Although berberine has significant pharmacological properties, its low water solubility and rapid metabolism restrict its clinical use and reduce its bioavailability, making it difficult to maintain therapeutic concentrations in target tissues (Wang et al., 2017). To overcome these limitations, researchers have used nanotechnology to add berberine to nanoparticle delivery methods. This approach enhances solubility, stability, and focused distribution, thereby increasing therapeutic effectiveness.

To restore heart function after myocardial infarction, Allijn et al. synthesized berberine in liposomes. Their results revealed that long-circulating liposomes enhanced the stability and bioavailability of berberine. By preventing ventricular remodeling, preserving the ejection fraction, and reducing the risk of heart failure, berberine liposomes provided significant cardioprotection after myocardial infarction. This demonstrates how liposomal technology can improve the medicinal and cardioprotective properties of berberine (Allijn et al., 2017). Zhu et al. investigated the use of platelet membrane-coated nanoparticles to treat MIRI with berberine. Their results revealed that extended drug release after reperfusion was made possible by berberine encapsulated in PLGA nanoparticles coated with a platelet membrane that was preferentially localized at the location of myocardial infarction. Platelet membrane-coated nanoparticles accumulated more in the heart tissue than standard PLGA nanoparticles, resulting in significantly fewer systemic side effects. Significant post-reperfusion cardiac function improvements resulted from this new delivery strategy, changing macrophage polarization, lowering inflammation and death, accelerating myocardial regeneration, and reducing fibrosis (Zhu K. et al., 2023).

While Allijn et al. demonstrated improved cardiac function preservation through liposomal berberine encapsulation, their study did not investigate the long-term stability and potential off-target effects beyond 28 days post-myocardial infarction, limiting comprehensive safety assessments (Allijn et al., 2017). Notably, Zhu et al. addressed nanoparticle delivery but did not quantitatively validate the *In vivo* drug release kinetics within the infarcted myocardium, leaving uncertainties regarding sustained therapeutic efficacy and dose optimization under physiological conditions (Zhu K. et al., 2023).

5.7 Tanshinone IIA

Tanshinone IIA, a lipophilic diterpenoid quinone (chemical formula $C_{19}H_{18}O_3$, molecular weight 294.35 Da), is unambiguously identified as a secondary metabolite derived from the dried roots and rhizomes of *S. miltiorrhiza* Bunge (Lamiaceae). This compound exerts core cardiovascular protective effects, including anti-atherosclerotic activity, myocardial ischemic protection, and platelet aggregation inhibition, through mechanisms involving suppression of the NF-κB inflammatory pathway and modulation of lipid metabolism (Gao et al., 2012). Tanshinone IIA exerts its cardioprotective effects in MIRI through various mechanisms, including scavenging ROS, inhibiting the NF-κB signaling pathway to reduce inflammation, regulating apoptosis-related proteins to prevent myocardial cell death, protecting mitochondrial function to mitigate oxidative stress, and preventing myocardial fibrosis to prevent additional damage to cardiac function (Zhu P.-C. et al., 2023). Through these multi-pathway, multi-target actions, tanshinone IIA's strong cardioprotective ability efficiently reduced cardiac damage induced by MIRI.

However, the poor solubility and low bioavailability of tanshinone IIA limit its clinical application (Huang et al., 2022). To address these challenges, researchers have employed nanocarrier technologies to enhance the pharmacological properties of carriers. One study developed a lipid-polymer nanocarrier system loaded with tanshinone IIA, modified with triphenylphosphine and D-α-tocopherol polyethylene glycol succinate, for targeted mitochondrial therapy in myocardial infarction. This system demonstrated significantly improved compatibility and therapeutic efficacy compared with free drugs and other similar nanocarriers in both *in vitro* and *in vivo* experiments. Pharmacokinetic and biodistribution studies confirmed the superior therapeutic effects of this nanocarrier system (Zhang et al., 2018).

Focusing on their effects on left ventricular remodeling after myocardial infarction, researchers in another study created monomethoxy polyethylene glycol-polylactic acid-D-α-tocopherol polyelsky nanoparticles containing tanshinone IIA. Within 4 weeks following myocardial infarction, tanshinone IIA nanoparticle treatment significantly recovered cardiac function, decreased infarct size, and effectively averted left ventricular dilatation in a mouse model. By lowering inhibitor of nuclear factor kappa B phosphorylation and the NF-κB signaling system, this drug clearly lowered cardiac inflammation, death, and fibrosis. Following myocardial infarction, tanshinone IIA nanoparticles lowered inhibitor of nuclear factor kappa B phosphorylation and NF-κB activity, hence improving heart remodeling (Mao et al., 2018). While the study demonstrates promising cardioprotective efficacy, its acute-phase dosing protocol (5-day post-MI administration) may be insufficient to mitigate persistent inflammatory and fibrotic cascades underlying chronic cardiac remodeling (Mao et al., 2018).

6 Discussion

Significant progress has been made in the treatment of MIRI using PDSM nanoparticles (Li et al., 2020; Li et al., 2022). The combination of modern nanotechnology with botanical drugs in this new strategy provides synergistic benefits for several targets and pathways (Chen et al., 2024). These nanoparticles overcome the main limitations of botanical drug treatments, such as restricted absorption and targeting (Liu C.-J. et al., 2021), thus improving therapeutic efficacy. Although initial results showed promise, considerable obstacles still exist in the therapeutic use of PDSM nanoparticles.

A key advantage of PDSM nanoparticles is their ability to exert synergistic effects across several targets and processes. Although many botanical drugs function through various pathways, PDSMs combined with nanotechnology provide significant benefits by simultaneously targeting many avenues. This technique enables the complete regulation of pathogenic processes, such as antioxidation, anti-inflammation, apoptosis suppression, and mitochondrial function modification. In MIRI models, quercetin-loaded nanoparticles demonstrated strong antioxidant effects, reducing oxidative stress, myocardial apoptosis, and inflammation while promoting angiogenesis and cardiac repair via the JAK2/STAT3 signaling pathway (Liu C.-J. et al., 2021). *Panax notoginseng* saponin-loaded nanoparticles decrease inflammation by blocking TNF-α and IL-6, activating the AKT and MAPK pathways, and reducing oxidative stress. As a result, post-reperfusion heart function has greatly improved (Li H. et al., 2022). Ginsenoside nanoparticles provide further cardioprotection by inhibiting apoptosis via the FoxO3a signaling pathway, as well as antioxidative and anti-inflammatory effects. This multifaceted approach makes PDSM nanoparticles a more effective therapeutic option for MIRI than traditional medicines.

The incorporation of nanotechnology has markedly enhanced the efficacy of the targeted delivery of PDSMs for MIRI treatment. Nanoparticles can precisely deliver drugs to damaged cardiac tissues while minimizing adverse effects in healthy areas by integrating passive and active targeting mechanisms. For instance, when vascular permeability increases during MIRI, nanoparticles using the EPR effect effectively aggregate in the injured regions (Lan et al., 2022). Drug localization can also be enhanced by active targeting strategies using nanoparticles covered with antibodies or peptides. Using external magnetic fields, magnetic targeting drives nanoparticles to the location of the injury, thereby increasing their therapeutic effects (Wei et al., 2024). By lowering the medication levels in non-targeted organs and reducing oxidative stress, mitochondria-targeted nanoparticles protect the mitochondria. This concentrated approach lowers adverse effects and increases medical efficacy (Gao et al., 2022).

Because they target many MIRI pathogen routes, multifunctional nanocarriers have synergistic therapeutic potential. By delivering antioxidants and anti-inflammatory medicines, these nanocarriers can effectively address several aspects of disease (Yang et al., 2023). For instance, while reducing inflammation and cardiomyocyte injury, nanoparticle solutions combining the EPR effect with tailored modifications can enhance drug delivery efficacy (Sun et al., 2012). Particularly pH- or ROS-responsive systems, liposomes, and polymeric nanoparticles provide precise control over drug release, thereby enhancing therapeutic effectiveness and reducing adverse effects (Li et al., 2020). Using these multifunctional nanocarriers in MIRI treatment showed their ability to cooperate across various systems, including anti-inflammation, anti-oxidation, and anti-apoptosis systems, thus producing considerably superior myocardial damage interventions.

Although PDSMs nanoparticles have shown potential therapeutic advantages in animal studies, various obstacles limit their clinical use. The long-term safety of nanocarriers requires further confirmation through clinical research, mostly in terms of their metabolism, excretion, and possible effects on other organs (Piscatelli et al., 2021). The complexity and variety of botanical drug constituents can impact the stability and efficacy of nanoparticles in clinical applications (Wei et al., 2022). Moreover, improving the pharmaceutical distribution and release techniques is a major challenge. Addressing the critical challenges in the clinical translation of botanical nanomedicines requires strategic advancements across material innovation, pharmacological optimization, and translational validation. In biodegradable carrier development, biocompatible polymers such as PLGA and natural polysaccharides are modified through surface engineering techniques (e.g., PEGylation) to reduce immunogenicity (Chatterjee and Chanda, 2022), with parallel long-term toxicological evaluations to assess organ-specific biodistribution profiles. Exploration of plant-derived natural vesicles, including exosomes and polysaccharide-based carriers, demonstrates potential for minimizing xenobiotic toxicity compared to synthetic alternatives (Basyoni et al., 2025; Chai et al., 2025). Following HPLC-MS-guided phytochemical screening and metabolomics-optimized drug loading (Plumb et al., 2023), nanocarriers are functionalized with immunomodulatory agents (e.g., siRNA targeting inflammatory mediators) to activate therapeutic pathways such as cGAS-STING signaling (Nagarajan et al., 2023). Translational validation employs 3D human organoid models and large-animal disease prototypes to quantify targeting specificity and biosafety parameters, integrated with standardized good manufacturing practice (GMP) protocols. Advanced pathology-responsive release systems, including oxidative stress-activated formulations, enable localized drug enrichment while maintaining systemic exposure below toxicity thresholds (Zheng et al., 2022).

Future studies should focus on integrating biomimetic nanotechnology with PDSMs to enhance biocompatibility and targeted efficacy. Encapsulating nanoparticles with myocardial or immune cell membranes may facilitate immune clearance and improve drug retention in the heart tissue (Liu et al., 2020; Zhou et al., 2023). This biomimetic approach improves the precise distribution of PDSM nanoparticles, enhancing their therapeutic efficacy in MIRI treatment. Moreover, the development of multifunctional hybrid nanoparticles has enhanced their potential for multitarget treatment. Future research should investigate how nanoparticles can concurrently carry genes, proteins, and other therapeutic compounds to address the complex disease processes of MIRI (Wang et al., 2021). For example, nanoparticle platforms integrating miRNA delivery methods have shown considerable promise in supporting myocardial regeneration and repair, indicating a possible breakthrough in the future treatment of cardiovascular disorders (Tan et al., 2021).

7 Conclusion

The clinical prospects of PDSM nanoparticles in the treatment of MIRI are highly promising. Nanotechnology not only boosts the bioavailability of bioactive phytochemicals but also enhances therapeutic outcomes through multi-target synergistic effects. However, successful translation to clinical practice requires further human trials to confirm long-term safety and efficacy. With advances in nanotechnology, more PDSM nanoparticles are expected to enter clinical trials, offering diverse and precise treatment options for MIRI.

Author contributions

WS: Visualization, Writing – original draft. YX: Data curation, Visualization, Writing – review and editing. JW: Data curation, Visualization, Writing – review and editing. XZ: Data curation, Visualization, Writing – review and editing. SZ: Data curation, Visualization, Writing – review and editing. HG: Validation, Writing – review and editing. QH: Validation, Writing – review and editing. CQ: Validation, Writing – review and editing. TH: Conceptualization, Project administration, Supervision, Writing – review and editing. YL: Conceptualization, Project administration, Supervision, Writing – review and editing. MY: Conceptualization, Project administration, Supervision, Writing – review and editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by the National Natural Science Foundation of China [no. 8207213], Research Fund of Anhui Institute of Translational Medicine [no. 2023zhyx-C64 and 2022zhyx-C76]; the Basic and Clinical Enhancement Project of Anhui Medical University [no. 2019xkjT028 and 2023xkjT042]; the Postgraduate Innovation Research and Practice Program of Anhui Medical University [no. YJS20230133]; Anhui Province Key Research and Development Plan High-tech Special Project [no. 202304a05020071]; Anhui University Excellent Young Talents Support Plan [no. gxyqZD2018026].

Acknowledgments

The authors would like to thank Editage for the English language editing of this manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

References

Abdulredha, A., Abosaooda, M., Al-Amran, F., and Hadi, N. R. (2021). Berberine protests the heart from ischemic reperfusion injury via interference with oxidative and inflammatory pathways. *Med. Arch.* 75, 174–179. doi:10.5455/medarh.2021.75.174-179

Alizadeh, S. R., and Ebrahimzadeh, M. A. (2022). Quercetin derivatives: drug design, development, and biological activities, a review. *Eur. J. Med. Chem.* 229, 114068. doi:10.1016/j.ejmech.2021.114068

Allijn, I. E., Czarny, B. M. S., Wang, X., Chong, S. Y., Weiler, M., da Silva, A. E., et al. (2017). Liposome encapsulated berberine treatment attenuates cardiac dysfunction after myocardial infarction. *J. Control Release* 247, 127–133. doi:10.1016/j.jconrel.2016.12.042

Bae, S., Park, M., Kang, C., Dilmen, S., Kang, T. H., Kang, D. G., et al. (2016). Hydrogen peroxide-responsive nanoparticle reduces myocardial ischemia/reperfusion injury. *J. Am. Heart Assoc.* 5, e003697. doi:10.1161/JAHA.116.003697

Basyoni, A. E., Atta, A., Salem, M. M., and Mohamed, T. M. (2025). Harnessing exosomes for targeted drug delivery systems to combat brain cancer. *Cancer Cell. Int.* 25, 150. doi:10.1186/s12935-025-03731-z

Boarescu, P.-M., Boarescu, I., Bocşan, I. C., Gheban, D., Bulboacă, A. E., Nicula, C., et al. (2019a). Antioxidant and anti-inflammatory effects of curcumin nanoparticles on drug-induced acute myocardial infarction in diabetic rats. *Antioxidants (Basel)* 8, 504. doi:10.3390/antiox8100504

Boarescu, P.-M., Boarescu, I., Bocșan, I. C., Pop, R. M., Gheban, D., Bulboacă, A. E., et al. (2019b). Curcumin nanoparticles protect against isoproterenol induced myocardial infarction by alleviating myocardial tissue oxidative stress, electrocardiogram, and biological changes. *Molecules* 24, 2802. doi:10.3390/molecules24152802

Chai, M., Gao, B., Wang, S., Zhang, L., Pei, X., Yue, B., et al. (2025). Leveraging plant-derived nanovesicles for advanced nucleic acid-based gene therapy. *Theranostics* 15, 324–339. doi:10.7150/thno.104507

Chang, X., Zhang, Q., Huang, Y., Liu, J., Wang, Y., Guan, X., et al. (2024). Quercetin inhibits necroptosis in cardiomyocytes after ischemia-reperfusion via DNA-PKcs-SIRT5-orchestrated mitochondrial quality control. *Phytother. Res.* 38, 2496–2517. doi:10.1002/ptr.8177

Chatterjee, M., and Chanda, N. (2022). Formulation of PLGA nano-carriers: specialized modification for cancer therapeutic applications. *Mat. Adv.* 3, 837–858. doi:10.1039/D1MA00600B

Chen, C., Liu, W., Gu, X., Zhang, L., Mao, X., Chen, Z., et al. (2024). Baicalin-loaded Polydopamine modified ZIF-8 NPs inhibits myocardial ischemia/reperfusion injury in rats. *J. Biomater. Sci. Polym. Ed.* 35, 1863–1878. doi:10.1080/09205063.2024.2358640

Chen, J.-T. (2020). Advances in ginsenosides. *Biomolecules* 10, 681. doi:10.3390/biom10050681

Cui, J., Wang, X., Dong, L., and Wang, Q. (2024a). Curcumin reduces myocardial ischemia-reperfusion injury, by increasing endogenous H2S levels and further modulating m6A. *Mol. Biol. Rep.* 51, 558. doi:10.1007/s11033-024-09478-6

Cui, J.-K., Fan, M., and Wang, Q. (2024b). Curcumin reduces hypoxia/reperfusion injury of cardiomyocytes byStimulating vascular endothelial cells to secrete FGF2. *Comb. Chem. High. Throughput Screen* 27, 2101–2109. doi:10.2174/0113862073239166231103102648

Ding, Y., Li, W., Peng, S., Zhou, G., Chen, S., Wei, Y., et al. (2023). Puerarin protects against myocardial ischemia/reperfusion injury by inhibiting ferroptosis. *Biol. Pharm. Bull.* 46, 524–532. doi:10.1248/bpb.b22-00174

Donato, M., Evelson, P., and Gelpi, R. J. (2017). Protecting the heart from ischemia/reperfusion injury: an update on remote ischemic preconditioning and postconditioning. *Curr. Opin. Cardiol.* 32, 784–790. doi:10.1097/HCO.0000000000000447

Dong, L., Shen, Z., Chi, H., Wang, Y., Shi, Z., Fang, H., et al. (2023). Research progress of Chinese medicine in the treatment of myocardial ischemia-reperfusion injury. *Am. J. Chin. Med.* 51, 1–17. doi:10.1142/S0192415X23500015

Dong, L., Zhao, Y., Luo, J., Li, X., Wang, S., Li, M., et al. (2024). Carbon dots derived from curcumae radix and their heartprotective effect. *IJN* 19, 3315–3332. doi:10.2147/IJN.S444125

Dong, Z., Guo, J., Xing, X., Zhang, X., Du, Y., and Lu, Q. (2017). RGD modified and PEGylated lipid nanoparticles loaded with puerarin: formulation, characterization and protective effects on acute myocardial ischemia model. *Biomed. Pharmacother.* 89, 297–304. doi:10.1016/j.biopha.2017.02.029

Du, L., Lu, H., Xiao, Y., Guo, Z., and Li, Y. (2024). Protective effect and pharmacokinetics of dihydromyricetin nanoparticles on oxidative damage of myocardium. *PLoS One* 19, e0301036. doi:10.1371/journal.pone.0301036

Feng, X., Sureda, A., Jafari, S., Memariani, Z., Tewari, D., Annunziata, G., et al. (2019). Berberine in cardiovascular and metabolic diseases: from mechanisms to therapeutics. *Theranostics* 9, 1923–1951. doi:10.7150/thno.30787

Gao, F., Zhao, Y., Zhang, B., Xiao, C., Sun, Z., Gao, Y., et al. (2022). Mitochondrial targeted astaxanthin liposomes for myocardial ischemia-reperfusion injury based on oxidative stress. *J. Biomater. Appl.* 37, 303–314. doi:10.1177/08853282221087102

Gao, S., Liu, Z., Li, H., Little, P. J., Liu, P., and Xu, S. (2012). Cardiovascular actions and therapeutic potential of tanshinone IIA. *Atherosclerosis* 220, 3–10. doi:10.1016/j.atherosclerosis.2011.06.041

Gao, Y., Li, Z., Sun, M., Li, H., Guo, C., Cui, J., et al. (2010). Preparation, characterization, pharmacokinetics, and tissue distribution of curcumin nanosuspension with TPGS as stabilizer. *Drug Dev. Ind. Pharm.* 36, 1225–1234. doi:10.3109/03639041003695139

Han, D., Wang, F., Jiang, Q., Qiao, Z., Zhuang, Y., An, Q., et al. (2024). Enhancing cardioprotection through neutrophil-mediated delivery of 18β-glycyrrhetinic acid in myocardial ischemia/reperfusion injury. *Adv. Sci. (Weinh)* 11, e2406124. doi:10.1002/advs.202406124

Han, Y., Wang, H., Wang, Y., Dong, P., Jia, J., and Yang, S. (2021). Puerarin protects cardiomyocytes from ischemia-reperfusion injury by upregulating LncRNA ANRIL and inhibiting autophagy. *Cell. Tissue Res.* 385, 739–751. doi:10.1007/s00441-021-03463-2

Hu, F., Hu, T., Qiao, Y., Huang, H., Zhang, Z., Huang, W., et al. (2024). Berberine inhibits excessive autophagy and protects myocardium against ischemia/reperfusion injury via the RhoE/AMPK pathway. *Int. J. Mol. Med.* 53, 49. doi:10.3892/ijmm.2024.5373

Huang, Q., Yao, Y., Wang, Y., Li, J., Chen, J., Wu, M., et al. (2023). Ginsenoside Rb2 inhibits p300-mediated SF3A2 acetylation at lysine 10 to promote Fscn1 alternative splicing against myocardial ischemic/reperfusion injury. *J. Adv. Res.* S2090-1232 (23), 365–379. doi:10.1016/j.jare.2023.12.012

Huang, X., Deng, H., Shen, Q.-K., and Quan, Z.-S. (2022). Tanshinone IIA: pharmacology, total synthesis, and progress in structure-modifications. *Curr. Med. Chem.* 29, 1959–1989. doi:10.2174/0929867328666211108110025

Jia, X., Shao, W., and Tian, S. (2022). Berberine alleviates myocardial ischemia-reperfusion injury by inhibiting inflammatory response and oxidative stress: the key function of miR-26b-5p-mediated PTGS2/MAPK signal transduction. *Pharm. Biol.* 60, 652–663. doi:10.1080/13880209.2022.2048029

Jing, J., Fang, S., Li, Y., Liu, W., Wang, C., Lan, Y., et al. (2024). An enhanced cardio-protective effect of nanoparticles loaded with active components from Polygonum orientale L. against isoproterenol-induced myocardial ischemia in rats. *Int. J. Pharm.* 655, 124047. doi:10.1016/j.ijpharm.2024.124047

Kim, H., Lee, J. H., Kim, J. E., Kim, Y. S., Ryu, C. H., Lee, H. J., et al. (2018). Micro-/nano-sized delivery systems of ginsenosides for improved systemic bioavailability. *J. Ginseng Res.* 42, 361–369. doi:10.1016/j.jgr.2017.12.003

Lan, M., Hou, M., Yan, J., Deng, Q., Zhao, Z., Lv, S., et al. (2022). Cardiomyocyte-targeted anti-inflammatory nanotherapeutics against myocardial ischemia reperfusion (IR) injury. *Nano Res.* 15, 9125–9134. doi:10.1007/s12274-022-4553-6

Lei, W., Yan, Y., Ma, Y., Jiang, M., Zhang, B., Zhang, H., et al. (2022). Notoginsenoside R1 regulates ischemic myocardial lipid metabolism by activating the AKT/mTOR signaling pathway. *Front. Pharmacol.* 13, 905092. doi:10.3389/fphar.2022.905092

Li, F., Li, D., Tang, S., Liu, J., Yan, J., Chen, H., et al. (2021a). Quercetin protects H9c2 cardiomyocytes against oxygen-glucose deprivation/reoxygenation-induced oxidative stress and mitochondrial apoptosis by regulating the ERK1/2/DRP1 signaling pathway. *Evid. Based Complement. Altern. Med.* 2021, 7522175. doi:10.1155/2021/7522175

Li, H., Li, M., Fu, J., Ao, H., Wang, W., and Wang, X. (2021b). Enhancement of oral bioavailability of quercetin by metabolic inhibitory nanosuspensions compared to conventional nanosuspensions. *Drug Deliv.* 28, 1226–1236. doi:10.1080/10717544.2021.1927244

Li, H., Zhu, J., Xu, Y.-W., Mou, F.-F., Shan, X.-L., Wang, Q.-L., et al. (2022a). Notoginsenoside R1-loaded mesoporous silica nanoparticles targeting the site of injury through inflammatory cells improves heart repair after myocardial infarction. *Redox Biol.* 54, 102384. doi:10.1016/j.redox.2022.102384

Li, L., Wang, Y., Guo, R., Li, S., Ni, J., Gao, S., et al. (2020). Ginsenoside Rg3-loaded, reactive oxygen species-responsive polymeric nanoparticles for alleviating myocardial ischemia-reperfusion injury. *J. Control Release* 317, 259–272. doi:10.1016/j.jconrel.2019.11.032

Li, M., Wu, J., Yang, T., Zhao, Y., Ren, P., Chang, L., et al. (2024). Engineered biomimetic nanoparticles-mediated targeting delivery of allicin against myocardial ischemia-reperfusion injury by inhibiting ferroptosis. *Int. J. Nanomedicine* 19, 11275–11292. doi:10.2147/IJN.S478276

Li, X., Wang, G., Sun, J., Hao, H., Xiong, Y., Yan, B., et al. (2007). Pharmacokinetic and absolute bioavailability study of total panax notoginsenoside, a typical multiple constituent traditional Chinese medicine (TCM) in rats. *Biol. Pharm. Bull.* 30, 847–851. doi:10.1248/bpb.30.847

Li, Y., Hao, H., Yu, H., Yu, L., Ma, H., and Zhang, H. (2022b). Ginsenoside Rg2 ameliorates myocardial ischemia/reperfusion injury by regulating TAK1 to inhibit necroptosis. *Front. Cardiovasc Med.* 9, 824657. doi:10.3389/fcvm.2022.824657

Liu, C., Zhang, X., Yang, H., Zhao, M., Liu, Y., Zhao, R., et al. (2024). PEG-modified nano liposomes co-deliver Apigenin and RAGE-siRNA to protect myocardial ischemia injury. *Int. J. Pharm.* 649, 123673. doi:10.1016/j.ijpharm.2023.123673

Liu, C.-J., Yao, L., Hu, Y.-M., and Zhao, B.-T. (2021a). Effect of quercetin-loaded mesoporous silica nanoparticles on myocardial ischemia-reperfusion injury in rats and its mechanism. *IJN* 16, 741–752. doi:10.2147/IJN.S277377

Liu, Y., Li, L., Wang, Z., Zhang, J., and Zhou, Z. (2023). Myocardial ischemia-reperfusion injury; Molecular mechanisms and prevention. *Microvasc. Res.* 149, 104565. doi:10.1016/j.mvr.2023.104565

Liu, Y., Song, Y., Li, S., and Mo, L. (2021b). Cardioprotective effect of quercetin against ischemia/reperfusion injury is mediated through NO system and mitochondrial K-ATP channels. *Cell. J.* 23, 184–190. doi:10.22074/cellj.2021.7183

Liu, Y., Xie, X., Chen, H., Hou, X., He, Y., Shen, J., et al. (2020). Advances in next-generation lipid-polymer hybrid nanocarriers with emphasis on polymer-modified functional liposomes and cell-based-biomimetic nanocarriers for active ingredients and fractions from Chinese medicine delivery. *Nanomedicine* 29, 102237. doi:10.1016/j.nano.2020.102237

Long, T., Pan, W., Li, F., Sheikh, S. A., Xie, Q., and Zhang, C. (2023). Berberine up-regulates miR-340-5p to protect myocardial ischaemia/reperfusion from HMGB1-mediated inflammatory injury. *Esc. Heart Fail* 10, 931–942. doi:10.1002/ehf2.14235

Lozano, O., Lázaro-Alfaro, A., Silva-Platas, C., Oropeza-Almazán, Y., Torres-Quintanilla, A., Bernal-Ramírez, J., et al. (2019). Nanoencapsulated quercetin improves cardioprotection during hypoxia-reoxygenation injury through preservation of mitochondrial function. *Oxid. Med. Cell. Longev.* 2019, 7683051. doi:10.1155/2019/7683051

Mao, S., Wang, L., Chen, P., Lan, Y., Guo, R., and Zhang, M. (2018). Nanoparticle-mediated delivery of Tanshinone IIA reduces adverse cardiac remodeling following

myocardial infarctions in a mice model: role of NF-κB pathway. *Artif. Cells Nanomed Biotechnol.* 46, S707–S716. doi:10.1080/21691401.2018.1508028

Mi, X., Hu, M., Dong, M., Yang, Z., Zhan, X., Chang, X., et al. (2021). Folic acid decorated zeolitic imidazolate framework (ZIF-8) loaded with baicalin as a nano-drug delivery system for breast cancer therapy. *Int. J. Nanomedicine* 16, 8337–8352. doi:10.2147/IJN.S340764

Nabofa, W. E. E., Alashe, O. O., Oyeyemi, O. T., Attah, A. F., Oyagbemi, A. A., Omobowale, T. O., et al. (2018). Cardioprotective effects of curcumin-nisin based poly lactic acid nanoparticle on myocardial infarction in Guinea pigs. *Sci. Rep.* 8, 16649. doi:10.1038/s41598-018-35145-5

Nagarajan, A. G., Neeley, N., Doroodian, P., Olazabel, A., and Kupfer, G. (2023). Genome wide siRNA screen identifies CGAS-sting pathway as a pharmacological target that promotes survival of hematopoietic stem cells deficient in fanconi genes. *Blood* 142, 1083. doi:10.1182/blood-2023-187180

Pan, W., Xue, B., Yang, C., Miao, L., Zhou, L., Chen, Q., et al. (2018). Biopharmaceutical characters and bioavailability improving strategies of ginsenosides. *Fitoterapia* 129, 272–282. doi:10.1016/j.fitote.2018.06.001

Pei, H., Wu, Y., Wei, Y., Yang, Y., Teng, S., and Zhang, H. (2014). Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: a meta-analysis of 11 randomized trials. *PLoS One* 9, e115500. doi:10.1371/journal.pone.0115500

Piscatelli, J. A., Ban, J., Lucas, A. T., and Zamboni, W. C. (2021). Complex factors and challenges that affect the pharmacology, safety and efficacy of nanocarrier drug delivery systems. *Pharmaceutics* 13, 114. doi:10.3390/pharmaceutics13010114

Plumb, R. S., Gethings, L. A., Rainville, P. D., Isaac, G., Trengove, R., King, A. M., et al. (2023). Advances in high throughput LC/MS based metabolomics: a review. *TrAC Trends Anal. Chem.* 160, 116954. doi:10.1016/j.trac.2023.116954

Qin, G.-W., Lu, P., Peng, L., and Jiang, W. (2021). Ginsenoside Rb1 inhibits cardiomyocyte autophagy via PI3K/Akt/mTOR signaling pathway and reduces myocardial ischemia/reperfusion injury. *Am. J. Chin. Med.* 49, 1913–1927. doi:10.1142/S0192415X21500907

Qiu, J., Cai, G., Liu, X., and Ma, D. (2017). αvβ3 integrin receptor specific peptide modified, salvianolic acid B and panax notoginsenoside loaded nanomedicine for the combination therapy of acute myocardial ischemia. *Biomed. Pharmacother.* 96, 1418–1426. doi:10.1016/j.biopha.2017.10.086

Safiri, S., Karamzad, N., Singh, K., Carson-Chahhoud, K., Adams, C., Nejadghaderi, S. A., et al. (2022). Burden of ischemic heart disease and its attributable risk factors in 204 countries and territories, 1990-2019. *Eur. J. Prev. Cardiol.* 29, 420–431. doi:10.1093/eurjpc/zwab213

Sarhene, M., Ni, J. Y., Duncan, E. S., Liu, Z., Li, S., Zhang, J., et al. (2021). Ginsenosides for cardiovascular diseases; update on pre-clinical and clinical evidence, pharmacological effects and the mechanisms of action. *Pharmacol. Res.* 166, 105481. doi:10.1016/j.phrs.2021.105481

Schäfer, A., König, T., Bauersachs, J., and Akin, M. (2022). Novel therapeutic strategies to reduce reperfusion injury after acute myocardial infarction. *Curr. Probl. Cardiol.* 47, 101398. doi:10.1016/j.cpcardiol.2022.101398

Song, D., Hao, J., and Fan, D. (2020). Biological properties and clinical applications of berberine. *Front. Med.* 14, 564–582. doi:10.1007/s11684-019-0724-6

Sun, G., Lin, X., Hong, Y., Feng, Y., Ruan, K., and Xu, D. (2012). PEGylation for drug delivery to ischemic myocardium: pharmacokinetics and cardiac distribution of poly(ethylene glycol)s in mice with normal and ischemic myocardium. *Eur. J. Pharm. Sci.* 46, 545–552. doi:10.1016/j.ejps.2012.04.010

Tan, H., Song, Y., Chen, J., Zhang, N., Wang, Q., Li, Q., et al. (2021). Platelet-like fusogenic liposome-mediated targeting delivery of miR-21 improves myocardial remodeling by reprogramming macrophages post myocardial ischemia-reperfusion injury. *Adv. Sci. (Weinh)* 8, e2100787. doi:10.1002/advs.202100787

Tong, Q., Zhu, P.-C., Zhuang, Z., Deng, L.-H., Wang, Z.-H., Zeng, H., et al. (2019). Notoginsenoside R1 for organs ischemia/reperfusion injury: a preclinical systematic review. *Front. Pharmacol.* 10, 1204. doi:10.3389/fphar.2019.01204

Upadhaya, S., Madala, S., Baniya, R., Subedi, S. K., Saginala, K., and Bachuwa, G. (2017). Impact of cyclosporine A use in the prevention of reperfusion injury in acute myocardial infarction: a meta-analysis. *Cardiol. J.* 24, 43–50. doi:10.5603/CJ.a2016.0091

Voronkov, N. S., Popov, S. V., Naryzhnaya, N. V., Prasad, N. R., Petrov, I. M., Kolpakov, V. V., et al. (2024). Effect of cold adaptation on the state of cardiovascular system and cardiac tolerance to ischemia/reperfusion injury. *Iran. Biomed. J.* 28, 59–70. doi:10.61186/ibj.3872

Wang, D., Bu, T., Li, Y., He, Y., Yang, F., and Zou, L. (2022). Pharmacological activity, pharmacokinetics, and clinical research progress of puerarin. *Antioxidants (Basel)* 11, 2121. doi:10.3390/antiox11112121

Wang, J., Liu, Y., Liu, Y., Huang, H., Roy, S., Song, Z., et al. (2023a). Recent advances in nanomedicines for imaging and therapy of myocardial ischemia-reperfusion injury. *J. Control Release* 353, 563–590. doi:10.1016/j.jconrel.2022.11.057

Wang, K., Feng, X., Chai, L., Cao, S., and Qiu, F. (2017). The metabolism of berberine and its contribution to the pharmacological effects. *Drug Metab. Rev.* 49, 139–157. doi:10.1080/03602532.2017.1306544

Wang, Q., Song, Y., Chen, J., Li, Q., Gao, J., Tan, H., et al. (2021). Direct *in vivo* reprogramming with non-viral sequential targeting nanoparticles promotes cardiac regeneration. *Biomaterials* 276, 121028. doi:10.1016/j.biomaterials.2021.121028

Wang, Y., Li, F., Wei, S., Li, W., Wu, J., Li, S., et al. (2024a). Puerarin-loaded liposomes Co-modified by ischemic myocardium-targeting peptide and triphenylphosphonium cations ameliorate myocardial ischemia-reperfusion injury. *Int. J. Nanomedicine* 19, 7997–8014. doi:10.2147/IJN.S468394

Wang, Y., Li, S., Li, W., Wu, J., Hu, X., Tang, T., et al. (2024b). Cardiac-targeted and ROS-responsive liposomes containing puerarin for attenuating myocardial ischemia-reperfusion injury. *Nanomedicine (Lond)* 19, 2335–2355. doi:10.1080/17435889.2024.2402678

Wang, Y., Wang, Q., Wang, X., Yao, P., Dai, Q., Qi, X., et al. (2023b). Docetaxel-loaded pH/ROS dual-responsive nanoparticles with self-supplied ROS for inhibiting metastasis and enhancing immunotherapy of breast cancer. *J. Nanobiotechnology* 21, 286. doi:10.1186/s12951-023-02013-y

Wang, Y., Wang, Y., Wang, X., and Hu, P. (2018). Tilianin-loaded reactive oxygen species-scavenging nano-micelles protect H9c2 cardiomyocyte against hypoxia/reoxygenation-induced injury. *J. Cardiovasc Pharmacol.* 72, 32–39. doi:10.1097/FJC.0000000000000587

Wang, Y., Zheng, J., Xiao, X., Feng, C., Li, Y., Su, H., et al. (2024c). Ginsenoside Rd attenuates myocardial ischemia/reperfusion injury by inhibiting inflammation and apoptosis through PI3K/akt signaling pathway. *Am. J. Chin. Med.* 52, 433–451. doi:10.1142/S0192415X24500186

Wang, Z.-K., Chen, R.-R., Li, J.-H., Chen, J.-Y., Li, W., Niu, X.-L., et al. (2020). Puerarin protects against myocardial ischemia/reperfusion injury by inhibiting inflammation and the NLRP3 inflammasome: the role of the SIRT1/NF-κB pathway. *Int. Immunopharmacol.* 89, 107086. doi:10.1016/j.intimp.2020.107086

Wei, D., Yang, H., Zhang, Y., Zhang, X., Wang, J., Wu, X., et al. (2022). Nano-traditional Chinese medicine: a promising strategy and its recent advances. *J. Mater Chem. B* 10, 2973–2994. doi:10.1039/D2TB00225F

Wei, Q., Xiao, Y., Du, L., and Li, Y. (2024). Advances in nanoparticles in the prevention and treatment of myocardial infarction. *Molecules* 29, 2415. doi:10.3390/molecules29112415

Welt, F. G. P., Batchelor, W., Spears, J. R., Penna, C., Pagliaro, P., Ibanez, B., et al. (2024). Reperfusion injury in patients with acute myocardial infarction: JACC scientific statement. *J. Am. Coll. Cardiol.* 83, 2196–2213. doi:10.1016/j.jacc.2024.02.056

Wu, H.-J., Zhang, K., Ma, J.-J., Wang, L., and Zhuang, Y. (2021). Mechanism of curcumin against myocardial ischaemia-reperfusion injury based on the P13K/Akt/mTOR signalling pathway. *Eur. Rev. Med. Pharmacol. Sci.* 25, 5490–5499. doi:10.26355/eurrev_202109_26658

Xie, Y., Shen, X., Xu, F., and Liang, X. (2024). Research progress of nano-delivery systems for the active ingredients from traditional Chinese medicine. *Phytochem. Anal.* doi:10.1002/pca.3381

Xu, H., Hu, M., Liu, M., An, S., Guan, K., Wang, M., et al. (2020). Nano-puerarin regulates tumor microenvironment and facilitates chemo- and immunotherapy in murine triple negative breast cancer model. *Biomaterials* 235, 119769. doi:10.1016/j.biomaterials.2020.119769

Xu, H., Zhang, X., Shi, Y., Yu, K., and Jiang, Y. (2022). Notoginsenoside R1 relieves the myocardial infarction via activating the JAK2/STAT3 signaling pathway *in vivo* and *in vitro*. *Bioengineered* 13, 5653–5662. doi:10.1080/21655979.2022.2037366

Xu, H.-X., Pan, W., Qian, J.-F., Liu, F., Dong, H.-Q., and Liu, Q.-J. (2019). MicroRNA-21 contributes to the puerarin-induced cardioprotection via suppression of apoptosis and oxidative stress in a cell model of ischemia/reperfusion injury. *Mol. Med. Rep.* 20, 719–727. doi:10.3892/mmr.2019.10266

Xu, S., Wu, B., Zhong, B., Lin, L., Ding, Y., Jin, X., et al. (2021). Naringenin alleviates myocardial ischemia/reperfusion injury by regulating the nuclear factor-erythroid factor 2-related factor 2 (Nrf2)/System xc-/glutathione peroxidase 4 (GPX4) axis to inhibit ferroptosis. *Bioengineered* 12, 10924–10934. doi:10.1080/21655979.2021.1995994

Xu, X., Diao, Z., Zhao, B., Xu, H., Yan, S., and Chen, H. (2024). Protective activities of silver nanoparticles containing *Panax japonicus* on apoptotic, inflammatory, and oxidative alterations in isoproterenol-induced cardiotoxicity. *Open Chem.* 22, 20240006. doi:10.1515/chem-2024-0006

Xue, Y., Fu, W., Liu, Y., Yu, P., Sun, M., Li, X., et al. (2020). Ginsenoside Rb2 alleviates myocardial ischemia/reperfusion injury in rats through SIRT1 activation. *J. Food Sci.* 85, 4039–4049. doi:10.1111/1750-3841.15505

Xue, Y., Fu, W., Yu, P., Li, Y., Yu, X., Xu, H., et al. (2023). Ginsenoside Rc alleviates myocardial ischemia-reperfusion injury by reducing mitochondrial oxidative stress and apoptosis: role of SIRT1 activation. *J. Agric. Food Chem.* 71, 1547–1561. doi:10.1021/acs.jafc.2c06926

Yalikong, A., Li, X.-Q., Zhou, P.-H., Qi, Z.-P., Li, B., Cai, S.-L., et al. (2021). A triptolide loaded HER2-targeted nano-drug delivery system significantly suppressed the proliferation of HER2-positive and BRAF mutant colon cancer. *Int. J. Nanomedicine* 16, 2323–2335. doi:10.2147/IJN.S287732

Yan, L., Pan, C.-S., Liu, Y.-Y., Cui, Y.-C., Hu, B.-H., Chang, X., et al. (2021). The composite of 3, 4-dihydroxyl-phenyl lactic acid and notoginsenoside R1 attenuates

myocardial ischemia and reperfusion injury through regulating mitochondrial respiratory chain. *Front. Physiol.* 12, 538962. doi:10.3389/fphys.2021.538962

Yan, S., Yue, Y., Zeng, L., Jiang, C., Li, W., Li, H., et al. (2019). Ligustrazine nanoparticles nano spray's activation on Nrf2/ARE pathway in oxidative stress injury in rats with postoperative abdominal adhesion. *Ann. Transl. Med.* 7, 379. doi:10.21037/atm.2019.07.72

Yang, C., Yang, S., Fang, S., Li, L., Jing, J., Liu, W., et al. (2023). PLGA nanoparticles enhanced cardio-protection of scutellarin and paeoniflorin against isoproterenol-induced myocardial ischemia in rats. *Int. J. Pharm.* 648, 123567. doi:10.1016/j.ijpharm.2023.123567

Yang, K.-T., Chao, T.-H., Wang, I.-C., Luo, Y.-P., Ting, P.-C., Lin, J.-H., et al. (2022). Berberine protects cardiac cells against ferroptosis. *Tzu Chi Med. J.* 34, 310–317. doi:10.4103/tcmj.tcmj_236_21

Yao, C., Shi, X., Lin, X., Shen, L., Xu, D., and Feng, Y. (2015). Increased cardiac distribution of mono-PEGylated Radix Ophiopogonis polysaccharide in both myocardial infarction and ischemia/reperfusion rats. *Int. J. Nanomedicine* 10, 409–418. doi:10.2147/IJN.S73462

Ye, J., Lyu, T.-J., Li, L.-Y., Liu, Y., Zhang, H., Wang, X., et al. (2023). Ginsenosi*de re* attenuates myocardial ischemia/reperfusion induced ferroptosis via miR-144-3p/SLC7A11. *Phytomedicine* 113, 154681. doi:10.1016/j.phymed.2023.154681

Yu, W., Ding, J., Chen, J., Jiang, Y., Zhao, J., Liu, J., et al. (2024). Magnesium ion-doped mesoporous bioactive glasses loaded with gallic acid against myocardial ischemia/reperfusion injury by affecting the biological functions of multiple cells. *Int. J. Nanomedicine* 19, 347–366. doi:10.2147/IJN.S444751

Zeng, J.-J., Shi, H.-Q., Ren, F.-F., Zhao, X.-S., Chen, Q.-Y., Wang, D.-J., et al. (2023). Notoginsenoside R1 protects against myocardial ischemia/reperfusion injury in mice via suppressing TAK1-JNK/p38 signaling. *Acta Pharmacol. Sin.* 44, 1366–1379. doi:10.1038/s41401-023-01057-y

Zhang, J., Han, X., Li, X., Luo, Y., Zhao, H., Yang, M., et al. (2012). Core-shell hybrid liposomal vesicles loaded with panax notoginsenoside: preparation, characterization and protective effects on global cerebral ischemia/reperfusion injury and acute myocardial ischemia in rats. *Int. J. Nanomedicine* 7, 4299–4310. doi:10.2147/IJN.S32385

Zhang, J., Liu, S., Jiang, L., Hou, J., and Yang, Z. (2022). Curcumin improves cardiopulmonary resuscitation outcomes by modulating mitochondrial metabolism and apoptosis in a rat model of cardiac arrest. *Front. Cardiovasc Med.* 9, 908755. doi:10.3389/fcvm.2022.908755

Zhang, S., Li, J., Hu, S., Wu, F., and Zhang, X. (2018). Triphenylphosphonium and D-α-tocopheryl polyethylene glycol 1000 succinate-modified, tanshinone IIA-loaded lipid-polymeric nanocarriers for the targeted therapy of myocardial infarction. *Int. J. Nanomedicine* 13, 4045–4057. doi:10.2147/IJN.S165590

Zhang, S., Xia, J., Zhu, Y., Dong, M., and Wang, J. (2024). Establishing Salvia miltiorrhiza-derived exosome-like nanoparticles and elucidating their role in angiogenesis. *Molecules* 29, 1599. doi:10.3390/molecules29071599

Zhang, Y.-M., Zhang, Z.-Y., and Wang, R.-X. (2020). Protective mechanisms of quercetin against myocardial ischemia reperfusion injury. *Front. Physiol.* 11, 956. doi:10.3389/fphys.2020.00956

Zheng, Y., Wang, Y., Xia, M., Gao, Y., Zhang, L., Song, Y., et al. (2022). The combination of nanotechnology and traditional Chinese medicine (TCM) inspires the modernization of TCM: review on nanotechnology in TCM-based drug delivery systems. *Drug Deliv. Transl. Res.* 12, 1306–1325. doi:10.1007/s13346-021-01029-x

Zhou, Y., Liang, Q., Wu, X., Duan, S., Ge, C., Ye, H., et al. (2023). siRNA delivery against myocardial ischemia reperfusion injury mediated by reversibly camouflaged biomimetic nanocomplexes. *Adv. Mater* 35, e2210691. doi:10.1002/adma.202210691

Zhou, Y.-X., Zhang, H., and Peng, C. (2014). Puerarin: a review of pharmacological effects. *Phytother. Res.* 28, 961–975. doi:10.1002/ptr.5083

Zhou, Y.-X., Zhang, H., and Peng, C. (2021). Effects of puerarin on the prevention and treatment of cardiovascular diseases. *Front. Pharmacol.* 12, 771793. doi:10.3389/fphar.2021.771793

Zhu, K., Yao, Y., Wang, K., Shao, F., Zhu, Z., Song, Y., et al. (2023a). Berberin sustained-release nanoparticles were enriched in infarcted rat myocardium and resolved inflammation. *J. Nanobiotechnol* 21, 33. doi:10.1186/s12951-023-01790-w

Zhu, P.-C., Shen, J., Qian, R.-Y., Xu, J., Liu, C., Hu, W.-M., et al. (2023b). Effect of tanshinone IIA for myocardial ischemia/reperfusion injury in animal model: preclinical evidence and possible mechanisms. *Front. Pharmacol.* 14, 1165212. doi:10.3389/fphar.2023.1165212

Zhu, T., and Wan, Q. (2023). Pharmacological properties and mechanisms of Notoginsenoside R1 in ischemia-reperfusion injury. *Chin. J. Traumatol.* 26, 20–26. doi:10.1016/j.cjtee.2022.06.008

Zhu, Y., Yue, M., Guo, T., Li, F., Li, Z., Yang, D., et al. (2021). PEI-PEG-Coated mesoporous silica nanoparticles enhance the antitumor activity of tanshinone IIA and serve as a gene transfer vector. *Evid. Based Complement. Altern. Med.* 2021, 6756763. doi:10.1155/2021/6756763

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 02 October 2025
DOI 10.3389/fphar.2025.1506234

OPEN ACCESS

EDITED BY
Yu-Qing Zhang,
McMaster University, Canada

REVIEWED BY
Zeliha Selamoglu,
Niğde Ömer Halisdemir University, Türkiye
Qian Li,
Dali University, China

*CORRESPONDENCE
Junnan Zhao,
13240050425@163.com
Fengqin Xu,
doctorxu@aliyun.com

RECEIVED 04 October 2024
ACCEPTED 16 September 2025
PUBLISHED 02 October 2025

CITATION
Hui J, Wang Y, Xu F and Zhao J (2025) Potential preventive effects of selected traditional Chinese medicine as adjuvant therapy on hypertensive heart disease progression by replenishing qi and activating blood circulation: a systematic review and meta-analysis of clinical trials.
Front. Pharmacol. 16:1506234.
doi: 10.3389/fphar.2025.1506234

Potential preventive effects of selected traditional Chinese medicine as adjuvant therapy on hypertensive heart disease progression by replenishing qi and activating blood circulation: a systematic review and meta-analysis of clinical trials

Jiaqi Hui[1,2], Ya Wang[3], Fengqin Xu[1,2]* and Junnan Zhao[1,2]*

[1]Institute of Geriatrics, Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Laboratory of Combining Diseases and Evidence to Prevent Vascular Aging, National Administration of Traditional Chinese Medicine, Beijing, China, [3]Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China

Objective: Hypertension remained an important public health problem with high morbidity and mortality and was emerging as a risk factor for future heart failure. The transition from hypertension to hypertensive heart disease (HHD) and heart failure grew progressively with time. Traditional Chinese medicine (TCM) has a history of several thousand years, where selected TCM for replenishing qi and activating blood circulation provides an alternative treatment for HHD.

Methods: An extensive literature search was conducted across eight electronic databases from their inception until 8 September 2023, to evaluate the potential preventive effects of selected TCM as an adjuvant therapy on the progression of HHD. The outcome measures included blood pressure and indicators of cardiac structure and function under cardiac ultrasound. The mean difference (MD) and 95% confidence interval (CI) were used to determine continuous outcomes. Risk ratio (RR) with 95% confidence interval (CI) was used to determine dichotomous outcomes. The information about the overall certainty of the evidence from studies was presented according to specific outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Guideline Development Tool (GDT) online software.

Results: Twenty-one randomized controlled trials (RCTs) involving 2, 055 participants were included. Meta-analyses favored integrated Chinese botanical drugs and Western medicine on blood pressure, New York Heart Association classification, left ventricular ejection fraction, transmitral peak early diastolic velocity/peak late diastolic velocity ratio, left ventricular internal diameters, left ventricular mass index, interventricular septum thickness in diastole, and B-type natriuretic peptide compared with Western medicine alone. Results on cardiac output should be interpreted with caution due to sample size limitations. No severe adverse events were identified. Most of the Chinese botanical drugs originated from classical TCM formulas. The dosage form of Chinese botanical drugs was oral. *Salvia miltiorrhiza* Bunge (Danshen),

Oreocome striata (DC.) Pimenov & Kljuykov (Chuanxiong), *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen), *Astragalus mongholicus* Bunge (Huangqi), and *Typha angustifolia* L. (Puhuang) were the top 5 Chinese botanical drugs, which might be associated with replenishing qi and activating blood circulation.

Conclusion: Selected TCM had the potential to be effective as an adjuvant therapy for alleviating adverse left ventricular remodeling and improving cardiac function after HHD, and therapy of replenishing qi and activating blood circulation may serve as a potential reference for treatment. To better assess Chinese botanical drugs' preventative effects, more long-term, high-quality RCTs are still necessary.

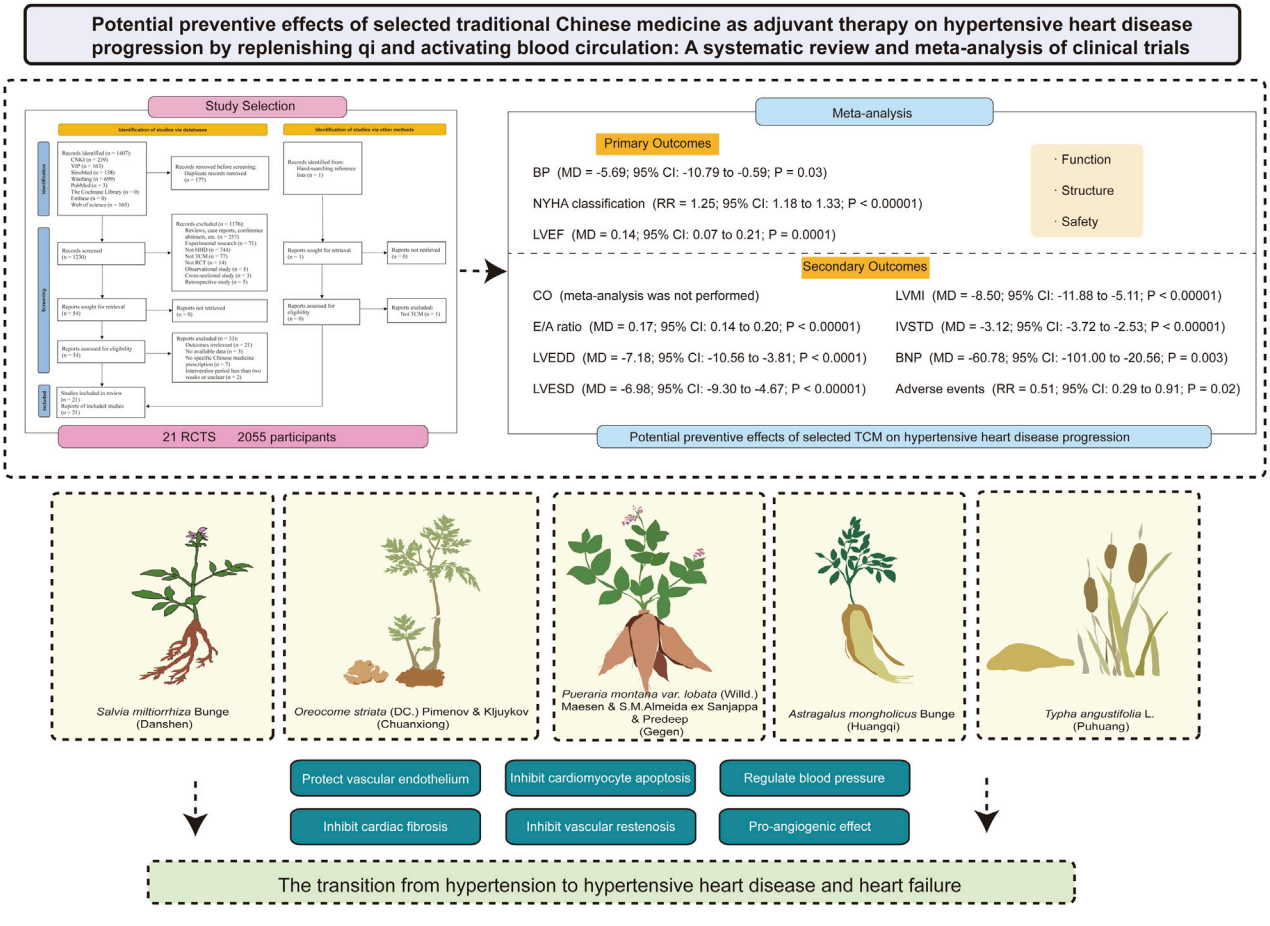
Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/#myprospero, identifier CRD42022346030.

KEYWORDS

traditional Chinese medicine, therapy of replenishing qi and activating bloodcirculation, hypertensive heart disease, randomized controlled trial, systematic review, meta-analysis

1 Introduction

Hypertensive Heart Disease (HHD), defined as symptomatic heart failure (HF) due to direct and long-term exposure to hypertension, was one of the most serious effects with its nonfatal burden derived from the model of HF (Escaned and Lerman, 2020; Roth et al., 2017). In a 20-year follow-up of 5, 143 participants from the Framingham Heart Study cohort, of all newly diagnosed HF patients, 91% had hypertension before developing HF (Levy et al., 1996). A recent study brought attention to the importance of early-stage hypertension as a significant aetiological risk factor for the development of early HF (Tromp et al., 2021) that compared the age variation in incident HF risk variables in the general population. In young participants, hypertension was associated with a threefold increase in the chance of developing HF later on. In contrast to a 1.4-fold risk in elderly participants (>65 years), in young participants (<55 years), hypertension was associated with a



GRAPHICAL ABSTRACT

three-fold increase in the chance of developing HF later on (Bayés-Genís and Díez, 2022). Thus, elevated blood pressure (BP) was an essential risk factor for HF and, at the same time, a preventable cause (Virani et al., 2020; GBD, 2017 Risk Factor Collaborators, 2018). However, the early identification of patients with hypertension at risk of developing HF remains a challenge for clinicians (Escaned and Lerman, 2020). Long-term hypertension could cause hemodynamic stress that eventually changes the structure and metabolism of the myocardium. This could lead to cardiac remodeling, which showed up as HF and left ventricular (LV) dysfunction, and irregularities in myocardial perfusion and cardiac rhythm (Drazner, 2011; González et al., 2018; Bayés-Genís and Díez, 2022). Based on the clinical effects and pathophysiology of hypertension in the heart, HHD was divided into four ascending categories, including Degree Ⅰ (Isolated LV diastolic dysfunction with no LV hypertrophy (LVH)), Degree Ⅱ (LV diastolic dysfunction with concentric LVH), Degree Ⅲ (Clinical HF (dyspnea and pulmonary edema with preserved ejection fraction)), Degree Ⅳ (Dilated cardiomyopathy with HF and reduced ejection fraction) (Messerli et al., 2017; Iriarte et al., 1993). Therefore, HHD could be clinically asymptomatic or present with palpitations, chest tightness, dyspnea, biventricular failure, and sudden death (Dai et al., 2021). The results in the diagnosis of HHD largely rely on echocardiography and electrocardiogram (Dai et al., 2021; Devereux et al., 1993). Transthoracic echocardiography is the gold standard for noninvasive evaluation of cardiac structure and function. This provides a basis for assessing changes in cardiac structure during the shift from hypertension to HHD and HF. Previous studies suggested the adverse effects of hypertension on the heart (Ekhteiari Salmas et al., 2018; Salmas et al., 2017; Selamoglu Talas, 2014). Propolis is a resinous product collected by honeybees from various plant sources, which decreases tyrosine hydroxylase activity of the heart in nitric oxide synthase-inhibited hypertensive rats and thereby may modulate the synthesis of catecholamine and BP (Gogebakan et al., 2012). Antihypertensive medications, by definition, reduce BP, and when used as initial therapy, the majority of antihypertensive medications slowed the progression from hypertension to HF. However, examining the research on antihypertensive medications showed that not all of them have the same ability to prevent HF, for example, once-daily, low-dose hydrochlorothiazide was not recommended (Messerli et al., 2017). Thus, it was urgently needed to search for supplementary and alternative medical treatments for more effective control of HHD.

The investigation of traditional Chinese medicine (TCM) has the potential to lay an invaluable foundation for the development of new therapeutics. Multiple traditional botanical drugs and their metabolites, which are well-known for their proven excellent pharmacological effects, have long been utilized to treat different diseases, specifically cardiovascular disorders (Tavolinejad et al., 2019; Yousefsani et al., 2021). With the increasingly clinical application of selected TCM for replenishing qi and activating blood circulation in the therapy and prevention of cardiovascular diseases (Liu and Huang, 2016), therapy of replenishing qi and activating blood circulation has become an important role as a supplement and alternative treatment in clinical practice. Up till now, some randomized controlled trials (RCTs) have reported the effect of TCM on patients with HHD. The impact of selected TCM as an adjuvant therapy for the advancement of HHD disease was examined in this meta-analysis.

2 Materials and methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline recommendations were adhered to in this systematic review (Page et al., 2021), and Supplementary Table S1 contained the PRISMA checklist. The systematic review protocol was registered with International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022346030) on 23 July 2022, prior to the initiation of study screening. Since this study involved a meta-analysis of data that had already been published, Ethics and Institutional Review Board approval was not necessary.

2.1 Search strategy

Eight electronic databases were systematically searched, including PubMed, the Cochrane Library, Embase, Web of Science, Wanfang Database, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (Chinese VIP Information), and Chinese Biomedical Database (SinoMed) from inception to 8 September 2023, with no language or publication restrictions applied. Grey literature searches included Web of Science Conference Proceedings Citation Index-Science (CPCI-S), ClinicalTrials.gov (www.clinicaltrials.gov/), the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp/en/), and International Traditional Medicine Clinical Trial Registry (ITMCTR) (itmctr.ccebtcm.org.cn/) using key terms and scanning reference lists of relevant reviews. 'Medicine, Chinese Traditional' was used as the Medical Subject Heading and matched with corresponding free words for enhancing accuracy. Given the discrepancy between databases, the keywords were adjusted flexibly for 'hypertensive heart disease' and 'hypertensive cardiovascular disease.' Search strategies were adapted to the specific syntax and controlled vocabulary of each database. Finally, all retrieval expressions were formed by logically connecting AND or OR. For example, the PubMed Database was searched as follows:

#1 (hypertensive heart disease [Title/Abstract]) OR (hypertensive cardiovascular disease [Title/Abstract])
#2 "Medicine, Chinese Traditional" [Mesh]
#3 (((((((((Traditional Chinese Medicine [Title/Abstract]) OR (Chung I Hsueh [Title/Abstract])) OR (Hsueh, Chung I [Title/Abstract])) OR (Traditional Medicine, Chinese [Title/Abstract])) OR (Zhong Yi Xue [Title/Abstract])) OR (Chinese Traditional Medicine [Title/Abstract])) OR (Chinese Medicine, Traditional [Title/Abstract])) OR (Drugs, Chinese Herbal [Title/Abstract])) OR (Complementary Therapies [Title/Abstract])) OR (Alternative Medicine [Title/Abstract])
#4 #2 OR #3.
#5 #1 AND #4.

The full search strategy is shown in Supplementary Table S2.

2.2 Inclusion and exclusion criteria

Study eligibility criteria were defined using the PICOS (Participants, Intervention, Comparators, Outcomes, Study design) approach. The inclusion criteria were as follows: (1) patients received a diagnosis of HHD without restrictions on gender, age, ethnicity, or disease stage; (2) patients in the TCM group were treated with Chinese botanical drugs based on those in the control group. Chinese botanical drugs was administered orally at least two-week-long treatment interventions, including Chinese patent medicine, single botanical drug, or TCM prescription; (3) the control group received conventional pharmacological interventions (Western medicine (WM); (4) the primary outcomes included BP (including systolic blood pressure (SBP) and diastolic blood pressure (DBP)), New York Heart Association (NYHA) classification, and left ventricular ejection fraction (LVEF); the secondary outcomes included cardiac output (CO), transmitral peak early diastolic velocity (E)/peak late diastolic velocity (A) ratio (E/A ratio), left ventricular internal diameters (including left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD)), left ventricular mass index (LVMI), interventricular septum thickness in diastole (IVSTD), B-type natriuretic peptide (BNP), and adverse events; (5) the included RCTs were reported in completed paper article. To prevent duplication, we kept the most current publication or the most informative single article where the same population was published in multiple publications.

The exclusion criteria were as follows: (1) interventions included nonoral Chinese botanical drugs or appropriate TCM techniques; (2) it was not reported which botanical drugs were included in the TCM prescription containing multiple botanical drugs, nor the dosage of each type of botanical drug used; (3) it was not reported the administration method of the Chinese patent medicine, including the frequency of administration and the single oral dosage; (4) no relevant outcomes or no available data were reported; (5) the intervention period was less than 2 weeks or not reported; (6) the types of studies were reviews, case reports, retrospective studies, etc.

2.3 Study selection and data extraction

All identified indexed records were downloaded into EndNote X9, and duplicates were removed. After that, two review authors (J. Hui and Y. Wang) separately went through the titles and abstracts and evaluated the full-text publications to look for studies that might be included. Following PRISMA criteria, a flow chart contained the records of the research selection within the systematic review. Until data extractors achieved convergence and agreement, a standard data extraction form was created and tested. Independently, two review authors retrieved study characteristics and outcome data, including characteristics of the author, year, patients (e.g., age, gender, sample size), medication details for the experimental and control group, and outcome indicators. When there were several endpoint indicators in the literature, the longest one was chosen. If any clarification or further information was required, the corresponding authors of the original studies were contacted. Conflicts in data extraction were handled by the third review author (J. Zhao).

2.4 Methodological quality assessment

Two review authors (J. Hui and Y. Wang) independently assessed the risk of bias of all included RCTs using the Cochrane tool for assessing the risk of bias (Higgins et al., 2011). We resolved differences by discussion or by appeal to a third review author (J. Zhao). Following the recommendations of the Cochrane Handbook, the methodological quality was evaluated using seven domains: incomplete outcome data (attrition bias), selective reporting (reporting bias), blinding of participants and personnel (performance bias), random sequence generation (selection bias), allocation concealment (selection bias), and other bias. Three categories were used to classify each domain: low risk of bias, high risk of bias, and uncertain risk of bias. The original authors were contacted to verify and authenticate the randomization and allocation concealment procedures. If the original authors did not communicate, disagreements were settled by debate.

2.5 Data synthesis and statistical analysis

Statistical analysis was carried out using Review Manager 5.3 software (Cochrane Collaboration, Denmark). The mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (CI) was used to integrate continuous outcomes. SMD was used when different scales were used across studies. Dichotomous outcomes were calculated as risk ratio (RR) with 95% CI. We used the Chi^2 (χ^2) test and I^2 statistic to quantify heterogeneity across included studies, where an I^2 of 25% or less was regarded as low heterogeneity, an I^2 of 26%–50% was regarded as moderate heterogeneity, and an I^2 of over 50% was regarded as substantial heterogeneity (Higgins et al., 2003). When there was little to no heterogeneity ($I^2 \leq 50\%$), a fixed-effects model was employed; when there was significant heterogeneity ($I^2 > 50\%$), a random-effects model was used. All two-tailed $P < 0.05$ were considered statistically significant. Numerous participant- or intervention-related characteristics might be connected to heterogeneity among studies. If substantial heterogeneity was detected, we would perform subgroup and sensitivity analyses to investigate possible sources of heterogeneity between studies. Subsequently, sensitivity analyses were carried out by repeating the meta-analysis and removing each study one at a time to assess the robustness and dependability of the findings.

2.6 Quality of evidence

We summarized the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Guideline Development Tool (GDT) (www.gradepro.org). A final quality rating of high, moderate, low, or very poor was assigned to the evidence based on factors such as research design, risk of bias, inconsistency, indirectness, imprecision, and other factors.

2.7 Publication bias

The assessment of publication bias may be limited if there are insufficient studies for the outcomes. Using Stata 12.0 software, a

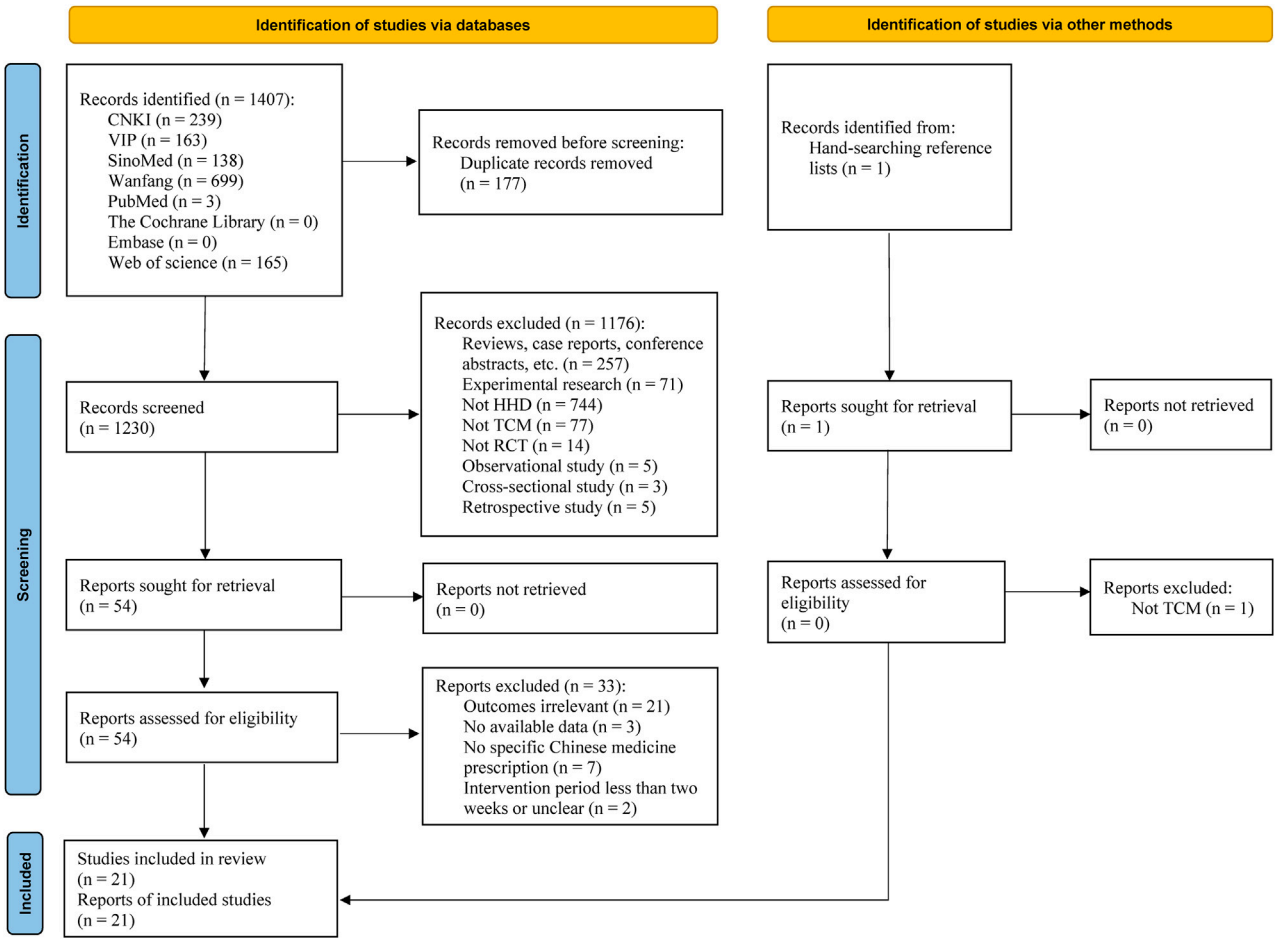


FIGURE 1
Flow diagram of the study selection process. Abbreviation: CNKI: China National Knowledge Infrastructure; HHD: hypertensive heart disease; RCT: randomized controlled trial; TCM: traditional Chinese medicine; VIP: Chinese Scientific Journal Database (Chinese VIP Information); SinoMed: Chinese Biomedical Database.

visual assessment of the funnel plot was used to assess publication bias. Asymmetry indicated publication bias. In the meantime, funnel plot asymmetry was statistically demonstrated using Egger's test. Publication bias does not exist if $P > 0.05$, and *vice versa*. The study's analysis was adjusted for the impact of publication bias using the Duval and Tweedie trim-and-fill method.

3 Results

3.1 Study selection

The literature searching process and research identification are summarized in Figure 1. A total of 1, 408 records were identified; 1, 407 from the database search approach, and one more study was found by looking through the reviews' recognized references. In brief, for the 1,407 records via databases, following the initial database search and the removal of duplicate records, 1, 230 records were found. 1, 176 records were removed after additional title and abstract screening, mostly due to their lack of relevance to the study's objectives. 33 of the 54 records that were subjected to a full-text review were eliminated because 21 of them contained only outcomes that were not relevant, three did not provide available outcome data, seven did not report the specific TCM prescription, and the other 2 records an unclear intervention periods or were of less than 2 weeks. Lastly, 21 studies were included in the review. Additionally, one study that was found by manually scanning the reference list was eliminated because it had no bearing on the goal of the investigation.

3.2 Characteristics of included studies

The baseline characteristics of included 21 RCTs were summarized in Table 1 (Cai, 2016; Cui, 2022; Du, 2016; Hou et al., 2015; Hu, 2012; Jin and Wu, 2006; Li et al., 2019; Liu, 2012; Peng, 2015; Song, 2011; Song, 2019; Tan, 2019; Tao, 2021; Wang and Wang, 2012; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002; Yuan, 2018; Zhang, 2013; Zhao, 2022; Zhu et al., 2019). The studies were published between 2002 and 2022. The demographics and clinical features of the population that was part of the meta-analysis were homogenous. A total of 2,055 individuals

10.3389/fphar.2025.1506234

TABLE 1 Characteristics of included studies.

References	Age (mean ± SD, year)		Gender (male/female)	Sample size (T/C)	Course of disease (mean ± SD, year)		Intervention (T/C)	Duration	Outcome indicator
	T	C			T	C			
Cai (2016)	56–76 (63.1 ± 2.2)	55–78 (63.5 ± 2.1)	41/34	38/37	NR	NR	TCM + WM/WM	2 months	①②⑤⑪
Cui (2022)	52–82 (67.13 ± 14.87)	49–83 (66.23 ± 16.77)	61/61	61/61	4–16 (10.33 ± 5.67)	5–15 (10.24 ± 4.76)	TCM + WM/WM	3 months	③⑪
Du (2016)	30–81 (55.3 ± 7.2)	31–78 (52.3 ± 6.8)	105/105	105/105	1–15 (7.8 ± 3.9)	1–16 (7.9 ± 3.8)	TCM + WM/WM	90 days	③④
Hou et al. (2015)	40–80 (59.44 ± 11.27)	39–78 (58.89 ± 11.39)	60/38	49/49	NR	NR	TCM + WM/WM	1 month	⑥⑧
Hu (2012)	34–75 (55 ± 6.7)	33–77 (55 ± 7.6)	95/47	72/70	1–21 (14 ± 2.1)	1–23 (14 ± 2.3)	TCM + WM/WM	25 days	②⑪
Jin and Wu (2006)	53–78	55–78	36/28	34/30	NR	NR	TCM + WM/WM	6 months	②③
Li et al. (2019)	18–70 (62.13 ± 8.24)	18–70 (61.02 ± 9.02)	71/41	56/56	6.88 ± 1.26	7.21 ± 1.37	TCM + WM/WM	2 months	②③⑤⑨
Liu (2012)	39–79 (56.3 ± 6.4)	36–78 (56.2 ± 6.5)	121/75	98/98	NR	NR	TCM + WM/WM	12 weeks	⑥⑧
Peng (2015)	32–76 (61.8 ± 10.2)	32–74 (60.2 ± 11.4)	44/52	48/48	NR	NR	TCM + WM/WM	12 months	①②⑪
Song (2011)	48–65		50/35	42/43	NR	NR	TCM + WM/WM	4 weeks	②⑩⑪
Song (2019)	41–72 (62.6 ± 7.3)	40–72 (62.5 ± 7.2)	57/39	48/48	1–6 (2.4 ± 0.5)	1–6 (2.3 ± 0.6)	TCM + WM/WM	4 weeks	③⑥
Tan (2019)	53–78 (65.5 ± 2.2)	51–76 (63.5 ± 1.8)	46/34	40/40	1–8 (4.5 ± 2.2)	1–6 (3.5 ± 1.5)	TCM + WM/WM	3 months	①②③⑥⑦⑨
Tao (2021)	31–74 (55.98 ± 8.7)	30–75 (56.23 ± 7.6)	33/27	30/30	1–16 (8.45 ± 0.94)	1–15 (8.49 ± 0.93)	TCM + WM/WM	2 months	③④
Wang and Wang (2012)	59–78	62–82	58/48	53/53	2–6	2–6	TCM + WM/WM	2 months	②⑤
Wang et al. (2012)	42–56	40–58	33/27	30/30	2–7		TCM + WM/WM	24 weeks	②③⑪
Wang and Sun (2018)	42–76 (68.59 ± 8.13)	40–81 (65.06 ± 7.28)	47/43	45/45	1–5 (2.19 ± 0.46)	1–6 (2.38 ± 0.61)	TCM + WM/WM	2 months	①②③⑥⑦⑨⑩⑪
Yang and Zhou (2002)	32–72 (58.88 ± 9.64)	34–73 (56.98 ± 8.52)	54/31	56/29	0.5–30 (4.00 ± 5.64)	0.67–32 (4.10 ± 4.82)	TCM + WM/WM	2 months	①③⑪
Yuan (2018)	46–77 (61.4 ± 8.5)	48–79 (63.0 ± 9.3)	59/33	46/46	1–5 (3.2 ± 1.7)	1–6 (3.5 ± 1.5)	TCM + WM/WM	2 months	①③⑥
Zhang (2013)	41–73 (63.9 ± 7.2)		41/27	30/38	1–5 (1.5 ± 0.4)		TCM + WM/WM	4 weeks	③⑥
Zhao (2022)	44–76 (63.58 ± 7.92)	43–75 (63.45 ± 7.89)	37/33	35/35	1–6.5 (2.40 ± 0.49)	1.5–6 (2.32 ± 0.52)	TCM + WM/WM	2 months	②⑥⑦⑩
Zhu et al. (2019)	45–75 (58.2 ± 6.5)	45–75 (56.5 ± 6.0)	28/20	25/23	21.5 ± 2.5	18.5 ± 1.8	TCM + WM/WM	6 months	③⑥⑦

C: the control group; NR: not reported; T: the TCM group; TCM: traditional Chinese medicine; WM: western medicine; ①: Blood pressure (including systolic and diastolic blood pressure); ②: New York Heart Association classification; ③: left ventricular ejection fraction; ④: cardiac output; ⑤: E/A ratio; ⑥: left ventricular end-diastolic diameter; ⑦: left ventricular end-systolic diameter; ⑧: left ventricular mass index; ⑨: interventricular septum thickness in diastole; ⑩: B-type natriuretic peptide; ⑪: adverse events.

were involved in the research, with 1, 177 males and 878 females. The ages of the participants varied from 18 to 83 years. In 15 studies, the course of disease was reported, but not in the others. With 1, 041 patients in the CHM group and 1, 014 patients in the control group, the sample sizes of the included trials varied from 48 to 210. The control group received only WM treatment, while all CHM groups received oral CHM plus WM. The included studies' treatment durations varied from 25 days to 12 months. For outcome measures, 6 (6/21, 28.6%) RCTs (Cai, 2016; Peng, 2015; Tan, 2019; Wang and Sun, 2018; Yang and Zhou, 2002; Yuan, 2018) reported BP, including SBP and DBP; 11 (11/21, 52.4%) RCTs (Cai, 2016; Hu, 2012; Li et al., 2019; Peng, 2015; Song, 2011; Tan, 2019; Wang and Wang, 2012; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002; Zhao, 2022) reported NYHA classification; 13 (13/21, 61.9%) RCTs (Cui, 2022; Du, 2016; Jin and Wu, 2006; Li et al., 2019; Song, 2019; Tan, 2019; Tao, 2021; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002; Yuan, 2018; Zhang, 2013; Zhu et al., 2019) reported LVEF; 2 (2/21, 9.5%) RCTs (Du, 2016; Tao, 2021) reported CO; 3 (3/21, 14.3%) RCTs (Cai, 2016; Li et al., 2019; Wang and Wang, 2012) reported E/A ratio; 9 (9/21, 42.9%) RCTs (Hou et al., 2015; Liu, 2012; Song, 2019;

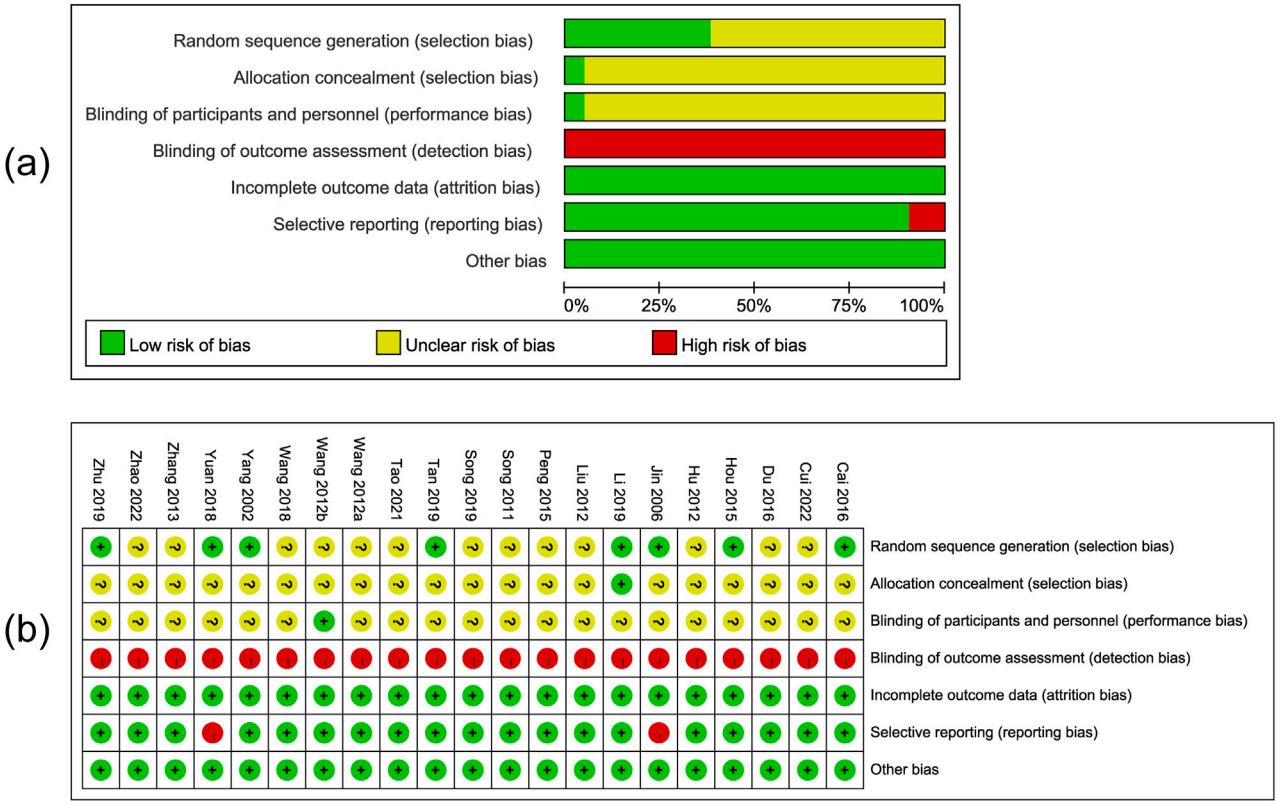


FIGURE 2
Risk of bias graph **(a)** and bias summary **(b)**. Note: Wang and Wang, 2012; Wang et al., 2012.

Tan, 2019; Wang and Sun, 2018; Yuan, 2018; Zhang, 2013; Zhao, 2022; Zhu et al., 2019) reported LVEDD; 4 (4/21, 19.0%) RCTs (Tan, 2019; Wang and Sun, 2018; Zhao, 2022; Zhu et al., 2019) reported LVESD; 2 (2/21, 9.5%) RCTs (Hou et al., 2015; Liu, 2012) reported LVMI; 3 (3/21, 14.3%) RCTs (Li et al., 2019; Tan, 2019; Wang and Sun, 2018) reported IVSTD; 3 (3/21, 14.3%) RCTs (Song, 2011; Wang and Sun, 2018; Zhao, 2022) reported BNP; and 8 (8/21, 38.1%) RCTs (Cai, 2016; Cui, 2022; Hu, 2012; Peng, 2015; Song, 2011; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002) reported adverse events.

3.3 Risk of bias

Two review authors evaluated the risk of bias of the included 21 RCTs and discrepancies were resolved via consensus. The results are shown in Figure 2. Among 21 RCTs, eight studies (Cai, 2016; Hou et al., 2015; Jin and Wu, 2006; Li et al., 2019; Tan, 2019; Yang and Zhou, 2002; Yuan, 2018; Zhu et al., 2019) presented a low risk of bias in the sequence generation process, one study (Li et al., 2019) presented a low risk of bias in allocation concealment, and one study (Wang et al., 2012) presented a low risk of bias in reporting blinding of participants. The studies did not describe blinding of outcome assessors and were thus judged as a high risk of bias. Twenty-one studies exhibited a low risk of attrition bias with complete outcome data. In terms of selective reporting bias, 19 trials (Cai, 2016; Cui, 2022; Du, 2016; Hou et al., 2015; Hu, 2012; Li et al., 2019; Liu, 2012; Peng, 2015; Song, 2011; Song, 2019; Tan, 2019; Tao, 2021; Wang and Wang, 2012; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002; Zhang, 2013; Zhao, 2022; Zhu et al., 2019) provided a low risk of bias and included all the outcomes specified in the methods section, while two trials (Jin and Wu, 2006; Yuan, 2018) showed a high risk of bias. We regarded all included studies as having a low risk of bias because we were unable to find any further sources of bias in any of them.

3.4 Description of TCM

In this study, sixteen TCM formulations were included, including Danxiong Tongluo decoction (*Salvia miltiorrhiza* Bunge (Danshen), *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen), *Crataegus monogyna* Jacq. (Shanzha), *Typha angustifolia* L. (Puhuang), *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong), *Xanthium strumarium* L. (Gualoupi), *Allium chinense* G.Don (Xiebai), and *Pinellia ternata* (Thunb.) Makino (Banxia)), Tongqiao Huoxue decoction (*O. striata* (DC.) Pimenov & Kljuykov (Chuanxiong), *Carthamus tinctorius* L. (Honghua), *S. miltiorrhiza* Bunge (Danshen), *Paeonia lactiflora* Pall. (Chishao), *Juglans regia* L. (Taoren), *P. montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen), *Typha angustifolia* L. (Puhuang), *Astragalus mongholicus* Bunge (Huangqi), and *Codonopsis pilosula* (Franch.) Nannf. (Dangshen)), Wenxin

TABLE 2 The botanical drugs of TCM used in the included studies.

References	Name of TCM	The botanical drugs of TCM
Cai (2016)	Danxiong Tongluo decoction	*Salvia miltiorrhiza* Bunge (Danshen) 30 g, *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) 30 g, *Crataegus monogyna* Jacq. (Shanzha) 15 g, *Typha angustifolia* L. (Puhuang) 15 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 10 g, *Xanthium strumarium* L. (Gualoupi) 10 g, *Allium chinense* G.Don (Xiebai) 10 g, and *Pinellia ternata* (Thunb.) Makino (Banxia)10 g
Cui (2022)	Wenxin granule (Z10950026)	Chinese patent medicine: *Codonopsis pilosula* (Franch.) Nannf. (Dangshen), *Vitex negundo* L. (Huangjing), *Basella alba* L. (Sanqi), *Cannabis sativa* L. (Hupo), and *Nardostachys jatamansi* (D.Don) DC. (Gansong). 9 g three times a day
Du (2016)	Danshen Dropping pill (Z10950111)	Chinese patent medicine: *Salvia miltiorrhiza* Bunge (Danshen), *Basella alba* L. (Sanqi), and *Camphora officinarum* Nees (Bingpian). 270 mg three times a day
Hou et al. (2015)	TCM decoction	*Gastrodia elata* Blume (Tianma) 15 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 15 g, *Uncaria rhynchophylla* (Miq.) Miq. (Gouteng) 15 g, *Salvia miltiorrhiza* Bunge (Danshen) 15 g, *Achyranthes bidentata* Blume (Niuxi) 15 g, *Taxillus chinensis* (DC.) Danser (Sangjisheng) 9 g, *Plantago asiatica* L. (Cheqianzi) 9 g, *Epimedium sagittatum* (Siebold & Zucc.) Maxim. (Yinyanghuo) 9 g, *Ligustrum lucidum* W.T.Aiton (Nvzhenzi) 9 g, and *Glycyrrhiza glabra* L. (Gancao) 9 g
Hu (2012)	TCM decoction	*Neolitsea cassia* (L.) Kosterm. (Guizhi) 15 g, *Panax ginseng* C.A.Mey. (Renshen) 9 g, *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Maidong) 12 g, *Lycium barbarum* L. (Gouqizi) 12 g, *Rehmannia glutinosa* (Gaertn.) DC. (Shudihuang) 12 g, *Angelica sinensis* (Oliv.) Diels (Danggui) 12 g, *Ziziphus jujuba* Mill. (Suanzaoren) 15 g, *Polygala tenuifolia* Willd. (Yuanzhi) 12 g, *Juglans regia* L. (Taoren) 12 g, and *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 12 g
Jin and Wu (2006)	Tianma Gouteng Yin formula	*Gastrodia elata* Blume (Tianma) 10 g, *Uncaria rhynchophylla* (Miq.) Miq. (Gouteng) 20 g, *Prosthechea radiata* (Lindl.) W.E.Higgins (Shijueming) 15 g, *Scutellaria baicalensis* Georgi (Huangqin) 10 g, *Eucommia ulmoides* Oliv. (Duzhong) 15 g, *Taxillus chinensis* (DC.) Danser (Sangjisheng) 15 g, *Panax quinquefolius* L. (Xiyangshen) 6 g, *Ziziphus jujuba* Mill. (Suanzaoren) 20 g, *Panax ginseng* C.A.Mey. (Fushen) 10 g, *Salvia miltiorrhiza* Bunge (Danshen) 15 g, and *Achyranthes bidentata* Blume (Niuxi) 10 g
Li et al. (2019)	Danxiong Tongluo decoction	*Salvia miltiorrhiza* Bunge (Danshen) 30 g, *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) 30 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 15 g, *Typha angustifolia* L. (Puhuang) 15 g, *Citrus* × *aurantium f. aurantium* (Zhishi) 15 g, *Crataegus monogyna* Jacq. (Shanzha) 15 g, *Basella alba* L. (Sanqi) 15 g, *Pinellia ternata* (Thunb.) Makino (Banxia) 10 g, *Allium chinense* G.Don (Xiebai) 10 g, *Xanthium strumarium* L. (Gualoupi) 10 g, and *Juglans regia* L. (Taoren) 10 g
Liu (2012)	TCM decoction	*Gastrodia elata* Blume (Tianma) 15 g, *Uncaria rhynchophylla* (Miq.) Miq. (Gouteng) 15 g, *Taxillus chinensis* (DC.) Danser (Sangjisheng) 12 g, *Ligustrum lucidum* W.T.Aiton (Nvzhenzi) 12 g, *Epimedium sagittatum* (Siebold & Zucc.) Maxim. (Yinyanghuo) 12 g, *Achyranthes bidentata* Blume (Niuxi) 15 g, *Salvia miltiorrhiza* Bunge (Danshen) 15 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 15 g, *Lathyrus sativus* L. (Guijia) 9 g, *Plantago asiatica* L. (Cheqianzi) 12 g, and *Glycyrrhiza glabra* L. (Gancao) 9 g
Peng (2015)	Shexiang Baoxin pill(Z31020068)	Chinese patent medicine: *Liquidambar orientalis* Mill. (Shexiang), *Panax ginseng* C.A.Mey. (Renshen), *Panax ginseng* C.A.Mey. (Niuhuang), *Neolitsea cassia* (L.) Kosterm. (Rougui), *Liquidambar orientalis* Mill. (Suhexiang), *Tagetes erecta* L. (Chansu), and *Camphora officinarum* Nees (Bingpian). 45 mg three times a day
Song (2011)	Yuyin Qianyang decoction	*Uncaria rhynchophylla* (Miq.) Miq. (Gouteng) 9 g, *Senna tora* (L.) Roxb. (Juemingzi) 30 g, *Prosthechea radiata* (Lindl.) W.E.Higgins (Shijueming) 30 g, *Cannabis sativa* L. (Muli) 30 g, *Zanthoxylum asiaticum* (L.) Appelhans, Groppo & J.Wen (Dilong) 9 g, *Xanthium strumarium* L. (Gualoupi) 15 g, *Pinellia ternata* (Thunb.) Makino (Banxia) 9 g, *Citrus reticulata* Blanco (Chenpi) 12 g, *Smilax glabra* Roxb. (Fuling) 15 g, *Salvia miltiorrhiza* Bunge (Danshen) 15 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 9 g, *Carthamus tinctorius* L. (Honghua) 6 g, *Rehmannia glutinosa* (Gaertn.) DC. (Dihuang) 12 g, and *Paeonia lactiflora* Pall. (Baishaoyao) 12 g
Song (2019)	TCM decoction	*Angelica sinensis* (Oliv.) Diels (Danggui) 30 g, *Scutellaria baicalensis* Georgi (Huangqin) 30 g, *Salvia miltiorrhiza* Bunge (Danshen) 15 g, *Gastrodia elata* Blume (Tianma) 15 g, *Epimedium sagittatum* (Siebold & Zucc.) Maxim. (Yinyanghuo) 12 g, *Paeonia lactiflora* Pall. (Baishaoyao) 12 g, *Lathyrus sativus* L. (Guijia) 9 g, *Achyranthes bidentata* Blume (Niuxi) 6 g, *Panax ginseng* C.A.Mey. (Renshen) 6 g, and *Asarum heterotropoides* F.Schmidt (Xixin) 5 g
Tan (2019)	Tongqiao Huoxue decoction	*Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 10 g, *Carthamus tinctorius* L. (Honghua) 9 g, *Salvia miltiorrhiza* Bunge (Danshen) 10 g, *Paeonia lactiflora* Pall. (Chishao) 10 g, *Juglans regia* L. (Taoren) 9 g, *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) 10 g, *Typha angustifolia* L. (Puhuang) 10 g, *Astragalus mongholicus* Bunge (Huangqi) 20 g, and *Codonopsis pilosula* (Franch.) Nannf. (Dangshen) 15 g
Tao (2021)	TCM decoction	*Glycyrrhiza glabra* L. (Gancao) 6 g, *Pinellia ternata* (Thunb.) Makino (Banxia) 6 g, *Atractylodes macrocephala* Koidz. (Baizhu) 9 g, *Gastrodia elata* Blume (Tianma) 9 g, *Smilax glabra* Roxb. (Fuling) 12 g, *Arisaema erubescens* (Wall.) Schott (Dannanxing) 12 g, *Citrus reticulata* Blanco (Chenpi) 12 g, and Citrus × aurantium L. (Zhike) 12 g
Wang and Wang (2012)	Shengmai Yin	*Panax ginseng* C.A.Mey. (Renshen) 15–20 g, *Rehmannia glutinosa* (Gaertn.) DC. (Shudihuang) 20 g, *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Maidong) 15 g, *Atractylodes macrocephala* Koidz. (Baizhu) 15 g, *Schisandra chinensis* (Turcz.) Baill. (Wuweizi) 10 g, *Astragalus mongholicus* Bunge (Huangqi) 30 g, *Salvia miltiorrhiza* Bunge (Danshen) 30 g, and *Smilax glabra* Roxb. (Fuling) 30 g

(Continued on following page)

TABLE 2 (*Continued*) The botanical drugs of TCM used in the included studies.

References	Name of TCM	The botanical drugs of TCM
Wang et al. (2012)	Diju Pinggan capsule	Diju Pinggan capsule (batch number: 100,605) was provided by the pharmaceutical preparation room in Shanxi Academy of Traditional Chinese Medicine without reporting each botanical drug and dosage. 1.5 g three times a day
Wang and Sun (2018)	Tongqiao Huoxue decoction	*Paeonia lactiflora* Pall. (Chishao) 10 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 10 g, *Juglans regia* L. (Taoren) 9 g, *Ziziphus jujuba* Mill. (Dazao) 7, *Carthamus tinctorius* L. (Honghua) 9 g, *Andrographis paniculata* (Burm.f.) Wall. ex Nees (Cong) 3, *Zingiber officinale* Roscoe (Shengjiang) 9 g, *Liquidambar orientalis* Mill. (Shexiang) 0.15 g, *Salvia miltiorrhiza* Bunge (Danshen) 10 g, *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) 10 g, *Typha angustifolia* L. (Puhuang) 10 g, *Astragalus mongholicus* Bunge (Huangqi) 20 g, and *Codonopsis pilosula* (Franch.) Nannf. (Dangshen) 15 g
Yang and Zhou (2002)	Danxiong Tongluo decoction	*Salvia miltiorrhiza* Bunge (Danshen) 30 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 10 g, *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) 30 g, *Typha angustifolia* L. (Puhuang) 15 g, *Xanthium strumarium* L. (Gualoupi) 10 g, *Allium chinense* G.Don (Xiebai) 10 g, *Pinellia ternata* (Thunb.) Makino (Banxia) 10 g, and *Crataegus monogyna* Jacq. (Shanzha) 15 g
Yuan (2018)	Danxiong Tongluo decoction	*Xanthium strumarium* L. (Gualoupi) 9 g, *Pinellia ternata* (Thunb.) Makino (Banxia) 9 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 10 g, *Allium chinense* G.Don (Xiebai) 11 g, *Crataegus monogyna* Jacq. (Shanzha) 14 g, *Typha angustifolia* L. (Puhuang) 14 g, *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) 28 g, and *Salvia miltiorrhiza* Bunge (Danshen) 28 g
Zhang (2013)	TCM decoction	*Panax ginseng* C.A.Mey. (Renshen) 6 g, *Astragalus mongholicus* Bunge (Huangqi) 30 g, *Angelica sinensis* (Oliv.) Diels (Danggui) 30 g, *Asarum heterotropoides* F.Schmidt (Xixin) 5 g, *Salvia miltiorrhiza* Bunge (Danshen) 15 g, *Gastrodia elata* Blume (Tianma) 15 g, *Paeonia lactiflora* Pall. (Baishaoyao) 12 g, *Achyranthes bidentata* Blume (Niuxi) 6 g, *Epimedium sagittatum* (Siebold & Zucc.) Maxim. (Yinyanghuo) 12 g, and *Lathyrus sativus* L. (Guijia) 9 g
Zhao (2022)	Tongqiao Huoxue decoction	*Codonopsis pilosula* (Franch.) Nannf. (Dangshen) 15 g, *Astragalus mongholicus* Bunge (Huangqi) 20 g, *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) 10 g, *Typha angustifolia* L. (Puhuang) 10 g, *Salvia miltiorrhiza* Bunge (Danshen) 10 g, *Paeonia lactiflora* Pall. (Chishao) 10 g, *Oreocome striata* (DC.) Pimenov & Kljuykov (Chuanxiong) 10 g, *Juglans regia* L. (Taoren) 9 g, *Carthamus tinctorius* L. (Honghua) 9 g, *Zingiber officinale* Roscoe (Shengjiang) 9 g, *Liquidambar orientalis* Mill. (Shexiang) 0.15 g, *Andrographis paniculata* (Burm.f.) Wall. ex Nees (Cong) 3, and *Ziziphus jujuba* Mill. (Dazao) 7
Zhu et al. (2019)	Yiqi Wenyang Tongluo decoction	*Astragalus mongholicus* Bunge (Huangqi) 30 g, *Panax ginseng* C.A.Mey. (Hongshen) 15 g, *Cyperus rotundus* L. (Fuzi) 12 g, *Neolitsea cassia* (L.) Kosterm. (Guizhi) 10 g, *Carthamus tinctorius* L. (Honghua) 12 g, *Terminalia chebula* Retz. (Shuizhi) 5 g, *Salvia miltiorrhiza* Bunge (Danshen) 30 g, *Descurainia sophia* (L.) Webb ex Prantl (Tinglizi) 15 g, and *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Wujiapi) 12 g

granule (*C. pilosula* (Franch.) Nannf. (Dangshen), *Vitex negundo* L. (Huangjing), *Basella alba* L. (Sanqi), *Cannabis sativa* L. (Hupo), and *Nardostachys jatamansi* (D.Don) DC. (Gansong)), Danshen Dropping pill (*S. miltiorrhiza* Bunge (Danshen), *B. alba* L. (Sanqi), and *Camphora officinarum* Nees (Bingpian)), Tianma Gouteng Yin formula (*Gastrodia elata* Blume (Tianma), *Uncaria rhynchophylla* (Miq.) Miq. (Gouteng), *Prosthechea radiata* (Lindl.) W.E.Higgins (Shijueming), *Scutellaria baicalensis* Georgi (Huangqin), *Eucommia ulmoides* Oliv. (Duzhong), *Taxillus chinensis* (DC.) Danser (Sangjisheng), *Panax quinquefolius* L. (Xiyangshen), *Ziziphus jujuba* Mill. (Suanzaoren), *Panax ginseng* C.A.Mey. (Fushen), *S. miltiorrhiza* Bunge (Danshen), and *Achyranthes bidentata* Blume (Niuxi)), Shexiang Baoxin pill (*Liquidambar orientalis* Mill. (Shexiang), *P. ginseng* C.A.Mey. (Renshen), *P. ginseng* C.A.Mey. (Niuhuang), *Neolitsea cassia* (L.). Kosterm. (Rougui), *L. orientalis* Mill. (Suhexiang), *Tagetes erecta* L. (Chansu), and *C. officinarum* Nees (Bingpian)), Shengmai Yin (*P. ginseng* C.A.Mey. (Renshen), *Rehmannia glutinosa* (Gaertn.) DC. (Shudihuang), *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Maidong), *Atractylodes macrocephala* Koidz. (Baizhu), *Schisandra chinensis* (Turcz.) Baill. (Wuweizi), *A. mongholicus* Bunge (Huangqi), *S. miltiorrhiza* Bunge (Danshen), and *Smilax glabra* Roxb. (Fuling)), Diju Pinggan capsule (Without reporting each botanical drug and dosage), and others. The botanical drug names have been checked with http://mpns.kew.org and http://www.worldfloraonline.org on 30 April 2024. The species involved have been taxonomically validated by searching their Latin names in the electronic version of Flora of China (http://www.efloras.org) to obtain descriptions of their morphological characteristics, type specimen information, and taxonomic status. Additionally, the original images of the type specimens of the species can be consulted through the International Plant Names Index (IPNI, https://www.ipni.org) or herbarium databases such as the Herbarium of the Institute of Botany, Chinese Academy of Sciences (PE, http://pe.ibcas.ac.cn). TCM formula Danxiong Tongluo decoction was the most commonly utilized (4/16, 25.00%), followed by Tongqiao Huoxue decoction (3/16, 18.75%).

Each Chinese botanical drug's frequency in this review was described using a manual summary. There were 72 Chinese botanical drugs in all. The top five ranked Chinese botanical drugs were *S. miltiorrhiza* Bunge (Danshen) (16/72, 22.22%), *O. striata* (DC.) Pimenov & Kljuykov (Chuanxiong) (11/72, 15.28%), *P. montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) (7/72, 9.72%), *A. mongholicus* Bunge (Huangqi) (7/72, 9.72%), and *Typha angustifolia* L. (Puhuang) (7/72, 9.72%). The provided formulations contained three to 14 Chinese botanical drugs. Among these formulas, Diju Pinggan capsule (batch number: 100,605) was provided by the pharmaceutical preparation room in Shanxi Academy of TCM without reporting each botanical drug and dosage.

Four dosage formulations of TCM reported, including decoction, pill, capsule, and granule, were all administered orally. The decoction was the most commonly used dosage formulation (17/21, 80.95%), followed by pill (2/21, 9.52%), granule (1/21, 4.76%), and capsule (1/21, 4.76%). The decoction was orally taken one dose every day. The TCM formulas and the specific botanical drugs are summarized concretely in Table 2.

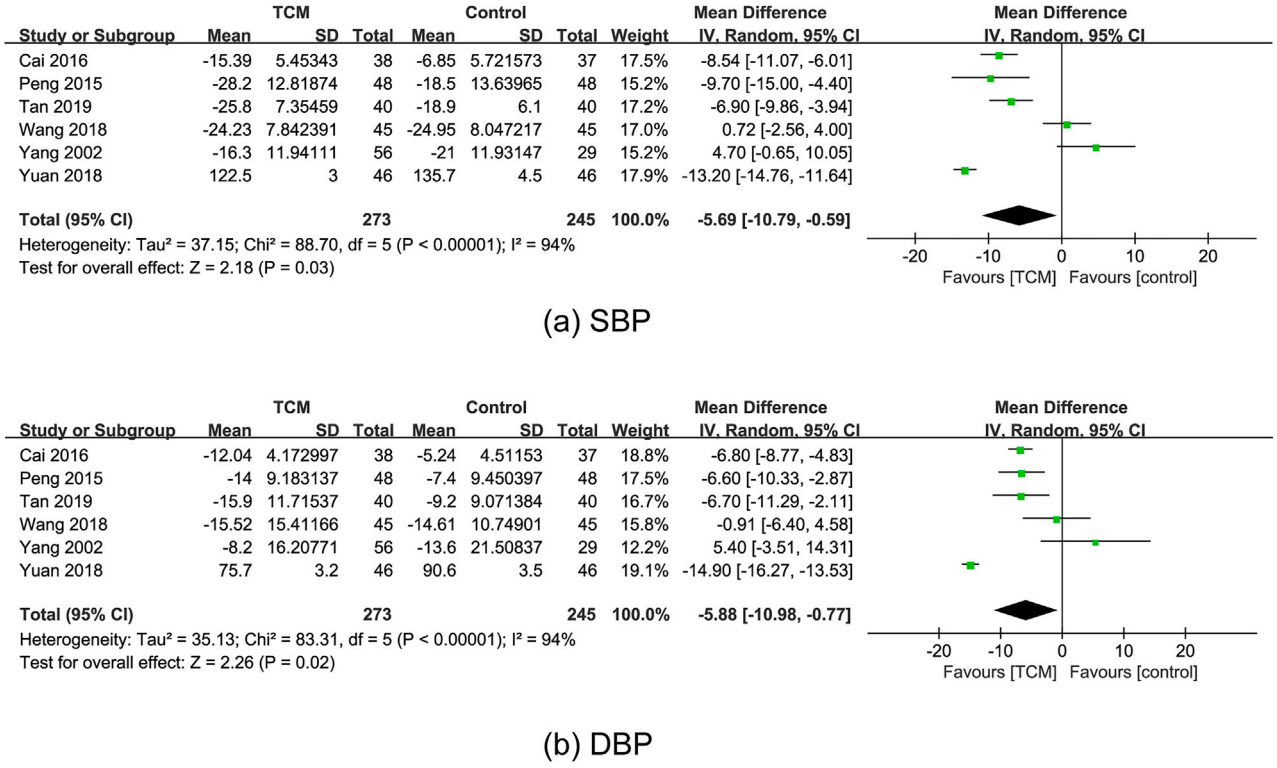


FIGURE 3
Forest plots for the meta-analysis of BP in the TCM group vs. the control group: **(a)** SBP and **(b)** DBP. Abbreviation: BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; TCM: traditional Chinese medicine.

3.5 Primary outcomes

3.5.1 BP

In total, six RCTs (Cai, 2016; Peng, 2015; Tan, 2019; Wang and Sun, 2018; Yang and Zhou, 2002; Yuan, 2018) reported the effect of TCM on BP. The results of the meta-analysis indicated that SBP was lower in the TCM group as compared to the control group (MD = −5.69; 95% CI: 10.79 to −0.59; P = 0.03), although the random-effects model exhibited statistical heterogeneity (χ^2 = 88.70; I^2 = 94%; P < 0.00001) (Figure 3a). Sensitivity analyses were performed to evaluate the robustness of the results. Thus, we repeated the meta-analysis after excluding, one by one, four studies (Cai, 2016; Peng, 2015; Tan, 2019; Yuan, 2018), P > 0.05 suggested nonsignificant difference and the unreliability of the result of SBP. In addition, another meta-analysis showed the efficacy of TCM on DBP (MD = −5.88; 95% CI: 10.98 to −0.77; P = 0.02), and also represented statistical heterogeneity (χ^2 = 83.31; I^2 = 94%; P < 0.00001) with the random-effects model (Figure 3b). The pooled effect estimates showed no significant difference for DBP after excluding Cai's, Peng's, and Tan's studies (Cai, 2016; Peng, 2015; Tan, 2019) one by one, which suggested that the result was not robust.

3.5.2 NYHA classification

In total, eleven RCTs (Cai, 2016; Hu, 2012; Li et al., 2019; Peng, 2015; Song, 2011; Tan, 2019; Wang and Wang, 2012; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002; Zhao, 2022) reported the effect of TCM on NYHA classification. A meta-analysis revealed that the TCM group's NYHA classification was substantially better than that of the control group (RR = 1.25; 95% CI: 1.18 to 1.33; P < 0.00001). There was moderate heterogeneity (χ^2 = 14.80; I^2 = 32%; P = 0.14) and the fixed-effects model was used (Figure 4). Sensitivity analyses indicated that the I^2 dropped to 0% (P < 0.00001) by excluding Wang's study (Wang and Wang, 2012), which might significantly impact the effect value and be the primary cause of heterogeneity.

3.5.3 LVEF

In total, thirteen RCTs (Cui, 2022; Du, 2016; Jin and Wu, 2006; Li et al., 2019; Song, 2019; Tan, 2019; Tao, 2021; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002; Yuan, 2018; Zhang, 2013; Zhu et al., 2019) reported the effect of TCM on LVEF. Two RCTs (Cui, 2022; Tao, 2021) were excluded because they did not measure or report baseline LVEF. The meta-analysis was performed with the 11 remaining studies containing 1, 005 patients (Du, 2016; Jin and Wu, 2006; Li et al., 2019; Song, 2019; Tan, 2019; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002; Yuan, 2018; Zhang, 2013; Zhu et al., 2019). The results of the meta-analysis indicated that LVEF of the TCM group was substantially greater than that of the control group (MD = 0.14; 95% CI: 0.07 to 0.21; P = 0.0001). However, the random-effects model exhibited statistical heterogeneity (χ^2 = 261.06; I^2 = 96%; P < 0.00001) (Figure 5). Sensitivity analyses demonstrated the robust results for LVEF.

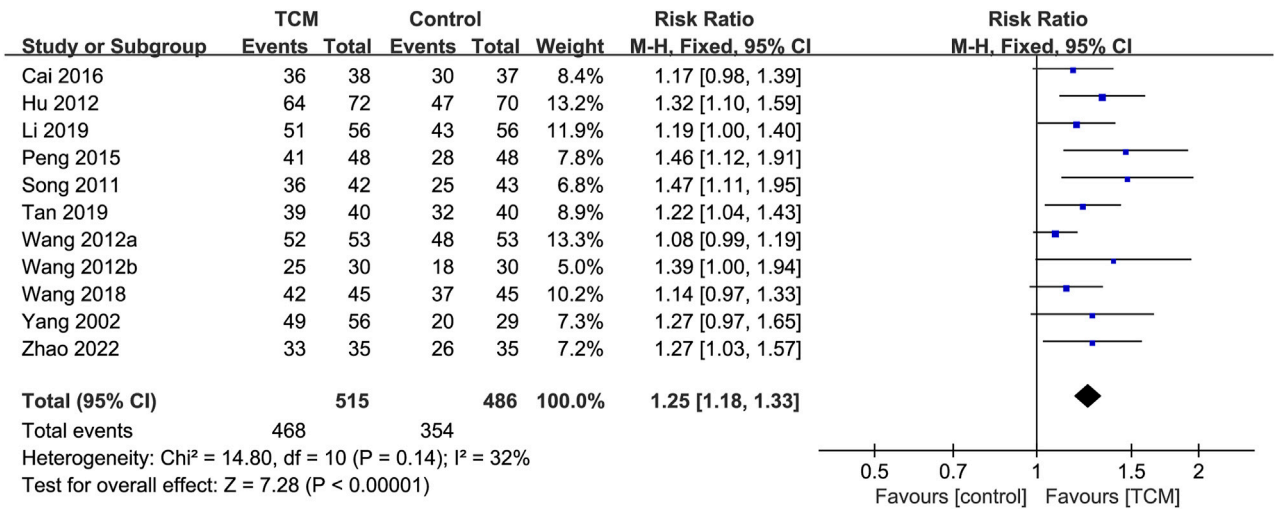


FIGURE 4
Forest plot for the meta-analysis of NYHA classification. Abbreviation: NYHA: New York Heart Association; TCM: traditional Chinese medicine. Note: Wang 2012a: Wang and Wang, 2012; Wang 2012b: Wang et al., 2012.

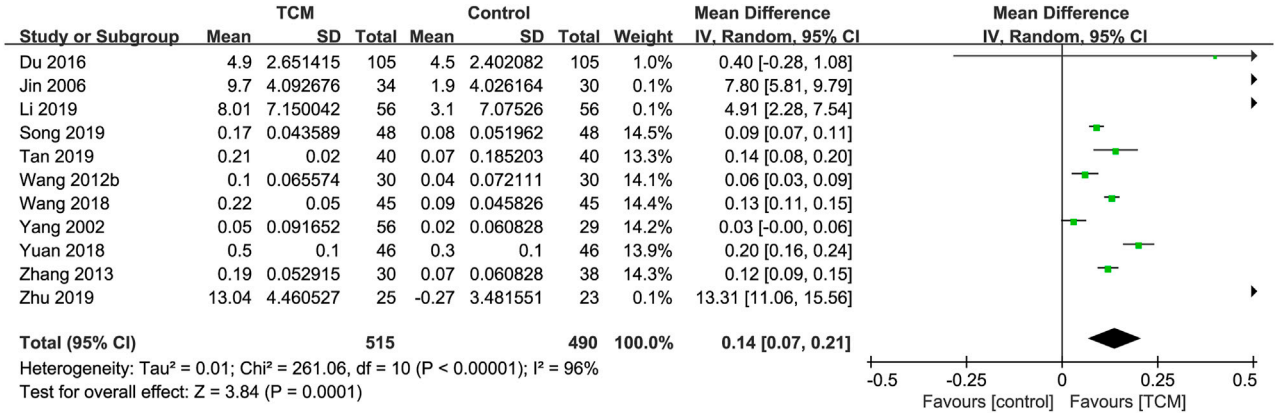


FIGURE 5
Forest plot for the meta-analysis of LVEF. Abbreviation: LVEF: left ventricular ejection fraction; TCM: traditional Chinese medicine. Note: Wang 2012b: Wang et al., 2012.

3.6 Secondary outcomes

3.6.1 CO

In total, two RCTs (Du, 2016; Tao, 2021) reported the effect of TCM on CO. One RCT (Tao, 2021) was excluded because it did not measure or report baseline CO. The meta-analysis was not performed due to insufficient available data. Only one study (Du, 2016) showed statistically significant difference in CO when comparing the TCM group to the control group. Given a lack of included trials, sensitivity analysis was not performed.

3.6.2 E/A ratio

In total, three RCTs (Cai, 2016; Li et al., 2019; Wang and Wang, 2012) reported the effect of TCM on E/A ratio. According to a meta-analysis, the TCM group's E/A ratio improved when compared to the control group (MD = 0.17; 95% CI: 0.14 to 0.20; P < 0.00001). There was low heterogeneity (χ^2 = 2.16; I^2 = 7%; P = 0.34) and the fixed-effects model was used (Figure 6). Sensitivity analyses demonstrated the robust results for E/A ratio.

3.6.3 LVEDD

In total, nine RCTs (Hou et al., 2015; Liu, 2012; Song, 2019; Tan, 2019; Wang and Sun, 2018; Yuan, 2018; Zhang, 2013; Zhao, 2022; Zhu et al., 2019) reported the effect of TCM on LVEDD. Three RCTs (Hou et al., 2015; Liu, 2012; Yuan, 2018) were excluded because they did not measure or report baseline LVEDD. The meta-analysis was performed with the six remaining studies containing 452 patients (Song, 2019; Tan, 2019; Wang and Sun, 2018; Zhang, 2013; Zhao, 2022; Zhu et al., 2019). The results of the meta-analysis indicated that the TCM group's LVEDD was considerably lower than that of the control group (MD = −7.18; 95% CI: 10.56 to −3.81; P < 0.0001).

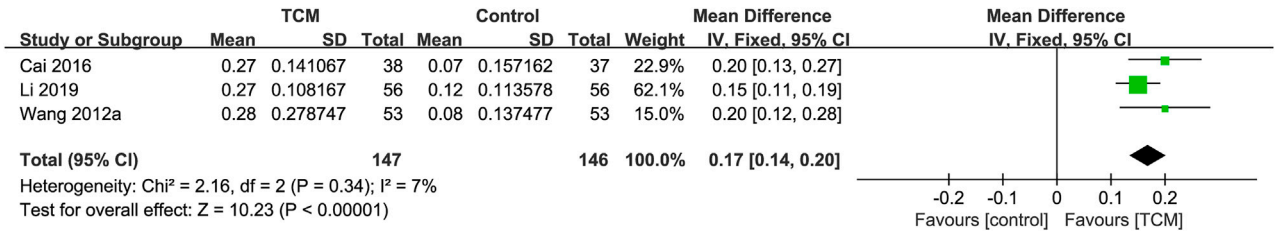


FIGURE 6
Forest plot for the meta-analysis of E/A ratio. Abbreviation: E/A: transmitral peak early diastolic velocity (E)/peak late diastolic velocity (A); TCM: traditional Chinese medicine. Note: Wang 2012a: Wang and Wang, 2012.

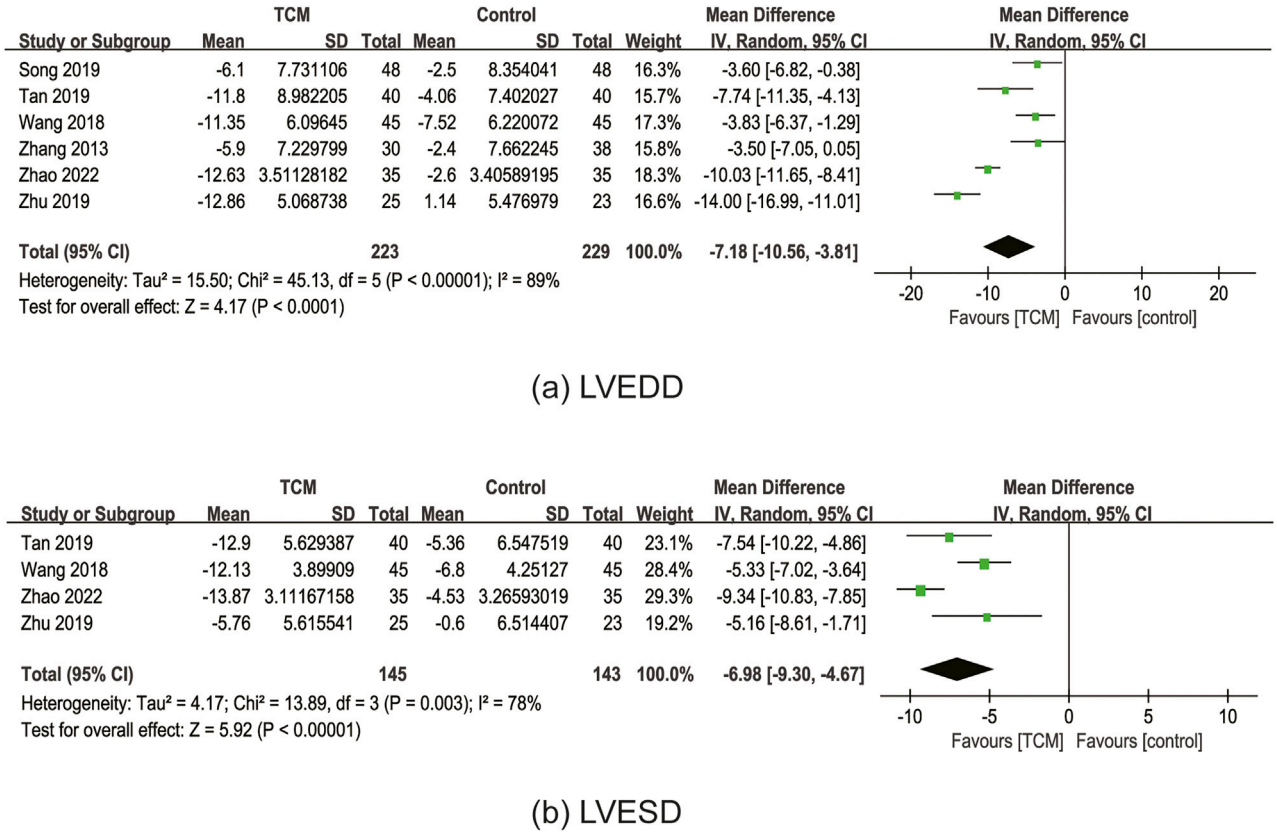


FIGURE 7
Forest plot for the meta-analysis of LVEDD **(a)** and LVESD **(b)**. Abbreviation: LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; TCM: traditional Chinese medicine.

However, the random-effects model exhibited statistical heterogeneity (χ^2 = 45.13; I^2 = 89%; P < 0.00001) (Figure 7a). Sensitivity analyses demonstrated the robust results for LVEDD.

3.6.4 LVESD

In total, four RCTs (Tan, 2019; Wang and Sun, 2018; Zhao, 2022; Zhu et al., 2019) reported the effect of TCM on LVESD. The results of the meta-analysis demonstrated that the TCM group's LVESD was considerably lower than that of the control group (MD = −6.98; 95% CI: 9.30 to −4.67; P < 0.00001). However, the random-effects model indicated statistical heterogeneity (χ^2 = 13.89; I^2 = 78%; P = 0.003) (Figure 7b). Sensitivity analyses showed that the I^2 dropped to 2% (P < 0.00001) by excluding Zhao's study (Zhao, 2022), which might significantly impact the effect value and be the primary cause of heterogeneity.

3.6.5 LVMI

In total, two RCTs (Hou et al., 2015; Liu, 2012) reported the effect of TCM on LVMI. A meta-analysis revealed that the TCM group's LVMI was considerably lower than that of the control group (MD = −8.50; 95% CI: 11.88 to −5.11; P < 0.00001). The fixed-effects model was applied, and there was low heterogeneity (χ^2 = 0.30;

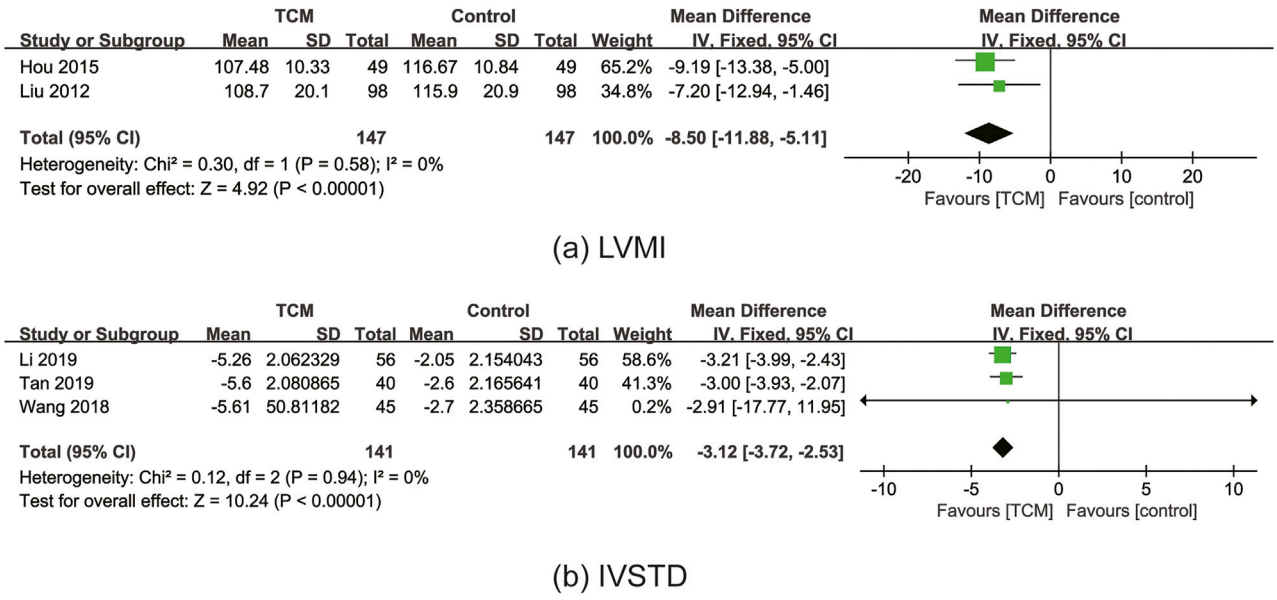


FIGURE 8
Forest plot for the meta-analysis of LVMI **(a)** and IVSTD **(b)**. Abbreviation: LVMI: left ventricular mass index; IVSTD: interventricular septum thickness in diastole; TCM: traditional Chinese medicine.

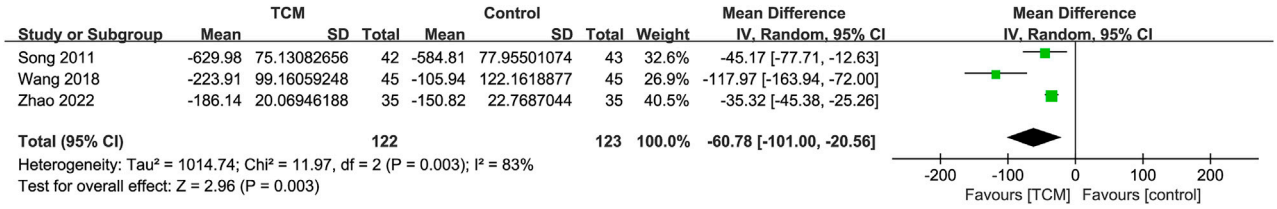


FIGURE 9
Forest plot for the meta-analysis of BNP. Abbreviation: BNP: B-type natriuretic peptide; TCM: traditional Chinese medicine.

I^2 = 0%; P = 0.58) (Figure 8a). Given a lack of included trials, sensitivity analysis was not performed.

3.6.6 IVSTD

In total, three RCTs (Li et al., 2019; Tan, 2019; Wang and Sun, 2018) reported the effect of TCM on IVSTD. A meta-analysis revealed that the TCM group's IVSTD was considerably lower than that of the control group (MD = −3.12; 95% CI: 3.72 to −2.53; P < 0.00001). The fixed-effects model was applied, and there was low heterogeneity (χ^2 = 0.12; I^2 = 0%; P = 0.94) (Figure 8b). Sensitivity analyses demonstrated the robust results for IVSTD.

3.6.7 BNP

In total, three RCTs (Song, 2011; Wang and Sun, 2018; Zhao, 2022) reported the effect of TCM on BNP. The results of the meta-analysis indicated that BNP was lower in the TCM group as compared to the control group (MD = −60.78; 95% CI: 101.00 to −20.56; P = 0.003), however, the random-effects model exhibited statistical heterogeneity (χ^2 = 11.97; I^2 = 83%; P = 0.003) (Figure 9). According to the results of the sensitivity analyses, after excluding Wang's study (Wang and Sun, 2018), I^2 dropped to 0% (P < 0.00001). In addition, after excluding Song's study (Song, 2011), the statistically significant difference did not exist between the control group and the TCM group. These unrobust results showed that the meta-analysis of BNP was not reliable.

3.6.8 Adverse events

In total, eight RCTs (Cai, 2016; Cui, 2022; Hu, 2012; Peng, 2015; Song, 2011; Wang et al., 2012; Wang and Sun, 2018; Yang and Zhou, 2002) reported adverse events, 16 in the TCM group, and 31 in the control group. According to a meta-analysis, individuals in the TCM group experienced fewer adverse events than those in the control group (RR = 0.51; 95% CI: 0.29 to 0.91; P = 0.02). The heterogeneity test showed low heterogeneity (χ^2 = 1.46; I^2 = 0%; P = 0.83), so the fixed-effects model was used (Figure 10). Sensitivity analyses revealed the unrobust results for adverse events. After excluding Hu's study (Hu, 2012), the statistically significant difference did not exist between the control group and the TCM group. The most common adverse events included gastrointestinal symptoms,

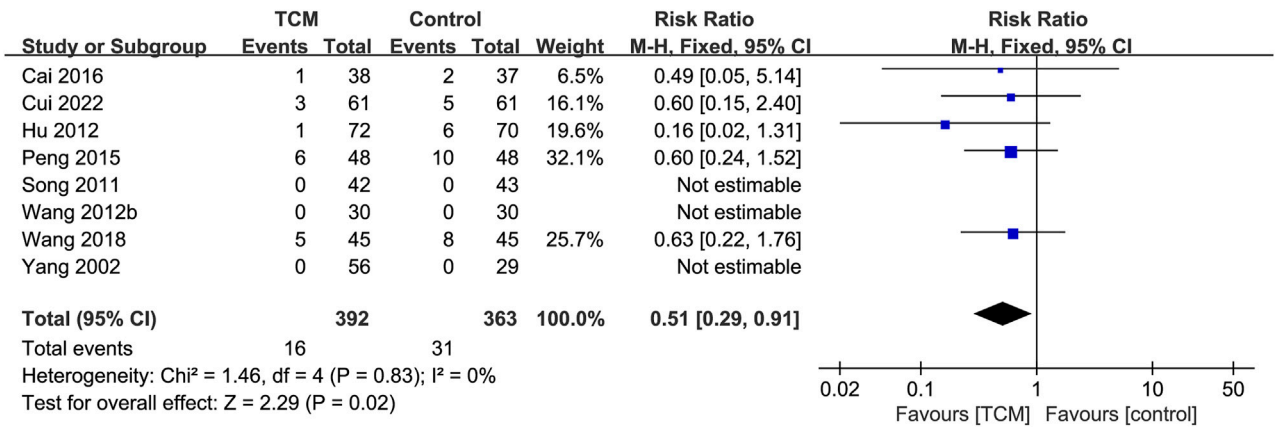


FIGURE 10
Forest plot for the meta-analysis of adverse events. Abbreviation: TCM: traditional Chinese medicine. Note: Wang 2012b: Wang et al., 2012.

headache, arrhythmia, abnormal liver function, electrolyte imbalance, and respiratory failure. Of the eight studies, three studies (Song, 2011; Wang et al., 2012; Yang and Zhou, 2002) reported that there were no adverse events during the research period between the TCM and the control group.

3.7 Quality assessment of the evidence

The evidence profile was displayed in Table 3 and the degree of certainty of the evidence was evaluated using GRADEpro GDT. There was moderate-quality evidence on NYHA classification, E/A ratio, LVMI, IVSTD, and adverse events; low-quality evidence on LVEDD, LVESD, and BNP; and very low-quality evidence on BP (SBP and DBP) and LVEF. The most frequent sources of bias in randomized trials were the lack of blinding for study personnel and participants and the outcome assessment blinding. Thus, the 'Risk of bias' domain was judged to be at serious risk of bias. For the research inconsistency, there was high heterogeneity in six pieces of evidence, and the 'Inconsistency' domain was judged to be at serious inconsistency. Regarding the study's imprecision, none of the indices went over the invalid line or received a downgrading. Regarding research indirectness, there was some inconsistency among the included studies in terms of interventions. However, there were no significant differences in their research purposes and no downgrades. The literature was carefully retrieved concerning publication bias, and no disclosed commercial conflicts of interest were present. In addition, publication bias was assessed for BP (SBP and DBP), NYHA classification, and LVEF. For BP (SBP and DBP) and LVEF, the assessment of publication bias was limited due to the insufficient number of studies for the outcomes. Thus, publication bias is strongly suspected.

3.8 Publication bias

The Egger's test was used for the funnel plot to evaluate publication bias. There was no risk of publication bias in the NYHA classification, according to the symmetrical funnel plot (Figure 11a), whereas the asymmetric funnel plot implied a higher risk of publication bias in LVEF (Figure 11b), SBP (Figure 11c), and DBP (Figure 11d). The results of the meta-analysis were not significantly impacted by publication bias if the trim and fill strategy was applied (Table 4).

4 Discussion

4.1 Summary of evidence

This meta-analysis included 21 studies that revealed the potential preventive effects of selected TCM as adjuvant therapy on HHD progression. In terms of BP, TCM as an adjunct in the treatment of hypertension could reduce BP to a certain extent. For the cardiac function, integrated TCM and WM significantly improved NYHA classification, LVEF, E/A ratio, and decreased LVEDD, LVESD, LVMI, IVSTD, and BNP, which indicated that TCM as adjuvant therapy played an important role in attenuating adverse LV remodeling and enhancing the heart's diastolic and systolic functions to a certain extent. Furthermore, adverse events did not appear to be occurring more frequently linked to WM in the TCM group. In general, patients treated with TCM experienced fewer adverse events overall than those in comparator groups.

Vascular incidents were closely associated with elevated BP. A meta-analysis by Ettehad and colleagues (Ettehad et al., 2016) reported that a 10 mmHg decrease in SBP was associated with a 20% lower risk of major cardiovascular disease events, HF by 28%, and all-cause mortality by 13%. For patients having the greatest absolute risk of heart-related incidents, reducing BP would have the most overall benefits. This meta-analysis suggested that TCM as a potential adjuvant therapy effectively reduced BP. However, the results were not robust. It was necessary to conduct more research on the impact of TCM, especially in patients with LVH and hypertension.

The NYHA functional classification was used to assess symptom status, which was characterized as asymptomatic for NYHA I and symptomatic for NYHA II-IV (Egbe et al., 2020). This meta-analysis

TABLE 3 The GRADE evidence profile for TCM in the treatment of patients with HHD.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCM	Control	Relative (a95% CI)	Absolute (95% CI)		
SBP												
6	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	Publication bias strongly suspected	273	245	-	MD 5.69 lower (10.79 lower to 0.59 lower)	⊕◯◯◯ Very low	CRITICAL
DBP												
6	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	Publication bias strongly suspected	273	245	-	MD 5.88 lower (10.98 lower to 0.77 lower)	⊕◯◯◯ Very low	CRITICAL
NYHA classification												
11	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	468/515 (90.9%)	354/486 (72.8%)	RR 1.25 (1.18–1.33)	182 more per 1,000 (from 131 more to 240 more)	⊕⊕⊕◯ Moderate	CRITICAL
LVEF												
11	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	Publication bias strongly suspected	515	490	-	MD 0.14 higher (0.07 higher to 0.21 higher)	⊕◯◯◯ Very low	CRITICAL
E/A ratio												
3	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None[c]	147	146	-	MD 0.17 higher (0.14 higher to 0.2 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
LVEDD												
6	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None[c]	223	229	-	MD 7.18 lower (10.56 lower to 3.81 lower)	⊕⊕◯◯ Low	IMPORTANT
LVESD												
4	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None[c]	145	143	-	MD 6.98 lower (9.3 lower to 4.67 lower)	⊕⊕◯◯ Low	IMPORTANT

(Continued on following page)

10.3389/fphar.2025.1506234

TABLE 3 (*Continued*) The GRADE evidence profile for TCM in the treatment of patients with HHD.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TCM	Control	Relative (a95% CI)	Absolute (95% CI)		
LVMI												
2	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None[c]	147	147	-	MD 8.5 lower (11.88 lower to 5.11 lower)	⊕⊕⊕◯ Moderate	IMPORTANT
IVSTD												
3	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None[c]	141	141	-	MD 3.12 lower (3.72 lower to 2.53 lower)	⊕⊕⊕◯ Moderate	IMPORTANT
BNP												
3	Randomized trials	Serious[a]	Serious[b]	Not serious	Not serious	None[c]	122	123	-	MD 60.78 lower (101 lower to 20.56 lower)	⊕⊕◯◯ Low	IMPORTANT
Adverse events												
8	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None[c]	16/ 392 (4.1%)	31/ 363 (8.5%)	RR 0.51 (0.29–0.91)	42 fewer per 1,000 (from 61 fewer to 8 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

[a] The quality of the majority of trials was not high. [b] Unexplained heterogeneity. [c] Funnel plots not completed due to<10 studies in the meta-analysis. BNP: B-type natriuretic peptide; CI: confidence interval; DBP: diastolic blood pressure; E/A: transmitral peak early diastolic velocity/peak late diastolic velocity; IVSTD: interventricular septum thickness in diastole; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVMI: left ventricular mass index; MD: mean difference; NYHA: new york heart association; RR: risk ratio; SBP: systolic blood pressure; TCM, traditional Chinese medicine.

10.3389/fphar.2025.1506234

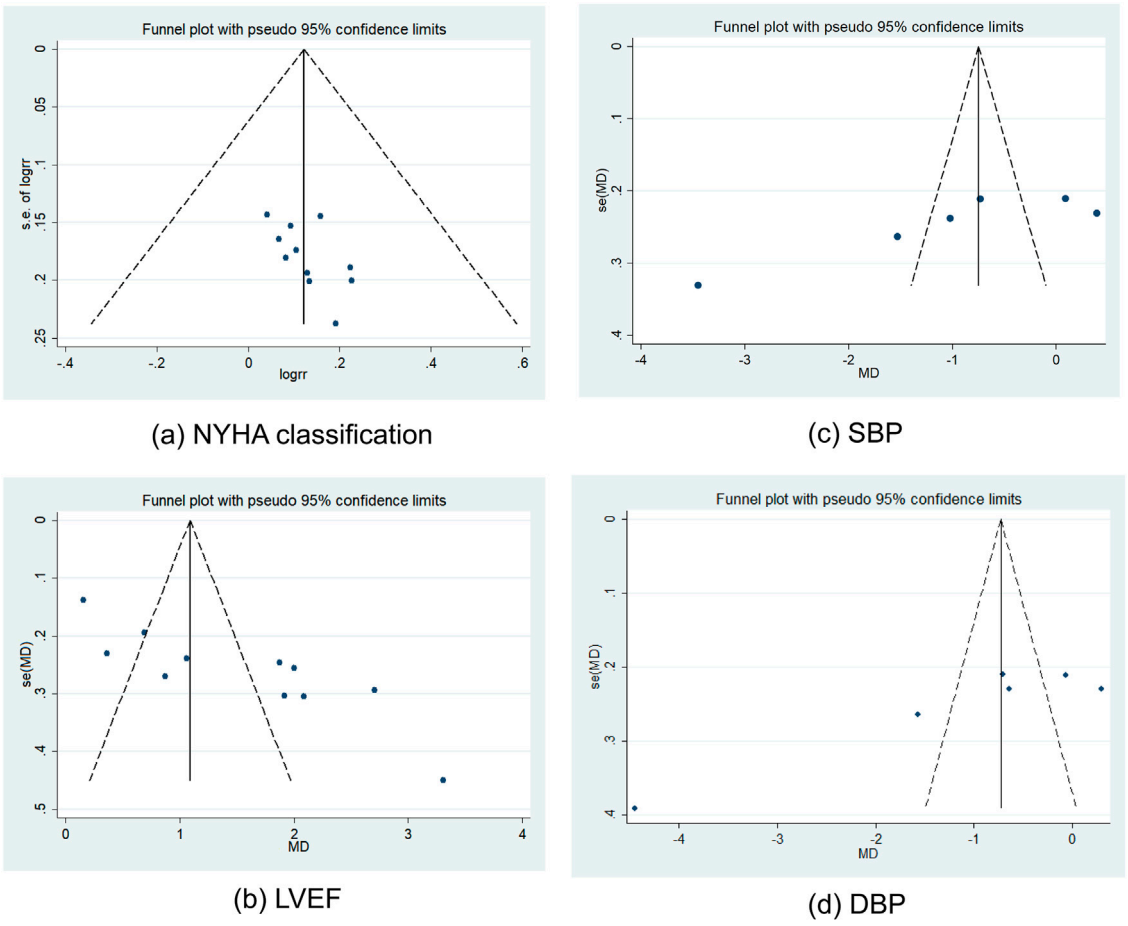


FIGURE 11
Funnel plots of NYHA classification **(a)**, LVEF **(b)**, SBP **(c)**, and DBP **(d)**. Abbreviation: DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SBP: systolic blood pressure.

TABLE 4 The results of Egger's test and trim and fill analysis.

Outcomes	Egger's test		Trim and fill analysis
	T	P	
SBP	−3.39	0.027	MD = −1.312; 95% CI: 2.332 to −0.293; P = 0.012 < 0.05
DBP	−4.33	0.012	MD = −1.454; 95% CI: 2.553 to −0.355; P = 0.010 < 0.05
NYHA classification	2.11	0.064	—
LVEF	5.23	0.001	MD = 1.514; 95% CI: 0.946 to 2.081; P = 0.000 < 0.05

CI: confidence interval; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; MD: mean difference; NYHA: new york heart association; SBP: systolic blood pressure.

showed that TCM improved the NYHA classification, indicating that TCM could reduce symptoms and improve cardiac function in HHD patients.

Moreover, it was critical to observe the change in clinical, comprehensive imaging, and biomarker characteristics from simple hypertension to symptomatic HF with preserved ejection fraction (HFpEF) (Ekström et al., 2020). Echocardiography, one of the cardiac imaging modalities, was essential for quantifying changes in the heart structure and function without invasive methods as HF progressed. In terms of LV structure, the most intuitive markers of LV diastolic function were LV size as determined by LVEDD and LVESD. LVMI and IVSTD were used to assess LVH. LV systolic function was assessed using LVEF. CO was used to measure the strength and normality of cardiac ejection function. Due to sample size limitations, results on CO should be interpreted with caution. E/A ratio <1 indicated diastolic dysfunction. However, the E/A ratio was affected by age and decreased with older age, which influenced the accuracy of the result to a certain extent. According to the above, TCM as an adjunct played a significant role in the progression of cardiac hypertrophy

and ventricular remodeling after HHD, which probably delayed the transition from HHD to HF.

Additionally, BNP could be used to screen patients with multiple HF risk factors and show a downward trend in HF and asymptomatic LV systolic dysfunction (Ledwidge et al., 2013; Slivnick and Lampert, 2019). This meta-analysis revealed that TCM combined with WM therapy effectively decreased BNP. Although the certainty of evidence about BNP was low and the result lacked robustness owing to the risk of bias, inconsistency, and insufficient data, this is an interesting proof-of-concept study that deserves further investigation (Slivnick and Lampert, 2019).

For the results with high heterogeneity, we explored several potential sources of heterogeneity, including the age of patients, the variations in TCM prescriptions, dosages, forms of dosage, modes of treatment, treatment duration, and different stages of HHD. These factors might also contribute to publication bias. However, subgroup age and TCM analysis were not possible owing to the small subgroup size. Some studies did not record the precise course of the disease, and none of the included RCTs mentioned the stage of HHD. In addition, despite doing additional sensitivity analyses to investigate the origins of heterogeneity, we were incapable of explaining the significant heterogeneity observed in the majority of our investigations. Thus, given the evidence overall ranged from moderate to very low certainty, care should be used when interpreting the findings.

4.2 The progression from hypertension to HHD and HF

Hypertension, characterized by raised systemic arterial pressure, is a chronic disease that has been considered an independent risk factor for cardiovascular disease and is associated with the development of HF (Liu et al., 2022; Ekström et al., 2020). Prolonged hypertension and the corresponding neurohormonal stimulation resulted in the malfunctioning of cardiomyocytes and the irregular build-up of cardiac extracellular matrix, which in turn caused cardiac fibrosis (Gülhan Mehmet et al., 2021; Mann and Felker, 2016; Salmas et al., 2017; Selamoglu Talas, 2014). Besides, the overactivated renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system also played an idiopathic role in cardiac fibrosis and LVH, which increased myocardial stiffness, caused aberrant myocardial systolic and diastolic function in the end by reducing ventricular compliance and restricting myocardial activity (Di Palo and Barone, 2020; Wright et al., 2008). HHD encompasses a spectrum of illnesses ranging from unmanaged hypertension to the ultimate development of HF (Slivnick and Lampert, 2019). Simple hypertension initiated the development of extracellular alterations and myocardial fibrosis, perhaps serving as a precursory mechanism in the development of HHD and HF from hypertension (Ekström et al., 2020). Diastolic dysfunction was thought to be the early developmental stage of HHD, and LVH was thought to be the trigger for the condition (Di Palo and Barone, 2020; Slivnick and Lampert, 2019). Persistent pressure overload in the heart due to persistent hypertension caused LVH and myocardial fibrosis, leading to progressive diastolic dysfunction, decompensation, increasing LV dilatation, and eccentric hypertrophy caused by sustained volume overload thereby causing systolic dysfunction to arise (Messerli et al., 2017). The heart is better protected and cardiac function is maintained in the early stages of cardiac hypertrophy (Hu et al., 2022; Bernardo et al., 2010). Prolonged hypertrophy, however, brought about inflammation, myocardial fibrosis, cardiomyocyte enlargement, and cardiac contractile dysfunction, all of which contributed to the development of chronic HF (Ritter and Neyses, 2003; Lieu and Koch, 2019; Hu et al., 2022). Once hypertensive LVH develops, the risk of developing heart failure, especially HFpHF, increases dramatically (Yao et al., 2017). Aggressive treatment might be able to reverse the development of LVH if it is identified early. However, the existence of LVH hastened the transition to HF and was irreversible once HF occurred (Slivnick and Lampert, 2019).

4.3 Pharmacological effects of TCM

TCM, referred to as botanical medicine, phytomedicine, or phytotherapy, is the practice for medicinal purposes with the roots, seeds, bark, leaves, or flowers of plants, which is regarded as TCM in China. According to the World Health Organization (WHO) (WHO Traditional, 2021), botanical drugs, TCM preparations, and complete metabolites are considered to be part of TCM. The field of medicine has given TCM, as one of the complementary and alternative medicines, considerable attention, with a primary focus on active pharmaceutical metabolites. In this meta-analysis, the top 5 Chinese botanical drugs for replenishing qi and activating blood circulation were *S. miltiorrhiza* Bunge (Danshen), *O. striata* (DC.) Pimenov & Kljuykov (Chuanxiong), *P. montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen), *A. mongholicus* Bunge (Huangqi), and *Typha angustifolia* L. (Puhuang) (Figure 12). The five botanical drugs possess the effects of replenishing qi and activating blood circulation. They are used in the treatment of the development of HHD and HF from hypertension. Studies have shown that the method of replenishing qi and activating blood circulation can improve cardiac fibrosis after pressure overload-induced cardiac hypertrophy (Anwaier et al., 2022). The QiShenYiQi pill is a Chinese medicine approved by the China State Food and Drug Administration in 2003 for the treatment of cardiac dysfunction, and it includes *A. mongholicus* Bunge (Huangqi), *Panax notoginseng* (Burkill) F. H. Chen (Sanqi), *S. miltiorrhiza* Bunge (Danshen), and *Dalbergia odorifera* T. C. Chen (Jiangxiang). It inhibited myocardial fibrosis after pressure overload, which was mediated by ribosomal protein S19-mediated transforming growth factor β1 signaling and decreased four-and-a-half LIM domains protein 2 (Anwaier et al., 2022). The QiShenYiQi pill can also relieve fatigue-induced cardiac hypertrophy and enhance heart function, which is correlated with its potential to improve energy metabolism by regulating insulin-like growth factor-1 receptor signaling (Huang et al., 2019).

Salvia miltiorrhiza Bunge (Danshen) was a traditional and precious Chinese botanical drug with high medicinal value, which was widely utilized to treat a variety of cardiovascular diseases. Clinically, *S. miltiorrhiza* Bunge (Danshen) could effectively enhance circulation, eliminate blood stasis, ameliorate inflammation, exert anti-oxidation, and inhibit vascular remodeling (Orgah et al., 2020). Maintaining endothelial function has been shown in earlier research to be a viable treatment approach for

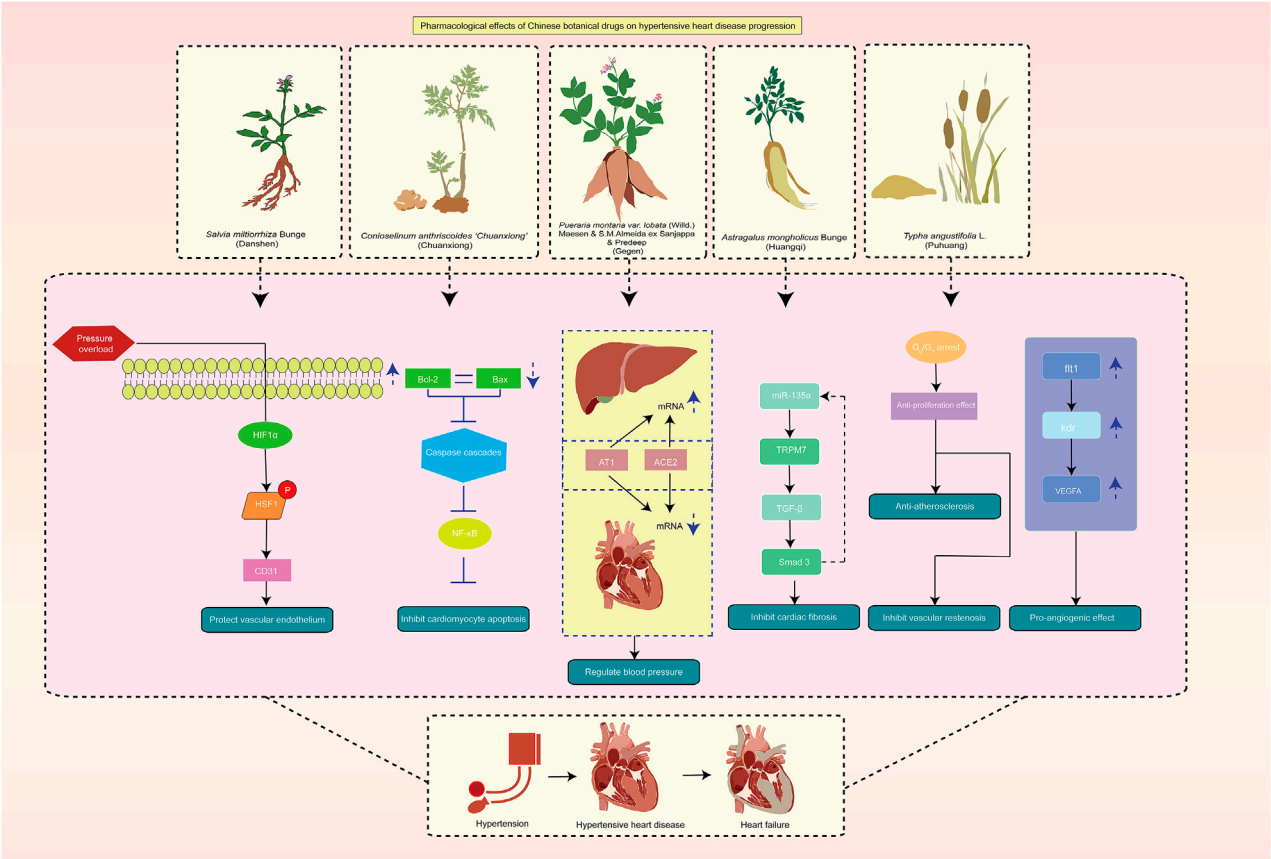


FIGURE 12
Pharmacological effects of TCM on HHD progression. Abbreviation: HHD: hypertensive heart disease; TCM: traditional Chinese medicine.

reducing pressure overload-induced heart damage (Wang et al., 2013; Su et al., 2015). Through endothelial protection, salvianolic acid, the main pharmacologic metabolites in *S. miltiorrhiza* Bunge (Danshen), reduced the effects of pressure overload-induced ventricular chamber expansion, cardiac dysfunction, and fibrosis. According to network pharmacology, salvianolic acid A (Figure 13a) was speculated the obstruct the important target proteins that mediate inflammatory responses such as apolipoprotein E, low-density lipoprotein cholesterol, and tumor necrosis factor, and protection for vascular endothelium in many ways (Sun et al., 2021). One experimental study in mice demonstrated that through an HIF1α/HSF1/CD31 pathway, salvianolic acid shielded cardiac endothelial cells from pressure overload, suggesting a possible use for salvianolic acid in HHD (Li N et al., 2022). In addition, A study revealed the role of salvianolic acid A in lowering cardiac fibrosis and hypertrophy in rats with spontaneous hypertension by inhibiting MMP-9 (Jiang et al., 2013). Neocryptotanshinone (NCTS) is a metabolite derived from *S. miltiorrhiza* Bunge (Danshen). It enhanced mitochondrial transcription factor A levels, promoted mitochondrial biogenesis, and increased myocardial adenosine triphosphate levels by activating retinoid X receptor α. The study has shown that NCTS improves myocardial energy metabolism, including fatty acid oxidation and mitochondrial biogenesis, by regulating the retinoid X receptor alpha α/peroxisome proliferator-activated receptor α pathway in mice with heart failure post-acute myocardial infarction (Ma et al., 2023).

Oreocome striata (DC.) Pimenov & Kljuykov (Chuanxiong) is a member of the Umbelliferae family and is grown mostly in Sichuan Province, China. It is a frequently prescribed TCM. In Shen Nong's Materia Medica (Shen Nong Ben Cao Jing), *O. striata* (DC.) Pimenov & Kljuykov (Chuanxiong) could activate the blood, relieve pain, and remove blood stasis. The bioactive metabolites contained in *O. striata* (DC.) Pimenov & Kljuykov (Chuanxiong) primarily included alkaloids, phenols and organic acids, phthalides, and polysaccharides (Lin et al., 2022). Among these, Tetramethylpyrazine (Figure 13b) has been isolated as an alkaloid from the rhizome of *O. striata* (DC.) Pimenov & Kljuykov (Chuanxiong) and has multiple bioactivities (Yang et al., 2019). Tetramethylpyrazine has been shown in prior research to have a wide range of physiological effects, including protection against endothelial damage, antioxidative stress, anti-inflammatory, antiapoptotic, and antiplatelet aggregation, as well as improvements in microcirculation, vascular smooth muscle cell proliferation and migration, and vasodilation (Su et al., 2019; Lin et al., 2022). Besides, Liguzinediol, as a novel para-dihydroxy derivative of Tetramethylpyrazine extracted from the TCM Chuanxiong, demonstrated the effect on increasing heart function and preventing myocardial cell apoptosis, which was linked to

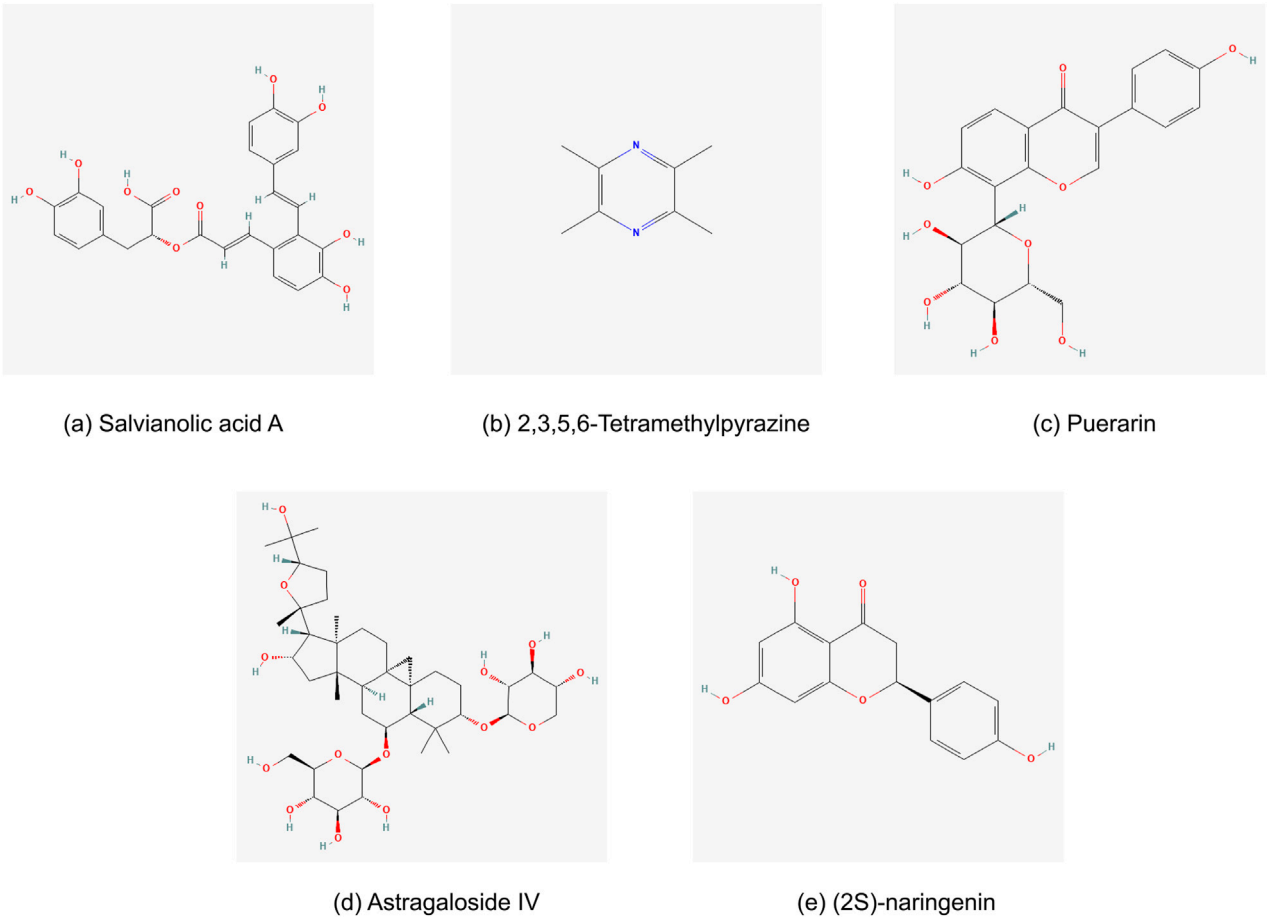


FIGURE 13
Chemical structures of main metabolites in the top 5 Chinese botanical drugs for the treatment of HHD: **(a)** Salvianolic acid A, **(b)** 2,3,5,6-Tetramethylpyrazine, **(c)** Puerarin, **(d)** Astragaloside IV, and **(e)** (2S)-naringenin.

controlling the expression of Bcl-s, Bax, caspase-s, and NF-κB expression in the rat model of HF (Li et al., 2014).

Pueraria montana var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) originated from Shen Nong's Materia Medica (Shen Nong Ben Cao Jing) and is a notable TCM botanical drug. It is used to stimulate Spleen Yang to stop diarrhea and promote the production of bodily fluids. It has a sweet and acrid flavor (Wong et al., 2011). In clinical application, *P. montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) is frequently used as a necessary botanical drug in TCM formulas to treat cardiovascular diseases, including hypertension, cardiac infarction, and angina pectoris. *Pueraria montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) contains more than 70 metabolites, of which isoflavones and triterpenoids make up the majority. Puerarin (Figure 13c), the main bioactive metabolite and approximately 60% of all isoflavones, has a broad range of pharmacological characteristics, such as cardioprotection, vasodilation, anti-inflammatory effects, antioxidant activity, etc. (Zhang et al., 2020). Numerous animal models and cell cultures have shown puerarin's pharmacological impacts on the cardiovascular system (Wong et al., 2011). A previous experiment revealed that puerarin inhibited β-adrenoceptors to provide its anti-hypertensive action (Lu et al., 1987). In another study, puerarin had a comparable impact to verapamil. Angiotensin II type 1 receptor (AT1) and angiotensin-converting enzyme 2 (ACE2) mRNA expressions were considerably upregulated in hepatic tissues, while AT1 and ACE2 mRNA expressions in cardiac tissues were suppressed (Ye et al., 2008).

Astragalus mongholicus Bunge (Huangqi) is Chinese medicine with tonic, diuretic, blood-nourishing, and detoxifying properties recorded originally in Shen Nong's Materia Medica (Shen Nong Ben Cao Jing) (Chinese Pharmacopoeia Commission, 2015). Previous study summarized that *A. mongholicus* Bunge (Huangqi) has obvious therapeutic effects on hypertension, cardiac hypertrophy, chronic HF, atherosclerosis, and other cardiovascular diseases (Li M et al., 2022). Furthermore, *A. mongholicus* Bunge (Huangqi) could strengthen myocardial contractility, protect myocardial cells, improve cardiac function, and increase myocardial energy metabolism (Lv et al., 2021; Chen et al., 2015). *Astragalus mongholicus* Bunge (Huangqi) contains various biological active metabolites, such as astragaloside, isoflavones, saponins, polysaccharides, and flavonoids. The primary mechanisms were anti-inflammatory, anti-oxidative damage, anti-apoptotic, immunomodulatory, and antithrombotic (Li et al., 2018). Astragaloside IV was one of the primary active metabolites of *A. mongholicus* Bunge (Huangqi) (Figure 13d). It has been found to

target the miR-135a-TRPM7-TGF-β/Smads pathway, which may reduce cardiac fibrosis (Wei et al., 2020). Through the signaling pathways for ten-eleven translocation 2 and DNA methyltransferase 1, Astragaloside IV protects against vascular remodeling brought on by hypertension. This activity is crucial for controlling the function of vascular smooth muscle cells (Li M et al., 2022). In addition, Astragalus polysaccharides (ASP), which have therapeutic benefits on cardiovascular disorders such as cardiac hypertrophy and vascular endothelial dysfunction, were thought to be another significant metabolite of *A. mongholicus* Bunge (Huangqi). By blocking calcium-mediated calcineurin/NFATc3 and CaMKII signaling, ASP reduces cardiac hypertrophy in isoproterenol-induced hypertrophic myocardium (Chen et al., 2007). According to other animal and cell experiments, ASP has shown protective effectiveness in MVRI/ISO-treated cardiomyocytes by preventing apoptosis (Liu et al., 2018). ASP improved the pathological state of myocardial damage and chronic myocardial fibrosis by reducing the expression of inflammatory markers in the heart, including Interleukin-1β, interleukin-6, Tumor necrosis factor-α, monocyte chemoattractant protein-1, and interferon-γ (Liu et al., 2019). In TCM, Astragali Radix was often combined with other botanical drugs in various complex prescription formulas.

Typha angustifolia L. (Puhuang), the dried pollen of typha, was originally recorded in Shen Nong's Materia Medica (Shen Nong Ben Cao Jing). The National Health Commission of the People's Republic of China recognized it as a functional food in 2002, and the 2015 edition of the Pharmacopoeia of the People's Republic of China included it (Gao et al., 2021). It was frequently used as TCM to treat angina pectoris, dysmenorrhea, hematuria, stranguria, stroke, metrorrhagia, and injuries from falls (Ding et al., 2018; Qin and Sun, 2005). *Typha angustifolia* L. (Puhuang) is mostly composed of flavonoids, sterols, amino acids, organic acids, long-chain hydrocarbons, and other chemicals (Ding et al., 2018). As is shown in pharmacological and clinical research, *Typha angustifolia* L. (Puhuang) is effective in improving microcirculation, raising cAMP levels, anti-inflammatory, antiplatelet aggregation, anti-atherosclerosis, anti-oxidant, preventing and treating hyperlipidemia, and coronary heart diseases (Qin and Sun, 2005; Hung and Wu, 2016; Chen et al., 2021; Ding et al., 2018). In cardiovascular effects, (2S)-naringenin (Figure 13e), as one of the active metabolites from *Typha angustifolia* L. (Puhuang), could suppress vascular smooth muscle cell proliferation induced platelet-derived growth factor receptor β through a G_0/G_1 arrest. This might be useful in managing vascular restenosis and atherosclerosis (Lee et al., 2012). And *Typha angustifolia* L. (Puhuang) also consisted mainly of the Korean herbal medicine Silsosangami. It reduced the expression of inducible nitric oxide synthase and cyclooxygenase-2, inhibited neutrophil activities, and produced prostaglandin E2 and nitric oxide. It also possessed anti-inflammatory properties (Park et al., 2004). Besides, another study demonstrated that *Typha angustifolia* L. (Puhuang) could upregulate the expression of kdr, flt1, and VEGFA to display the pro-angiogenic effect (Gao et al., 2021).

However, it should be acknowledged that the current attempt to clarify the pharmacological links between traditional therapeutic concepts and the findings has inherent limitations, which require systematic elaboration. This study primarily focuses on the concept of replenishing qi and activating blood circulation, and explores its potential association with specific pharmacological mechanisms, such as the regulation of energy metabolism pathways and the enhancement of immune function. To some extent, it reflects a reductionist tendency, which simplifies the complex, holistic traditional concept into measurable biological indicators, leading to an incomplete understanding of its connotations. Therefore, the findings of this study should be interpreted with caution. They only reflect a preliminary association between a certain pharmacological mechanism and one aspect of replenishing qi and activating blood circulation, rather than a comprehensive explanation. Future research needs to integrate multi-omics approaches, establish more systematic experimental models, and combine clinical syndrome differentiation data to further explore the complex links between traditional therapeutic concepts and modern pharmacology, thereby avoiding the narrow interpretation caused by over-reliance on reductionist methods. In the present study, replenishing qi and activating blood circulation emerge as a potential therapeutic approach for mitigating the progression of hypertensive heart disease. However, its efficacy, underlying mechanisms, and optimal clinical application scenarios warrant further in-depth investigation in future research to validate its therapeutic value and clarify its role within a broader context of treatment strategies.

4.4 Comparison to previous systematic review evidence

The differences from other systematic reviews (Mohammed et al., 2023; Ren et al., 2020; Xiong et al., 2019; Zhang et al., 2022) were given in the following three points. Firstly, in addition to BP, other necessary objective outcome measures, including NYHA classification, LVEF, CO, E/A ratio, LVEDD, LVESD, LVMI, IVSTD, BNP, and adverse events, were used to assess the effect of TCM on HHD. That's the biggest difference compared to the previous research of TCM, which just focuses on hypertension. This meta-analysis focused on the impact of long-term hypertension on cardiac structure, function, and prognosis, with a particular emphasis on the progression from hypertension to HHD and HF, which had not been addressed in previous meta-analyses. Unfortunately, due to inadequate data in the included RCTs, long-term outcome endpoints such as cardiovascular death, HF incidence, hospitalization, and all-cause mortality were not investigated in this analysis. Secondly, the included studies did not place limitations on the TCM formula. Oral dose forms were the only available for TCM, including decoctions, pills, granules, and capsules. In contrast to conventional medicine, TCM has a long tradition of using food as medication. The third and fourth most often used Chinese botanical drugs in this meta-analysis, *P. montana* var. *lobata* (Willd.) Maesen & S.M.Almeida ex Sanjappa & Predeep (Gegen) and *A. mongholicus* Bunge (Huangqi), were found in the National Health Commission of the People's Republic of China's list of items that were 'both food and medicine' (also known as 'medicine and food come from the same source' or 'medicine food homology,' or MFH) (National Health Commission of the People's Republic of China, 2023; National Health Commission of the People's Republic of China, 2022). The other four Chinese botanical drugs were found in the

National Health Commission of the People's Republic of China's list of Chinese medicines that could be used as health food. The efficacy of oral TCM for HHD was comprehensively evaluated, and its edible safety was well-guaranteed. Thirdly, other strengths, such as adherence to the guidelines of PRISMA and the previously registered protocol in PROSPERO, were also worth mentioning. The GRADE system was used to assess the quality of supporting evidence, and the Cochrane Risk of Bias Tool was utilized to evaluate the risk of bias in the included studies to facilitate the creation of recommendations.

4.5 Limitations

First, despite our thorough search, every included RCT was only done in China, which limited the generalizability. Future randomized, double-blind, placebo-controlled RCTs with a longer-term duration are required. Second, this meta-analysis was subjected to methodological weaknesses of the original studies. Only one study reported allocation concealment that could result in selection bias, and one study described blinding of participants and personnel that could cause performance bias. Blinding of outcome assessment was not mentioned in any of the studies, which could result in detection bias. The majority of the included studies' low quality had an impact on the accuracy of the results. Subsequent research endeavors ought to incorporate methods that mitigate the possibility of bias in reporting, like blinding result assessors, randomization, and allocation concealment. However, because TCM consists of many metabolites, conducting adequate blinding for TCM investigations may prove challenging. Moreover, many ancient forms, such as decoctions, pills, and powders, had special tastes and scents, which made it difficult to confirm that placebos were identical. More information is needed on the reported side effects, interactions, and general safety aspects of this preparation. Third, the onset and progression of HHD are complicated processes. To date, there are no guidelines or expert consensus providing recommendations on the stage of HHD. It is still difficult to recognize patients with hypertension at risk of developing HF in the long run promptly, even with the availability of targeted antihypertensive medications. Finally, because the included studies only provided a limited number of outcome indicators, this article was unable to assess the impact of TCM on HHD in its entirety. Thus, it is necessary to extend the follow-up time and conduct an RCT to identify the efficacy of TCM on HHD and observe the occurrence of long-term cardiovascular adverse events.

4.6 Future perspectives

The analysis we had done to reflect the changes in heart structure and function following HHD, but it was still not enough to show how this intricate shift in the development of HHD and HF occurs after hypertension. Further research should observe blood indicators for endothelial dysfunction, inflammation, and cardiac fibrosis, which could be analyzed to describe, track, and identify phenotypes that are at risk of developing HHD and HFpEF (Ekström et al., 2020). Additionally, TCM has been demonstrated to be an alternate and complementary strategy for both primary and secondary cardiovascular disease prevention (Hao et al., 2017). Typically, two or more botanical drugs are combined in a TCM recipe to create a synergistic effect. Botanical drug or botanical drug-pair interactions should be closely monitored from a clinical standpoint, particularly when several botanical drugs are utilized at once (Zuo et al., 2020). Our goal is to find new hypertension treatment strategies to prevent HF. More RCTs are required to evaluate how therapy of replenishing qi and activating blood circulation affects patients with HHD's long-term challenging endpoints. The results are expected to guide healthcare providers in hospitals to offer personalized treatment (Ekström et al., 2020).

5 Conclusion

In general, the results of this meta-analysis suggested that the use of TCM and WM together may be more effective than using WM alone in the treatment of HHD. This combination might also reduce unfavorable LV remodeling and enhance cardiac systolic and diastolic function, which might slow the disease's progression. In addition to being a new approach to treating hypertension to avoid HF, therapy of replenishing qi and activating blood circulation offers a reference as an auxiliary treatment for secondary prevention following HHD. However, it was important to interpret these results cautiously, considering the limitations of the original trials. To support this clinical evidence, more rigorous trials for herbal therapy are advised.

6 Chemical metabolites studied in this article

Salvianolic acid A (PubChem CID: 5281793); 2,3,5,6-Tetramethylpyrazine (PubChem CID: 14296); Puerarin (PubChem CID: 5281807); Astragaloside IV (PubChem CID: 13943297); (2S)-naringenin (PubChem CID: 439246).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

JH: Conceptualization, Data curation, Software, Visualization, Writing – original draft. YW: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft. FX: Formal Analysis, Funding acquisition, Resources, Supervision, Validation, Visualization, Writing – review & editing. JZ: Funding acquisition, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work

was supported by the Department of Medical Administration of the National Administration of Traditional Chinese Medicine: Preventive intervention program for chronic diseases (ZYZB-2020-196), National Natural Science Foundation of China (No. 81904195), and the Qihuang Project for Inheritance and Innovation of Traditional Chinese Medicine. The funder had no role in the study design, data analysis, or decision to publish.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1506234/full#supplementary-material

References

Anwaier, G., Xie, T. T., Pan, C. S., Li, A. Q., Yan, L., Wang, D., et al. (2022). QiShenYiQi pill ameliorates cardiac fibrosis after pressure overload-induced cardiac hypertrophy by regulating FHL2 and the macrophage RP S19/TGF-β1 signaling pathway. *Front. Pharmacol.* 13, 918335. doi:10.3389/fphar.2022.918335

Bayés-Genís, A., and Díez, J. (2022). Transition to heart failure in hypertension: going to the heart of the matter. *Eur. Heart J.* 43 (35), 3332–3334. doi:10.1093/eurheartj/ehab651

Bernardo, B. C., Weeks, K. L., Pretorius, L., and McMullen, J. R. (2010). Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. *Pharmacol. Ther.* 128 (1), 191–227. doi:10.1016/j.pharmthera.2010.04.005

Cai, F. (2016). Clinical observation of 38 cases of hypertensive heart disease complicated with left ventricular diastolic dysfunction treated with traditional Chinese medicine decoction. *Cardiovasc. Dis. Prev. Knowl. Acad. Ed.* 22, 8–10.

Chen, W., Li, Y. M., and Yu, M. H. (2007). Effects of Astragalus polysaccharides on chymase, angiotensin-converting enzyme and angiotensin II in diabetic cardiomyopathy in hamsters. *J. Int. Med. Res.* 35 (6), 873–877. doi:10.1177/147323000703500615

Chen, W., Lai, Y., Wang, L., Xia, Y., Chen, W., Zhao, X., et al. (2015). Astragalus polysaccharides repress myocardial lipotoxicity in a PPARalpha-dependent manner *in vitro* and *in vivo* in mice. *J. Diabetes Complicat.* 29 (2), 164–175. doi:10.1016/j.jdiacomp.2014.11.007

Chen, T., Chen, C., Huang, Y., Baskaran, R., Tsai, J. J. P., and Hu, R. (2021). Ethanolic extract of Puhuang (Pollen Typhae) modulates lipopolysaccharide-induced inflammatory response through inducible nitric oxide synthase/cyclooxygenase-2 signaling in RAW 264.7 macrophage. *J. Tradit. Chin. Med.* 41 (6), 836–844. doi:10.19852/j.cnki.jtcm.2021.06.002

Chinese Pharmacopoeia Commission (2015). *Pharmacopoeia of the People's Republic of China*. Beijing: China Medical Science and Technology Press.

Cui, J. (2022). Clinical observation of metoprolol combined with Wenxin granule in the treatment of hypertensive heart disease with premature ventricular beat. *Database Chin. Sci-tech Period. (Med.).* 4, 0039–0042.

Dai, H., Bragazzi, N. L., Younis, A., Zhong, W., Liu, X., Wu, J., et al. (2021). Worldwide trends in prevalence, mortality, and disability-adjusted Life years for hypertensive heart disease from 1990 to 2017. *Hypertension* 77 (4), 1223–1233. doi:10.1161/HYPERTENSIONAHA.120.16483

Devereux, R. B., Koren, M. J., de Simone, G., Okin, P. M., and Kligfield, P. (1993). Methods for detection of left ventricular hypertrophy: application to hypertensive heart disease. *Eur. Heart J.* 14 (Suppl. D), 8–15. doi:10.1093/eurheartj/14.suppl_d.8

Di Palo, K. E., and Barone, N. J. (2020). Hypertension and heart failure: prevention, targets, and treatment. *Heart fail. Clin.* 16 (1), 99–106. doi:10.1016/j.hfc.2019.09.001

Ding, M., Jiang, Y., Yu, X., Zhang, D., Li, J., Wang, H., et al. (2018). Screening of combinatorial quality markers for natural products by metabolomics coupled with chemometrics. A case study on pollen typhae. *Front. Pharmacol.* 9, 691. doi:10.3389/fphar.2018.00691

Drazner, M. H. (2011). The progression of hypertensive heart disease. *Circulation* 123 (3), 327–334. doi:10.1161/CIRCULATIONAHA.108.845792

Du, H. (2016). Analysis of clinical effect of integrated traditional Chinese and Western medicine on hypertensive heart disease. *Cardiovasc. Dis. J. Integr. Tradit. Chin. West. Med.* 4 (34), 181.

Egbe, A. C., Anderson, J. H., Ammash, N. M., and Taggart, N. W. (2020). Left ventricular remodeling after transcatheter versus surgical therapy in adults with coarctation of aorta. *JACC Cardiovasc. Imaging.* 13 (9), 1863–1872. doi:10.1016/j.jcmg.2020.01.016

Ekhteiari Salmas, R., Durdagi, S., Gulhan, M. F., Duruyurek, M., Abdullah, H. I., and Selamoglu, Z. (2018). The effects of pollen, propolis, and caffeic acid phenethyl ester on tyrosine hydroxylase activity and total RNA levels in hypertensive rats caused by nitric oxide synthase inhibition: experimental, docking and molecular dynamic studies. *J. Biomol. Struct. Dyn.* 36 (3), 609–620. doi:10.1080/07391102.2017.1288660

Ekström, M., Hellman, A., Hasselström, J., Hage, C., Kahan, T., Ugander, M., et al. (2020). The transition from hypertension to hypertensive heart disease and heart failure: the PREFERS Hypertension study. *Esc. Heart Fail* 7 (2), 737–746. doi:10.1002/ehf2.12612

Escaned, J., and Lerman, L. O. (2020). Coronary microcirculation and hypertensive heart failure. *Eur. Heart J.* 41 (25), 2376–2378. doi:10.1093/eurheartj/ehaa437

Ettehad, D., Emdin, C. A., Kiran, A., Anderson, S. G., Callender, T., Emberson, J., et al. (2016). Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 387 (10022), 957–967. doi:10.1016/S0140-6736(15)01225-8

Gao, M., Ge, Z., Deng, R., Bao, B., Yao, W., Cao, Y., et al. (2021). Evaluation of VEGF mediated pro-angiogenic and hemostatic effects and chemical marker investigation for Typhae Pollen and its processed product. *J. Ethnopharmacol.* 268, 113591. doi:10.1016/j.jep.2020.113591

GBD 2017 Risk Factor Collaborators (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 392 (10159), 1923–1994. doi:10.1016/S0140-6736(18)32225-6

Gogebakan, A., Talas, Z. S., Ozdemir, I., and Sahna, E. (2012). Role of propolis on tyrosine hydroxylase activity and blood pressure in nitric oxide synthase-inhibited hypertensive rats. *Clin. Exp. Hypertens.* 34 (6), 424–428. doi:10.3109/10641963.2012.665542

González, A., Ravassa, S., López, B., Moreno, M. U., Beaumont, J., San José, G., et al. (2018). Myocardial remodeling in hypertension. *Hypertension* 72 (3), 549–558. doi:10.1161/HYPERTENSIONAHA.118.11125

Gülhan Mehmet, F., Özdemir, B., Selamoglu, Z., and Şahna, E. (2021). The effects of apitherapeutic agents on oxidative stress in serum metabolic parameters of hypertensive

rats created by nitric oxide synthase inhibited. *Sains Malays.* 50 (6), 1745–1754. doi:10.17576/jsm-2021-5006-20

Hao, P., Jiang, F., Cheng, J., Ma, L., Zhang, Y., and Zhao, Y. (2017). Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. *J. Am. Coll. Cardiol.* 69 (24), 2952–2966. doi:10.1016/j.jacc.2017.04.041

Higgins, J. P., Thompson, S. G., Deeks, J. J., and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ* 327 (7414), 557–560. doi:10.1136/bmj.327.7414.557

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343, d5928. doi:10.1136/bmj.d5928

Hou, B., Liu, X., Song, Y., and Zhang, T. (2015). Clinical study of 98 patients with hypertensive heart disease treated by combination of Chinese and Western medicine. *Glob. Tradit. Chin. Med.* 8 (S1), 242.

Hu, X. (2012). Clinical observation of patients with hypertensive heart disease treated by combination of traditional Chinese and Western medicine. *World Health Dig. Med. Period.* 36, 184–185. doi:10.3969/j.issn.1672-5085.2012.36.172

Hu, L., Wei, J., Zhang, Y., Wang, Z., Tang, J., Tang, J., et al. (2022). ANGPTL8 is a negative regulator in pathological cardiac hypertrophy. *Cell Death Dis.* 13 (7), 621. doi:10.1038/s41419-022-05029-8

Huang, R., Cui, Y. C., Wei, X. H., Pan, C. S., Li, Q., He, S. Y., et al. (2019). A novel traditional Chinese medicine ameliorates fatigue-induced cardiac hypertrophy and dysfunction via regulation of energy metabolism. *Am. J. Physiol. Heart Circ. Physiol.* 316 (6), H1378–H1388. doi:10.1152/ajpheart.00731.2018

Hung, H. Y., and Wu, T. S. (2016). Recent progress on the traditional Chinese medicines that regulate the blood. *J. Food Drug Anal.* 24 (2), 221–238. doi:10.1016/j.jfda.2015.10.009

Iriarte, M., Murga, N., Sagastagoitia, D., Morillas, M., Boveda, J., Molinero, E., et al. (1993). Classification of hypertensive cardiomyopathy. *Eur. Heart J.* 14 (Suppl. J), 95–101.

Jiang, B., Li, D., Deng, Y., Teng, F., Chen, J., Xue, S., et al. (2013). Salvianolic acid A, a novel matrix metalloproteinase-9 inhibitor, prevents cardiac remodeling in spontaneously hypertensive rats. *PLoS One* 8 (3), e59621. doi:10.1371/journal.pone.0059621

Jin, L., and Wu, D. (2006). The influence of modified Tianma Gouteng decoction on blood pressure heart function and cardiac ventricle remodeling in hypertensive heart disease. *Hunan J. Tradit. Chin. Med.* 22 (6), 3–5. doi:10.16808/j.cnki.issn1003-7705.2006.06.002

Ledwidge, M., Gallagher, J., Conlon, C., Tallon, E., O'Connell, E., Dawkins, I., et al. (2013). Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 310 (1), 66–74. doi:10.1001/jama.2013.7588

Lee, J. J., Yi, H., Kim, I. S., Kim, Y., Nhiem, N. X., Kim, Y. H., et al. (2012). (2S)-naringenin from Typha angustata inhibits vascular smooth muscle cell proliferation via a G0/G1 arrest. *J. Ethnopharmacol.* 139 (3), 873–878. doi:10.1016/j.jep.2011.12.038

Levy, D., Larson, M. G., Vasan, R. S., Kannel, W. B., and Ho, K. K. (1996). The progression from hypertension to congestive heart failure. *JAMA* 275 (20), 1557–1562. doi:10.1001/jama.1996.03530440037034

Li, Y., Song, P., Zhu, Q., Yin, Q. Y., Ji, J. W., Li, W., et al. (2014). Liguzinediol improved the heart function and inhibited myocardial cell apoptosis in rats with heart failure. *Acta. Pharmacol. Sin.* 35 (10), 1257–1264. doi:10.1038/aps.2014.75

Li, N. Y., Yu, H., Li, X. L., Wang, Q. Y., Zhang, X. W., Ma, R. X., et al. (2018). Astragalus membranaceus improving asymptomatic left ventricular diastolic dysfunction in postmenopausal hypertensive women with metabolic syndrome: a prospective, open-labeled, randomized controlled trial. *Chin. Med. J. (Engl.).* 131 (5), 516–526. doi:10.4103/0366-6999.226077

Li, Q., Liu, D., and Chen, M. (2019). Effect of Danxiong Tongluo Decoction combined with metoprolol on left ventricular diastolic function in patients with hypertensive heart disease. *J. Sichuan Tradit. Chin. Med.* 37 (09), 70–72.

Li M, M., Han, B., Zhao, H., Xu, C., Xu, D., Sieniawska, E., et al. (2022). Biological active ingredients of Astragali Radix and its mechanisms in treating cardiovascular and cerebrovascular diseases. *Phytomedicine* 98, 153918. doi:10.1016/j.phymed.2021.153918

Li N, N., Hang, W., Shu, H., Wen, Z., Ceesay, B. M., and Zhou, N. (2022). Salvianolic acid ameliorates pressure overload-induced cardiac endothelial dysfunction via activating HIF1[formula: see text]/HSF1/CD31 pathway. *Am. J. Chin. Med.* 50 (7), 1869–1885. doi:10.1142/S0192415X22500793

Lieu, M., and Koch, W. J. (2019). GRK2 and GRK5 as therapeutic targets and their role in maladaptive and pathological cardiac hypertrophy. *Expert. Opin. Ther. Targets* 23 (3), 201–214. doi:10.1080/14728222.2019.1575363

Lin, J., Wang, Q., Zhou, S., Xu, S., and Yao, K. (2022). Tetramethylpyrazine: a review on its mechanisms and functions. *Biomed. Pharmacother.* 150, 113005. doi:10.1016/j.biopha.2022.113005

Liu, C. (2012). Clinical study of 98 patients with hypertensive heart disease treated by combination of Chinese and Western medicine. *China Health Care & Nutr* 22 (16), 3514.

Liu, C., and Huang, Y. (2016). Chinese herbal medicine on cardiovascular diseases and the mechanisms of action. *Front. Pharmacol.* 7, 469. doi:10.3389/fphar.2016.00469

Liu, D., Chen, L., Zhao, J., and Cui, K. (2018). Cardioprotection activity and mechanism of Astragalus polysaccharide *in vivo* and *in vitro*. *Int. J. Biol. Macromol.* 111, 947–952. doi:10.1016/j.ijbiomac.2018.01.048

Liu, T., Zhang, M., Niu, H., Liu, J., Ruilian, M., Wang, Y., et al. (2019). Astragalus polysaccharide from Astragalus Melittin ameliorates inflammation via suppressing the activation of TLR-4/NF-κB p65 signal pathway and protects mice from CVB3-induced virus myocarditis. *Int. J. Biol. Macromol.* 126, 179–186. doi:10.1016/j.ijbiomac.2018.12.207

Liu, M., Long, X., Xu, J., Chen, M., Yang, H., Guo, X., et al. (2022). Hypertensive heart disease and myocardial fibrosis: how traditional Chinese medicine can help addressing unmet therapeutical needs. *Pharmacol. Res.* 185, 106515. doi:10.1016/j.phrs.2022.106515

Lu, X. R., Gao, E., Xu, L. Z., Li, H. Z., Kang, B., Chen, W. N., et al. (1987). Puerarin beta-adrenergic receptor blocking effect. *Chin. Med. J. (Engl.).* 100 (1), 25–28.

Lv, S., Yuan, P., Lu, C., Dong, J., Li, M., Qu, F., et al. (2021). QiShenYiQi pill activates autophagy to attenuate reactive myocardial fibrosis via the PI3K/AKT/mTOR pathway. *Aging (Albany NY)* 13 (4), 5525–5538. doi:10.18632/aging.202482

Ma, L., Shao, M., Cheng, W., Jiang, J., Chen, X., Tan, N., et al. (2023). Neocryptotanshinone ameliorates insufficient energy production in heart failure by targeting retinoid X receptor alpha. *Biomed. Pharmacother.* 163, 114868. doi:10.1016/j.biopha.2023.114868

Mann, D. L., and Felker, G. M. (2016). *Heart failure: a companion to Braunwald's heart disease*. 3rd edition. Philadelphia: Elsevier-Saunders.

Messerli, F. H., Rimoldi, S. F., and Bangalore, S. (2017). The transition from hypertension to heart failure: contemporary update. *JACC Heart Fail* 5 (8), 543–551. doi:10.1016/j.jchf.2017.04.012

Mohammed, S. A. D., Hanxing, L., Fang, L., Algradi, A. M., Alradhi, M., Safi, M., et al. (2023). Integrated Chinese herbal medicine with Western Medicine versus Western Medicine in the effectiveness of primary hypertension treatment: a systematic review and meta-analysis of randomized controlled trials. *J. Ethnopharmacol.* 300, 115703. doi:10.1016/j.jep.2022.115703

National Health Commission of the People's Republic of China (2022). A list of items that are both food and medicine. Available online at: http://www.nhc.gov.cn/zwgk/wtwj/201304/3312183b2f954e35a29c77921a88d730.shtml (Accessed February 15, 2022).

National Health Commission of the People's Republic of China (2023). Announcement on 9 new substances of Codonopsis pilosula and other new substances which are both food and traditional Chinese medicines in accordance with tradition. Available online at: http://www.nhc.gov.cn/sps/s7892/202311/f0d6ef3033b54333a882e3d009ff49bf.shtml (Accessed November 9, 2023).

Orgah, J. O., He, S., Wang, Y., Jiang, M., Wang, Y., Orgah, E. A., et al. (2020). Pharmacological potential of the combination of Salvia miltiorrhiza (Danshen) and Carthamus tinctorius (Honghua) for diabetes mellitus and its cardiovascular complications. *Pharmacol. Res.* 153, 104654. doi:10.1016/j.phrs.2020.104654

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematicreviews. *BMJ* 372, n71. doi:10.1136/bmj.n71

Park, W. H., Kim, C. H., Lee, Y. C., and Kim, C. H. (2004). Anti-inflammatory effects of a traditional Korean herbal formulation, Silsosangami, consisting of seven medicinal herbs: effect on hemolysis, neutrophil function, and gene expressions of iNOS and COX-2. *Vasc. Pharmacol.* 42 (1), 7–15. doi:10.1016/j.vph.2004.11.002

Peng, X. (2015). Effects of Shexiang Baoxin Pill combined with amiodarone on heart rate, blood pressure and atrial fibrillation in hypertensive heart disease patients with atrial fibrillation in community. *J. New Chin. Med.* 47 (04), 16–17. doi:10.13457/j.cnki.jncm.2015.04.008

Qin, F., and Sun, H. X. (2005). Immunosuppressive activity of Pollen Typhae ethanol extract on the immune responses in mice. *J. Ethnopharmacol.* 102 (3), 424–429. doi:10.1016/j.jep.2005.06.027

Ren, W., Wang, M., Liao, J., Li, L., Yang, D., Yao, R., et al. (2020). The effect of Chinese herbal medicine combined with western medicine on vascular endothelial function in patients with hypertension: a systematic review and meta-analysis of randomized controlled trials. *Front. Pharmacol.* 11, 823. doi:10.3389/fphar.2020.00823

Ritter, O., and Neyses, L. (2003). The molecular basis of myocardial hypertrophy and heart failure. *Trends Mol. Med.* 9 (7), 313–321. doi:10.1016/s1471-4914(03)00114-x

Roth, G. A., Johnson, C., Abajobir, A., Abd-Allah, F., Abera, S. F., Abyu, G., et al. (2017). Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J. Am. Coll. Cardiol.* 70 (1), 1–25. doi:10.1016/j.jacc.2017.04.052

Salmas, R. E., Gulhan, M. F., Durdagi, S., Sahna, E., Abdullah, H. I., and Selamoglu, Z. (2017). Effects of propolis, caffeic acid phenethyl ester, and pollen on renal injury in hypertensive rat: an experimental and theoretical approach. *Cell biochem. Funct.* 35 (6), 304–314. doi:10.1002/cbf.3277

Selamoglu Talas, Z. (2014). Propolis reduces oxidative stress in l-NAME-induced hypertension rats. *Cell biochem. Funct.* 32 (2), 150–154. doi:10.1002/cbf.2986

Slivnick, J., and Lampert, B. C. (2019). Hypertension and heart failure. *Heart fail. Clin.* 15 (4), 531–541. doi:10.1016/j.hfc.2019.06.007

Song, H. (2011). Observation of the effect of nourishing Yin and suppressing liver Yang decoction combined with western medicine on hypertensive cardiopathy. *Mod. J. Integr. Tradit. Chin. West. Med.* 20 (34), 4329–4330+4395.

Song, B. (2019). The therapeutic effect of integrated Chinese and Western medicine in the treatment of hypertensive heart disease. *Health friend* 7 (97)–96.

Su, X., Zhi, X., Cui, T., Zheng, Q., Wang, S., Cao, Y., et al. (2015). Vasorelaxant activities of Danhong injection and their differential effects on the rat abdominal aorta and mesenteric artery. *J. Cardiovasc. Pharmacol.* 65 (1), 62–71. doi:10.1097/FJC.0000000000000164

Su, Q., Lv, X., and Ye, Z. (2019). Ligustrazine attenuates myocardial injury induced by coronary microembolization in rats by activating the PI3K/akt pathway. *Oxid. Med. Cell Longev.* 2019, 6791457. doi:10.1155/2019/6791457

Sun, G., Li, X., Wei, J., Zhang, T., Li, B., Chen, M., et al. (2021). Pharmacodynamic substances in Salvia miltiorrhiza for prevention and treatment of hyperlipidemia and coronary heart disease based on lipidomics technology and network pharmacology analysis. *Biomed. Pharmacother.* 141, 111846. doi:10.1016/j.biopha.2021.111846

Tan, Q. (2019). Curative effect of Chinese medicine combined with metoprolol on hypertensive heart disease. *Inn. Mong. J. Tradit. Chin. Med.* 38 (6), 43–44.

Tao, R. (2021). Clinical effect of the method of phlegm-resolving and wind-calming therapy on patients with hypertensive heart disease. *Qingdao Med. J.* 53 (2), 148–150.

Tavolinejad, H., Soltani, D., Zargaran, A., Rezaeizadeh, H., and Vasheghani-Farahani, A. (2019). The story of amiodarone. *Eur. Heart J.* 40 (33), 2758–2759. doi:10.1093/eurheartj/ehz583

Tromp, J., Paniagua, S. M. A., Lau, E. S., Allen, N. B., Blaha, M. J., Gansevoort, R. T., et al. (2021). Age dependent associations of risk factors with heart failure: pooled population based cohort study. *BMJ* 372, n461. doi:10.1136/bmj.n461

Virani, S. S., Alonso, A., Benjamin, E. J., Bittencourt, M. S., Callaway, C. W., Carson, A. P., et al. (2020). Heart disease and stroke statistics-2020 update: a report from the American heart association. *Circulation* 141 (9), e139–e596. doi:10.1161/CIR.0000000000000757

Wang, J., and Sun, X. (2018). Clinical observation of modified Tongqiao Huoxue Decoction combined with Metoprolol tartrate tablet in the treatment of hypertensive heart disease. *Hebei J. TCM.* 40 (4), 566–568+627.

Wang, Z., and Wang, J. (2012). Observation on the curative effect of Qi-yin nourishing therapy on hypertensive heart disease with left ventricular diastolic dysfunction. *J. Emerg. Tradit. Chin. Med.* 21 (7), 1145–1146.

Wang, S., Niu, T., Qi, H., Geng, Q., Wang, J., Yang, X., et al. (2012). Clinical obsevation of therapy of traditional Chinese and western medicine on hypertensive heart disease. *Shanxi J. TCM.* 28 (5), 24–25.

Wang, D., Fan, G., Wang, Y., Liu, H., Wang, B., Dong, J., et al. (2013). Vascular reactivity screen of Chinese medicine danhong injection identifies Danshensu as a NO-independent but PGI2-mediated relaxation factor. *J. Cardiovasc. Pharmacol.* 62 (5), 457–465. doi:10.1097/FJC.0b013e3182a29657

Wei, Y., Wu, Y., Feng, K., Zhao, Y., Tao, R., Xu, H., et al. (2020). Astragaloside IV inhibits cardiac fibrosis via miR-135a-TRPM7-TGF-β/Smads pathway. *J. Ethnopharmacol.* 249, 112404. doi:10.1016/j.jep.2019.112404

WHO Traditional (2021). Complementary and integrative medicine. Available online at: https://www.who.int/health-topics/traditional-complementary-and-integrative-medicine#tab=tab_1 (Accessed May 22, 2021).

Wong, K. H., Li, G. Q., and Li, K. M. (2011). Kudzu root: traditional uses and potential medicinal benefits in diabetes and cardiovascular diseases. *J. Ethnopharmacol.* 134 (3), 584–607. doi:10.1016/j.jep.2011.02.001

Wright, J. W., Mizutani, S., and Harding, J. W. (2008). Pathways involved in the transition from hypertension to hypertrophy to heart failure. Treatment strategies. *Treat. Strateg. Heart Fail. Rev.* 13 (3), 367–375. doi:10.1007/s10741-007-9060-z

Xiong, X., Yang, X., Li, X., Yue, G., Xing, Y., and Cho, W. C. (2019). Efficacy and safety of Chinese herbal medicine for patients with postmenopausal hypertension: a systematic review and meta-analysis. *Pharmacol. Res.* 141, 481–500. doi:10.1016/j.phrs.2019.01.018

Yang, W., and Zhou, S. (2002). Clinical observation on effect of Danxiong Tongluo decoction in treating patients of hypertensive heart disease complicated with left ventricle diastolic malfunction. *Chin. J. Integr. Tradit. West. Med.* 22 (11), 819–821.

Yang, B., Li, H., Qiao, Y., Zhou, Q., Chen, S., Yin, D., et al. (2019). Tetramethylpyrazine Attenuates the Endotheliotoxicity and the mitochondrial dysfunction by Doxorubicin via 14-3-3γ/Bcl-2. *Oxid. Med. Cell Longev.* 2019, 5820415. doi:10.1155/2019/5820415

Yao, Y., Lu, Q., Hu, Z., Yu, Y., Chen, Q., and Wang, Q. K. (2017). A non-canonical pathway regulates ER stress signaling and blocks ER stress-induced apoptosis and heart failure. *Nat. Commun.* 8 (1), 133. doi:10.1038/s41467-017-00171-w

Ye, X. Y., Song, H., and Lu, C. Z. (2008). Effect of puerarin injection on the mRNA expressions of AT1 and ACE2 in spontaneous hypertension rats. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 28 (09), 824–827.

Yousefsani, B. S., Jamshidi, A., and Dadmehr, M. (2021). Herbal medicine in cardiovascular medicine: a discussion of herbal medications described by the Persian physician, Avicenna. *Eur. Heart J.* 42 (32), 3037–3039. doi:10.1093/eurheartj/ehab053

Yuan, C. (2018). Analysis of the curative effect of integrated Chinese and Western medicine on hypertensive heart disease. *Inn. Mong. J. Tradit. Chin. Med.* 37, 41–42.

Zhang, H. (2013). Clinical analysis of 68 cases of hypertensive heart disease treated by integrated Chinese and Western medicine. *Mod. Diagn. Treat.* 24 (13), 2923–2924.

Zhang, G., Liu, J., Gao, M., Kong, W., Zhao, Q., Shi, L., et al. (2020). Tracing the edible and medicinal plant Pueraria Montana and its products in the Marketplace Yields subspecies level distinction using DNA Barcoding and DNA metabarcoding. *Front. Pharmacol.* 20, 336. doi:10.3389/fphar.2020.00336

Zhang, Q., Shao, W., Xiao, Y., Wang, Y., Zhang, J., and Ao, M. (2022). Chinese herbal medicine formula combined with calcium antagonist in the treatment of hypertension: a systematic review and meta-analysis. *Clin. Exp. Hypertens.* 44 (22), 181–190. doi:10.1080/10641963.2021.2013491

Zhao, Q. (2022). Clinical analysis on the treatment of hypertensive heart disease by combining metoprolol tartrate Tablets with jiaweitongqiaohuoxue decoction. *World J. Complex Med.* 8 (12), 136–139.

Zhu, Y., Fan, M., Fan, R., Yao, W., Deng, Z., Tian, Z., et al. (2019). Effect of Yifengyangtongluo prescription on the improvement of traditional Chinese medicine syndrome and heart function of hypertensive heart disease with Yang deficiency and collateral-blocking type. *Chin. J. Tradit. Med. Sci. Technol.* 26 (01), 54–55.

Zuo, H. L., Linghu, K. G., Wang, Y. L., Liu, K. M., Gao, Y., Yu, H., et al. (2020). Interactions of antithrombotic herbal medicines with Western cardiovascular drugs. *Pharmacol. Res.* 159, 104963. doi:10.1016/j.phrs.2020.104963

Glossary

ACE2	angiotensin-converting enzyme 2
ASP	Astragalus polysaccharides
AT1	angiotensin Ⅱ type 1 receptor
BNP	B-type natriuretic peptide
BP	blood pressure
C	the control group
CI	confidence interval
CNKI	China National Knowledge Infrastructure
CO	cardiac output
DBP	diastolic blood pressure
E/A	transmitral peak early diastolic velocity (E)/peak late diastolic velocity (A)
GDT	Guideline Development Tool
GRADE	Grading of Recommendations Assessment Development and Evaluation
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HHD	hypertensive heart disease
HM	herbal medicine
IVSTD	interventricular septum thickness in diastole
LV	left ventricular
LVEDD	left ventricular end-diastolic diameter
LVEF	left ventricular ejection fraction
LVESD	left ventricular end-systolic diameter
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
MD	mean difference
NR	not reported
NYHA	New York Heart Association
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RAAS	renin-angiotensin-aldosterone system
RCTs	randomized controlled trials
RR	risk ratio
SBP	systolic blood pressure
SinoMed	Chinese Biomedical Database
SMD	standardized mean difference
T	the TCM group
TCM	traditional Chinese medicine
VIP	Chinese Scientific Journal Database (Chinese VIP Information)
WHO	World Health Organization
WM	Western medicine

Frontiers in Pharmacology

Explores the interactions between chemicals and living beings

The most cited journal in its field, which advances access to pharmacological discoveries to prevent and treat human disease.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact