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Salvianolic acid B: a promising cardioprotective agent

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Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] is a core herb in traditional Chinese medicine widely used for treating cardiovascular diseases (CVD). Its key bioactive compound, salvianolic acid B (SalB), has emerged as a promising therapeutic agent for CVD. Modern pharmacological studies have demonstrated that SalB exerts comprehensive cardioprotective effects through multiple mechanisms, including antioxidant and anti-inflammatory activities, induction of mitochondrial autophagy, enhancement of endothelial function, anti-fibrotic actions, and improvement of hemorheology. These properties underscore its significant value in both the prevention and treatment of CVD. However, current research on SalB in the context of CVD remains relatively fragmented. To address this gap, this review systematically consolidates existing research findings on SalB in the cardiovascular field, providing an in-depth analysis of its sources, pharmacological mechanisms, efficacy characteristics, compatibility strategies, and dosage form optimization. Furthermore, by integrating both preclinical and clinical data, this review comprehensively evaluates the safety and efficacy of SalB, aiming to offer theoretical support and clear research directions to facilitate the substantive transformation of this traditional bioactive compound into a modern CVD therapeutic drug.

KEYWORDS

polyphenols, salvianolic acid B, cardiovascular diseases, CVD, signaling pathways

1 Introduction

Salvia miltiorrhiza Bunge [Lamiaceae; Salviae miltiorrhizae radix et rhizoma] is widely used in clinical practice for its therapeutic effects, including coronary artery dilation, anti-myocardial ischemia, microcirculatory improvement, reduction of myocardial oxygen consumption, enhancement of cardiac function, and modulation of blood pressure, lipid levels, anticoagulation, and thrombosis, along with liver protection and immune regulation (1–3). Salvianolic acid B (SalB), the primary active compound in *S. miltiorrhiza*, has shown significant potential in the prevention and treatment of cardiovascular diseases (CVD) owing to its diverse pharmacological properties.

SalB demonstrates a broad spectrum of biological activities, including antioxidant, anti-inflammatory, anti-thrombotic, anti-apoptotic, anti-aging, and vascular and mitochondrial

protection (4–6), establishing it as a central focus in CVD research. Numerous studies have emphasized SalB's ability to neutralize reactive oxygen species, thereby reducing oxidative stress-induced cellular damage (7–9), which is critical for CVD prevention. Moreover, SalB inhibits platelet aggregation and thrombosis (10–12), playing a key role in the prevention of acute cardiovascular events such as myocardial infarction and stroke. Its multi-target mechanism of action further supports its broad applicability in treating cardiovascular conditions. Additionally, its natural origin and low toxicity make SalB a promising candidate for long-term adjuvant therapy, positioning it as a potential cardioprotective agent.

Currently, *S. miltiorrhiza* injection and salvianolate are extensively used in clinical practice for the treatment of coronary heart disease, angina, cerebral infarction, and related liver, kidney, and lung disorders, with SalB as the primary active component. However, a monomeric preparation of SalB has yet to be developed, limiting the full utilization of its medicinal potential. This review systematically examines the sources, limitations, and pharmacological mechanisms of SalB, providing a comprehensive summary of recent advancements in CVD research, drug compatibility, and the latest developments in formulation design and clinical studies. The review aims to provide theoretical support and practical guidance for the clinical translation of SalB, addressing existing research fragmentation and promoting its transformation into a modern cardiovascular therapeutic agent. Furthermore, the in-depth analysis of SalB's pharmacological characteristics and mechanisms of action presented here serves as a valuable template for future pharmaceutical chemistry research, paving the way for the development of novel structural drugs with enhanced efficacy, reduced toxicity, and improved pharmacokinetic properties.

Abbreviations: MAPK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; PTCH1, Patched1; Hh, Hedgehog; CD36, Cluster of differentiation 36; PI3K/AKT, Phosphatidylinositol 3-kinases/protein kinase B; FGF19, Fibroblast growth factor 19; FGFR4, Fibroblast growth factor receptor 4; EZH2, Enhancer of zeste homolog 2; PTEN, Phosphatase and tensin homolog; SIRT1, Sirtuin 1; PDGF-C, Platelet-derived growth factor C; PDGFR-α, Platelet-derived growth factor receptor alpha; AMPK, AMP-activated protein kinase; FOXO1, Factor Forkhead Box O1; HPSE, Heparinase; SDC1, Syndecan 1; TRIM8, Tripartite motif containing protein 8; GPX1, Glutathione peroxidase 1; GSK3β, Glycogen synthase kinase 3beta; Nrf2, Nuclear factor E2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; Nox4, NADPH oxidase 4; JNK, C-Jun N-terminal kinase; 4EBP1, 4E-binding protein 1; MKK3/6, Mitogen-activated protein kinase 3/6; ATF2, Activating transcription factor 2; MEK, Mitogen-activated protein kinase; ERK1/2, Extracellular regulated kinase 1/2; SOD2, Superoxide dismutase 2; TLR4, Toll-like receptor 4; MyD88, Myeloid differentiation primary response 88; NLRP3, NOD-like receptor protein 3; TRAF-6, Tumor necrosis factor receptor associated factor 6; RECK, REversion-inducing-Cysteine-rich protein with Kazal motifs; NDRG2, N-myc downstream-regulated gene 2; CREB, cAMP response element binding protein; BDNF, Brain-derived neurotrophic factor; SOX6, SRY-box transcription factor 6; GATA4, GATA binding protein 4; HMGB1, High mobility group box-1; Rac1, RAS-related C3 botulinum toxin substrate 1; BNIP3, Bcl-2/adenovirus E1B 19kDa interacting protein 3; ATG5, Autophagy related 5; RagD, RAG deficiency; AP-1, Activating protein-1; PAI-1, Plasminogen activator inhibitor-1.

2 The source and limitations of SalB

SalB ($C_{36}H_{30}O_{16}$) is a monomeric compound extracted from the dried roots of *S. miltiorrhiza* Bunge (13–15). As one of the most significant water-soluble components of *S. miltiorrhiza*, SalB is distinguished by its high concentration and potent bioactivity (16–18). Maximizing the extraction of SalB from *S. miltiorrhiza* is therefore critical for enhancing its medicinal value. Current methods for SalB separation and purification include water extraction, ethanol precipitation, macroporous resin adsorption, ultrasonic extraction, high-speed countercurrent chromatography, subcritical water extraction, and supercritical CO_2 extraction (19–21). However, the molecular structure of SalB, formed by the condensation of three molecules of danshensu and one molecule of caffeic acid, contains ester bonds and a five-membered ring, which makes it prone to ester hydrolysis and ring-opening reactions (22–24). Moreover, while the parent compound of SalB can be quantified in systemic circulation following oral administration, its absolute bioavailability is severely limited by factors such as intestinal instability, poor membrane permeability, and susceptibility to structural degradation, all of which restrict its systemic exposure (25–27). These challenges pose safety risks in clinical settings and hinder the use of SalB in oral liquid formulations. Therefore, to address the challenge of its low oral bioavailability, several strategies can be employed. First, modifications to dosage formsecati as nanoparticles, injectable hydrogels, and core-shell nanofibersles, enhance SalB's stability and delivery efficiency. Additionally, structural modifications to SalB itself represent an effective means to optimize its pharmacokinetic properties and improve bioavailability. Moreover, selecting high-quality *S. miltiorrhiza* varieties, can increase SalB extraction yields. Simultaneously, the entire extraction processionus raw material selection to extraction, purification, and storageation,y be systematically optimized, incorporating advanced technologies like supercritical CO2 extraction and subcritical water extraction. These innovations have significantly enhanced the therapeutic efficacy of SalB and paved the way for future drug development.

3 The pharmacological action pathway of SalB

SalB is a multi-target natural compound with remarkable pharmacological activity. By modulating various signaling pathways, it exerts biological effects such as anti-oxidation, anti-inflammation, anti-fibrosis, anti-cancer, cardiovascular protection, and neuroprotection. For instance, SalB regulates TGF-β1/Smad (28), MAPK/ERK (28), NF-κB/IκB (29), miR-152/PTCH1/Hh (30), CD36/PI3K/AKT (31), FGF19/FGFR4 (32), EZH2/PTEN/AKT (33), SIRT1-autophagy (34), PDGF-C/PDGFR-α (35), AMPK/

FOXO1/miR-148a-3p (36), and HPSE/SDC1 (37) signaling pathways to exert anti-fibrotic effects (Figure 1A). It also regulates TRIM8/GPX1 (38), AKT/GSK3β (39), Nrf2/Keap1 (40), Nrf2/Nox4 (41), PI3K/AKT (42), JNK/MAPK (43), AKT/mTOR/4EBP1 (44), MKK3/6-p38MAPK/ATF2 (44), MEK/ERK1/2 (45), miR-19a/SIRT1 (46), and SIRT3/FOXO1/SOD2 (47) signaling pathways for antioxidant effects (Figure 1B) and modulates NF-κB/NLRP3 (48), LTR4/MyD88/NLRP3 (49), MAPKs/NF-κB (50), CD36/PI3K/AKT (31), IL2/STAT5 (51), TLR4/MyD88/TRAF6 (52), miR-486a-5p/FOXO1 (53), and AKT/mTOR (54) signaling pathways to exert anti-inflammatory effects (Figure 1C). In addition, SalB regulates AKT/mTOR (55), Hippo/YAP (56), PI3K/AKT/HIF-1α (57), TGF-β1/Smad (58), mortalin/RECK/STAT3 (59), and NDRG2/PTEN/PI3K/AKT (60) signaling pathways to promote anti-cancer effects (Figure 1C) and exerts neuroprotective effects by modulating CD40/NF-κB (61), IGF-1/AKT (62), ERK/CREB/BDNF (63), and miRNA-1/MLCK (64) signaling pathways (Figure 1D). Furthermore, SalB confers myocardial protection by regulating circTRRAP/miR-214-3p/SOX6 (65), ERK1/2/GATA4 (66), Nrf2/ARE (67), PI3K/AKT/HMGB1 (68), and TLR4/NF-κ-B/TNF-α (69) signaling pathways (Figure 1D). Notably, the pharmacological effects of SalB are not isolated but interact through intricate signaling pathways in various pathological states, forming an extensive regulatory network. For example, SalB exerts anti-fibrotic effects via the CD36/PI3K/AKT pathway while simultaneously exhibiting antioxidant, anti-inflammatory, and anti-cancer effects through the AKT/mTOR pathway, thereby establishing a multi-layered regulatory mechanism. Moreover, SalB synergistically inhibits oxidative stress and inflammation through the Nrf2/NLRP3 and NF-κB/NLRP3 pathways. This multi-pathway synergy significantly enhances SalB's therapeutic potential, offering a unique advantage in treating complex diseases.

4 The therapeutic effect of SalB on CVD

Various preparations derived from *S. miltiorrhiza* are currently widely used in clinical practice, including *S. miltiorrhiza* injection, oral liquids, tablets, compound granules, and *S. miltiorrhiza*-ligustrazine injection, all of which primarily contain active components from *S. miltiorrhiza*. Additionally, the *S. miltiorrhiza* extract tanshinone IIA has been developed into a monomeric preparation—sodium tanshinone IIA sulfonate injection—used clinically as an adjunct therapy for coronary heart disease, angina pectoris, and myocardial infarction (MI). Furthermore, preparations containing salvianolic acids, such as salvianolic acids for injection and salvianolate for injection, are employed to

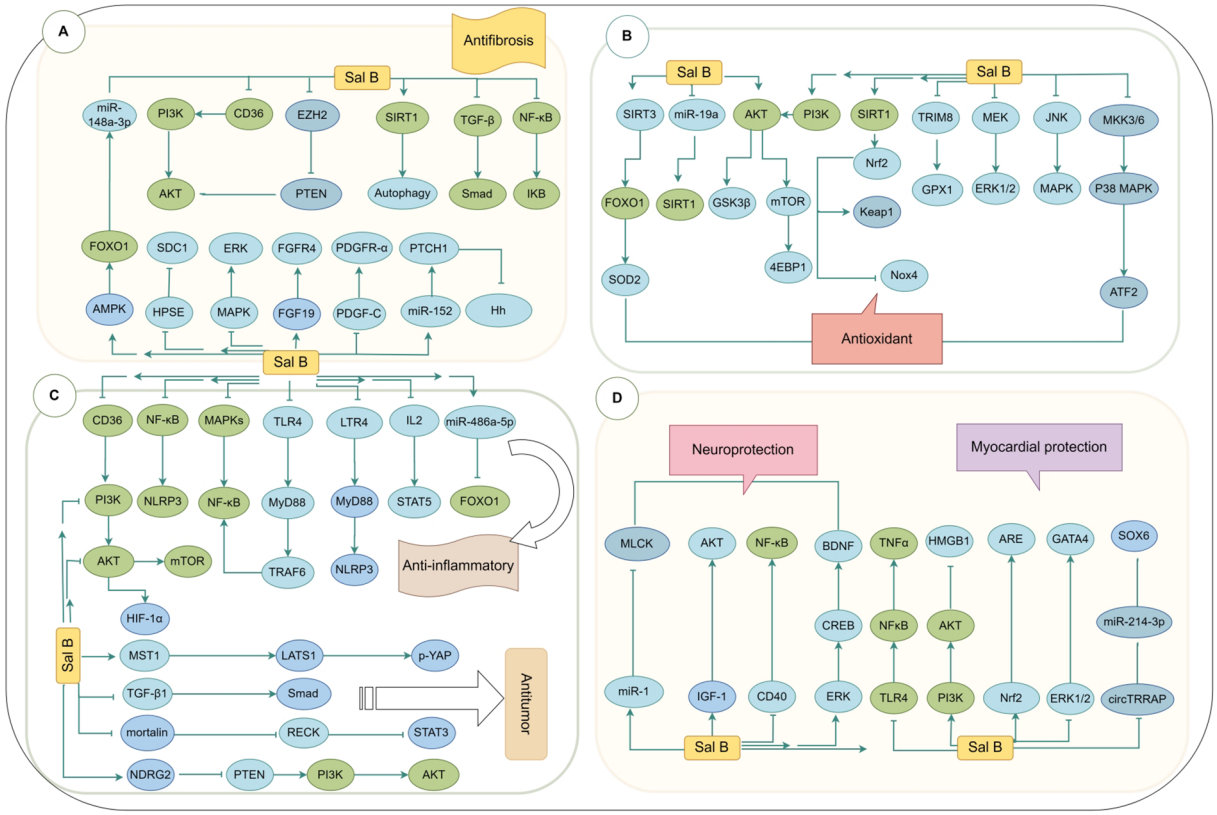

FIGURE 1
The pharmacological action pathway of SalB. **(A)** The mechanism of SalB in inhibiting fibrosis. **(B)** The mechanism by which SalB alleviates ROS-induced injury. **(C)** The mechanism of SalB's anti-inflammatory and anti-tumor effects. **(D)** The mechanism by which SalB regulates neuronal function and myocardial injury.

promote blood circulation and alleviate collateral obstruction, treating conditions like mild to moderate cerebral infarction and stable angina pectoris in coronary heart disease. However, there are currently no clinical applications for SalB, a primary monomer component of salvianolic acids, in the treatment of cardiovascular and cerebrovascular diseases, with related research still largely in the basic research phase.

4.1 Atherosclerosis

Atherosclerosis is closely linked to vascular endothelial dysfunction and inflammation (70–72). SalB alleviates inflammation and thrombosis by inhibiting the activation of the TNF-α-induced NF-κB/NLRP3 pathway and platelet activation (48, 73–75). Additionally, SalB protects blood vessels by reducing lipid accumulation in the vessel walls and inhibiting VEGF-induced vascular hyperpermeability, which prevents the uptake of 125I-LDL and thereby slows the progression of atherosclerosis (76–78). Furthermore, SalB safeguards endothelial cells by inhibiting arginase activity and the activation of Piezo1 (79, 80). It also prevents NLRP3 inflammasome activation and pyroptosis triggered by endoplasmic reticulum (ER) stress through the suppression of the AMPK/FOXO4/KLF4 and Syndecan-4/Rac1/ATF2 signaling pathways, effectively protecting endothelial progenitor cells from damage (81). Additionally, in LPS-induced human aortic smooth muscle cells and ApoE$^{-/-}$ mice, SalB inhibited the expression of COX-2, MMP-2, and MMP-9 both *in vitro* and *in vivo* (82), suggesting that SalB may slow the progression of atherosclerosis through its anti-inflammatory effects and by decreasing vascular matrix degradation. LDL oxidation exacerbates inflammation within the vessel wall and promotes foam cell formation, accelerating atherosclerosis. As an antioxidant, SalB inhibits LDL oxidation and reduces the associated inflammatory response by blocking JAK/STAT1 activation induced by IFN-γ (83, 84). Furthermore, CD36, a high-affinity receptor for oxidized LDL (ox-LDL), is widely expressed in various cell types and plays a critical role in lipid metabolism, inflammation, and atherosclerosis (85–87). Previous studies have demonstrated that SalB effectively inhibits the binding of CD36 to its ligand, thereby mitigating its detrimental effects in atherosclerosis and inflammation (88, 89).

SalB also exerts regulatory effects on dendritic cells, macrophages, and pericytes in the context of atherosclerosis. Additionally, SalB interferes with the maturation process of dendritic cells by activating PPARγ, thus reducing their ability to stimulate immune responses (90). It also effectively inhibits inflammation and autophagy dysfunction in LDLR$^{-/-}$ mice and RAW264.7 cells by regulating the MAPKs/NF-κB and AKT/mTOR signaling pathways, reducing the progression of atherosclerosis (50, 91). Additionally, by inhibiting the YAP/TAZ/JNK signaling pathway, SalB reduces the abnormal proliferation of pericytes and the release of inflammatory factors, offering a novel intervention strategy for preventing and treating atherosclerosis (92). The protective mechanism of SalB on atherosclerosis is summarized in Figure 2.

In summary, SalB effectively mitigates multiple pathological aspects of atherosclerosis by modulating mechanisms in endothelial

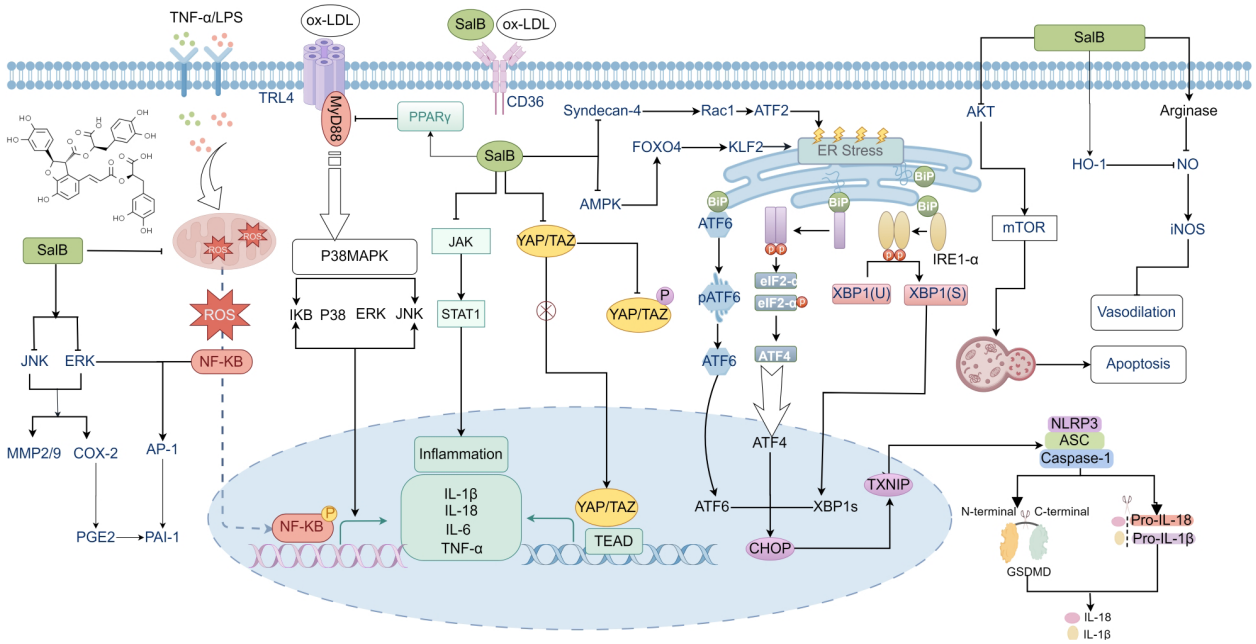

FIGURE 2
The protective mechanism of SalB against atherosclerosis (AS). SalB ameliorates AS by modulating multiple signaling pathways, including ERK/JNK/MMP-9/2, ERK/JNK/COX-2/PGE2, NF-κB/ERK/AP-1/PAI-1, PPARγ/TLR4/MyD88/p38MAPK, JAK/STAT1, YAP/TAZ/JNK, Syndecan-4/Rac1/ATF2, AMPK/FOXO4/KLF2, AKT/mTOR, and HO-1/NO/iNOS axes.

cells, macrophages, dendritic cells, pericytes, and immune responses. Its ability to inhibit inflammation, reduce lipid deposition, prevent vascular fibrosis, and enhance endothelial function provides a strong scientific foundation for its potential as a therapeutic agent in the treatment of atherosclerosis.

4.2 MI

In 2008, He et al. first reported that SalB exhibited myocardial protection in mice with MI, though these findings were later retracted (93). However, research into SalB's protective effects against MI continued, with significant advancements in subsequent years. In 2009, Tan et al. demonstrated that pre-treatment of endogenous precursor cells (EPCs) with SalB, followed by transplantation alongside bone marrow mesenchymal stem cells (BMSCs) into the ischemic myocardium, resulted in notable improvements, suggesting SalB's protective role in MI (94). In 2010, Jiang et al. identified SalB as a competitive inhibitor of matrix metalloproteinase-9 (MMP-9), which effectively reduced ischemic myocardial fibrosis, further supporting its myocardial protective effects (95). Zhao et al. (2012) confirmed Tan et al.'s findings, showing that SalB promoted the expansion of EPCs, improved the ischemic microenvironment, and enhanced BMSC survival and differentiation into cardiomyocytes (96). In 2014, Han et al. discovered that SalB's protective effect in MI was linked to the promotion of mesenchymal stem cell (MSC) differentiation into endothelial cells, rather than cardiomyocytes (97). These studies collectively suggest that SalB's myocardial protection is associated with the differentiation of EPCs, BMSCs, and MSCs. Further research has elucidated the mechanisms underlying SalB's protection against MI, including its role in promoting nitric oxide (NO) production, autophagy, angiogenesis, and inhibiting the NLRP3 inflammasome, apoptosis, and ferroptosis (98–103). The compatibility of traditional Chinese medicines has also demonstrated therapeutic advantages in clinical settings, with early studies exploring SalB's potential in MI treatment. For example, Deng et al. found that combining SalB with ginsenoside Rg1 in a 2:5 ratio improved cardiac contractility in MI rats (104). To address the challenge of SalB's low bioavailability in MI treatment, various drug carriers have been developed for more effective delivery. Qiu et al. created lipid-polymer mixed nanoparticles (LPNs) for co-delivery of SalB and panax notoginseng saponins (PNS), modified with arginyl-glycyl-aspartic acid (RGD) to form RGD-S/P-LPNs nanoparticles (105). These nanoparticles exhibited excellent serum stability and sustained drug release, significantly enhancing the therapeutic effect on MI *in vivo* (105). Shoba et al. developed a core-shell nanofiber system designed for phased delivery, releasing SalB from the core and magnesium L-ascorbic acid 2-phosphate (MAAP) from the shell, providing an effective vector for MI treatment (106). Chen et al. designed an elastin-mimicking peptide hydrogel (EMH) for delivering SalB-loaded dopamine nanoparticles (SalB-PDA), forming a SalB-PDA/EMH injectable peptide hydrogel with self-healing and slow-release properties (107). This hydrogel has been shown to inhibit ventricular remodeling and promote angiogenesis, offering a novel approach to MI treatment (107). These innovative drug carriers not only enhance SalB's efficacy but also open new possibilities for the treatment of MI and related diseases. In summary, the core mechanisms of SalB's protection in MI primarily involve modulating stem cell behavior, enhancing angiogenesis, and suppressing maladaptive inflammatory responses and cell death pathways. The above content is summarized in Figure 3.

4.3 Myocardial ischemia-reperfusion injury (MI/RI)

In 2011, Qiao et al. investigated the effects of the ethanol extract of *S. miltiorrhiza* Bunge on MI/RI and found that SalB, a key component of the extract, exhibited protective effects, particularly in preventing MI/R-induced oxidative damage in the myocardium (108). Subsequent studies by Qiao et al. and Gao et al. further confirmed SalB's myocardial protective effect in MI/RI, showing significant improvements in cardiac function and tissue integrity (109, 110). Further investigations revealed that SalB's protective mechanisms in MI/R were linked to enhancing cardiac contractility, scavenging reactive oxygen species, reducing inflammation, lipid peroxidation, apoptosis, and ferroptosis, and inhibiting autophagy (111–113). Key regulatory mechanisms involved the activation of the PI3K/AKT and SIRT1/MAPK pathways, alongside inhibition of the circTRRAP/miR-214-3p/SOX6 and TRIM8/GPX1 axes (38, 65, 68, 114) (Figure 4). Additionally, Deng et al. demonstrated that combining SalB with ginsenoside Rg1 in a 2:5 ratio could protect against MI and improve MI/RI outcomes (104, 115). Overall, the core mechanisms by which SalB protects against MI/RI—focused on antioxidation, anti-inflammation, and regulation of various cell death pathways—overlap with its effects in MI, underscoring its broad role in counteracting ischemic damage. However, SalB's role in MI/RI appears to emphasize mitigating reperfusion-specific injuries, such as the acute oxidative burst, distinguishing it from its action in MI alone.

4.4 Cardiac hypertrophy

Studies on SalB's therapeutic effects in cardiac hypertrophy remain limited, but some important findings have emerged. Liu et al. demonstrated that SalB effectively blocked the hypertrophic response in neonatal rat cardiomyocytes exposed to angiotensin II (116). The anti-hypertrophic effect of SalB was linked to its inhibition of poly (ADP-ribose) polymerase-1 (PARP-1), preventing NAD^+ depletion in cells (116). This inhibition occurred through SalB's suppression of the antioxidant functions of NOX2 and NOX4 (116). Further research by Yu et al. using a transverse aortic constriction (TAC)-induced cardiac hypertrophy model revealed that SalB provided superior protection against myocardial damage compared to metoprolol (66). Moreover, Ma et al. suggested that SalB may offer advantages over carvedilol in

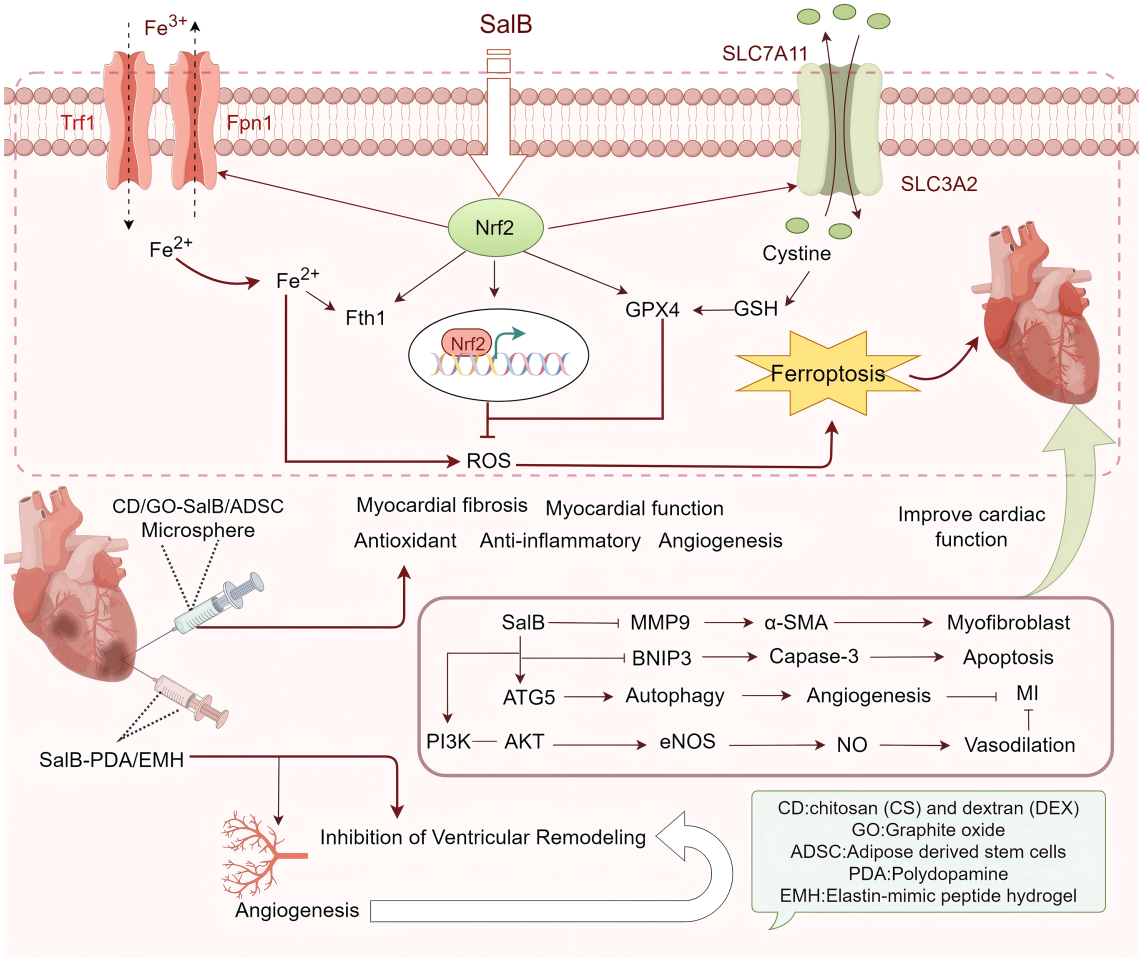

FIGURE 3
Protective mechanism of SalB against myocardial infarction (MI). It can play a significant myocardial protective role in MI by regulating Nrf2/ferroptosis, MMP9/α-SMA, BNIP3/caspase3, PI3K/AKT, ATG5/autophagy signaling pathways.

treating left ventricular hypertrophy, as SalB inhibits both the ERK signaling pathway and the β-adrenergic receptor, whereas carvedilol acts solely as a β-receptor blocker (117). These findings highlight SalB's potential as a novel therapeutic agent for cardiac hypertrophy.

4.5 Diabetic cardiomyopathy (DCM)

DCM, a condition commonly associated with diabetes mellitus, is characterized by structural and functional abnormalities in the myocardium (118–120). SalB exerts significant protective effects against DCM. Specifically, Li et al. found that SalB alleviates diabetic myocardial fibrosis by inhibiting insulin-like growth factor binding protein 3 (IGFBP3) and promoting angiogenesis (121). Furthermore, Luo et al. demonstrated that SalB inhibits the TGF-β1 signaling pathway by upregulating Smad7 expression, which reduces myocardial fibrosis and inflammatory cell infiltration, effectively alleviating diabetic myocardial damage (122). In summary, SalB exhibits substantial therapeutic potential in mitigating myocardial pathological damage caused by diabetes through multiple mechanisms, including anti-fibrosis, anti-inflammation, and pro-angiogenesis, supporting its use in treating DCM.

4.6 Septic cardiomyopathy (SCM)

SCM is a systemic inflammatory response triggered by infection that impairs heart function (123–125). Due to its potent anti-inflammatory and antioxidant properties, SalB has shown protective effects against myocardial damage caused by sepsis. Chen et al. found that SalB enhances the mitochondrial unfolded protein response (UPRmt) by activating transcription factor 5 (ATF5), restoring protein folding balance in mitochondria and alleviating mitochondrial damage induced by sepsis (126). The core mechanism of SalB in SCM revolves around mitochondrial protection through ATF5-mediated UPRmt activation, a pathway distinct from its roles in fibrosis inhibition or stem cell regulation observed in conditions like MI, cardiac hypertrophy, or DCM. While SalB's anti-inflammatory and antioxidant effects are common across various cardiac pathologies, its specific

engagement with mitochondrial quality control in SCM underscores its capacity to address disease-specific mechanisms driven by severe infection and metabolic stress. This mechanism forms a theoretical foundation for the clinical application of SalB in treating SCM, offering new approaches for managing this condition.

4.7 Uremic cardiomyopathy (UC)

UC, a heart disease associated with renal failure, is often characterized by myocardial fibrosis, declining cardiac function, and elevated oxidative stress (127–129). Ma et al. developed a rat model of UC to study the effects of SalB on cardiac function, ventricular hypertrophy, myocardial fibrosis, and inflammatory markers at various time points (130). Their findings indicated that SalB treatment improved cardiac function, reduced myocardial fibrosis, and alleviated inflammation in UC rats, thereby delaying disease progression. The cardioprotective effect of SalB in UC primarily results from its anti-fibrotic and anti-inflammatory properties, mechanisms that align with its actions in other cardiovascular conditions, such as DCM and cardiac hypertrophy.

4.8 Doxorubicin-induced cardiomyopathy (DIC)

Doxorubicin (DOX), a widely used chemotherapeutic agent, is known for its cardiotoxicity, which induces oxidative stress, inflammation, and ER stress in cardiomyocytes, ultimately leading to cardiomyocyte apoptosis and heart injury (131–133). SalB mitigates ER stress by activating the PI3K/AKT signaling pathway, thereby inhibiting DOX-induced cardiomyocyte apoptosis (134). Additionally, SalB pretreatment prevents calcium overload and ER stress caused by DOX, with its protective mechanism involving the inhibition of TRP channel subfamily members 3 (TRPC3) and 6 (TRPC6) expression (135). These findings confirm that SalB exerts its protective effects against DOX-induced cardiotoxicity primarily by regulating ER stress and calcium homeostasis, highlighting its potential clinical value in treating DIC.

4.9 Cisplatin-induced cardiac injury

Cisplatin, a widely used chemotherapeutic agent, is commonly linked to severe cardiotoxicity and oxidative stress, resulting in cardiac dysfunction (136–138). SalB effectively mitigates cisplatin-induced cardiac damage and oxidative stress, with its protective effect closely associated with the activation of the Nrf2 signaling pathway (67, 139). These findings establish Nrf2-mediated antioxidant pathway activation as the core mechanism through which SalB combats cisplatin-induced cardiotoxicity. This redox balance modulation differentiates its action from the calcium homeostasis regulation observed in DIC or the anti-fibrotic effects observed in DCM, highlighting SalB's ability to selectively target specific pathological triggers.

5 Research on the compatibility and dosage forms of SalB

To overcome the limitations of SalB, numerous strategies, including drug compatibility and dosage form modifications, have been explored. In CVD, combining SalB with ascorbic acid has been shown to enhance the differentiation of MSCs into cardiomyocyte-like cells mediated by valproic acid and 5-azacytidine (140). This combination offers a promising approach for stem cell-based cardiac regeneration therapy. Moreover, combining SalB with astragaloside IV or ginsenoside Re significantly reduces arterial plaque area and lipid deposition (141, 142). Furthermore, the combination of SalB and ginsenoside Rg1 provides notable protection for cardiac function in patients with subacute MI, and it synergistically improves stroke treatment outcomes (143–145). Importantly, studies have demonstrated that this combined regimen does not cause any abnormal changes in the tissue structure of the brain, heart, kidneys, liver, or lungs within seven days (146), ensuring the safety of the combination and providing strong support for its clinical application. Beyond CVD, the combined drug strategy of SalB has also been explored in treating cerebrovascular diseases, cancer, liver damage, kidney disease, and oral mucosal fibrosis (Figure 5).

In terms of dosage form research, innovative drug carrier systems have been developed in recent years to improve the oral bioavailability, targeted delivery, stability, and efficacy of SalB. Nanoparticles, as a key drug delivery platform, can enhance the therapeutic effects of SalB by improving stability, targeting, and absorption efficiency. For instance, Zhang et al. employed methoxypolyethylene glycol-chitosan (PCS)-derived nanoparticles to load SalB, enhancing its oral delivery capability and kidney-targeted distribution (147). Catechol-modified chitosan nanocarriers can also assemble SalB through coordination, enabling its targeted delivery to the kidneys and enhancing its anti-renal fibrosis effects (148). Moreover, the nanoparticle system developed by Grossi et al., capable of crossing the blood-brain barrier, efficiently delivers SalB to the central nervous system, improving its neuroprotective effects (149).

Liposomes have also been demonstrated to be effective as SalB drug delivery systems. Isacchi et al. developed SalB-loaded liposomes, which significantly improved the bioavailability and prolonged the pharmacodynamic effects of SalB (150), offering a new therapeutic option for treating neuropathic pain. Additionally, Shi et al. encapsulated SalB in liposomes modified with the cell-penetrating peptide TAT to enhance its skin repair potential (151).

In the development of composite scaffolds, Qin et al. used 3D bioprinting technology to create a SalB-sodium alginate-gelatin composite porous scaffold, which was applied to diabetic wounds. This scaffold was found to accelerate wound healing significantly (152). Similarly, Li et al. loaded SalB into chitosan microspheres, evenly distributing them in three dimensions and fixing them on

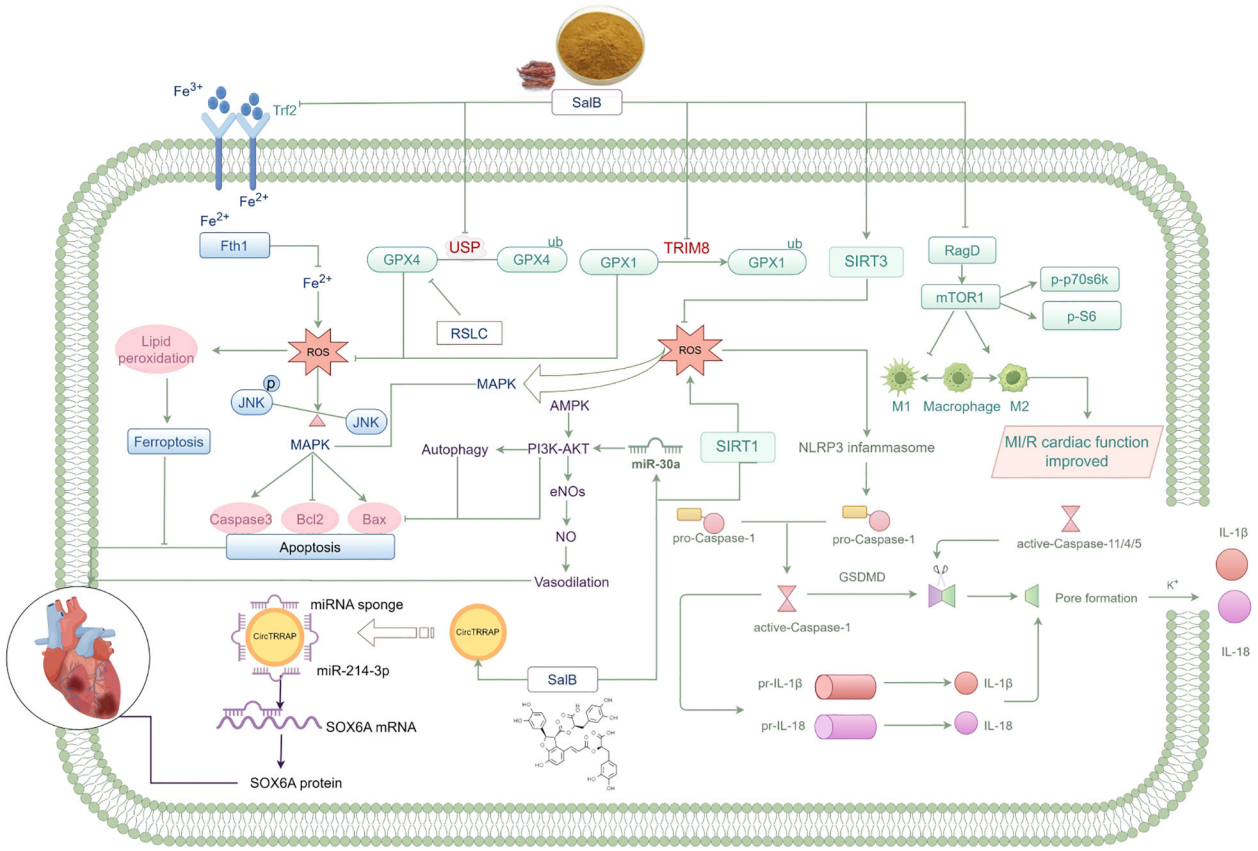

FIGURE 4
Protective mechanism of SalB on myocardial ischemia/reperfusion (MI/RI) injury. SalB confers cardioprotection against MI/RI by modulating the GPX4/ROS/ferroptosis, TRIM8/GPX1, SIRT3/ROS/NLRP3 inflammasome, SIRT1/ROS/MAPK, RagD/mTOR1, AMPK/PI3K/AKT/eNOS/NO, miR-30a/PI3K/AKT, and circTRRAP/miR-214-3p/SOX6A signaling axes, thereby attenuating oxidative stress, inflammation, apoptosis, and autophagic dysfunction while preserving myocardial function.

the surface of porous hydroxyapatite (HA) scaffolds, thus creating a new type of bone tissue engineering scaffold (153). This composite scaffold demonstrated significant effects in promoting cell proliferation, adhesion, and differentiation, highlighting its potential for bone tissue regeneration. Additionally, polylactic acid (PLA) and graphene oxide (GO) have been utilized as composite scaffolds for SalB, enabling sustained release of SalB to promote bone tissue regeneration (154).

Based on the drug-loading capabilities of hydrogels, Chen et al. developed a SalB-polydopamine nanoparticle/elastin-mimic peptide hydrogel with suitable mechanical strength and self-healing properties (107). This hydrogel facilitates myocardial tissue repair and regeneration by enabling the long-term release of SalB directly to the infarct area. In another approach, injectable hydrogels composed of hyaluronic acid and gelatin were designed to deliver SalB and vascular endothelial growth factor, promoting synergistic brain tissue repair (155).

Bioactive glass scaffolds have also been explored for SalB delivery. Wu et al. loaded SalB into a mesoporous bioactive glass scaffold (MBG) via physical adsorption, forming a SalB-MBG scaffold. This scaffold effectively sustained SalB release and significantly promoted new bone formation and angiogenesis in bone defect sites (156). Kan et al. developed SalB microporous osmotic pump controlled-release pellets (157), which exhibited excellent *in vitro* drug release performance and favorable *in vivo* pharmacokinetic properties, making them a promising option for treating CVD.

In conclusion, nanoparticles and liposomes improve the delivery efficiency and therapeutic efficacy of SalB by enhancing drug stability, targeting, and absorption. Composite scaffolds and hydrogels offer unique advantages for tissue repair and regeneration, thanks to their customizable and sustainable release properties. Additionally, innovative carrier materials, such as mesoporous bioactive glass scaffolds and controlled-release pellets, have expanded the potential applications of SalB, particularly in regenerative medicine and the treatment of CVD.

6 Preclinical and clinical research status

Preclinical studies have shown that SalB provides significant protective effects across multiple organs, including the heart, liver (158–160), brain (161–163), kidneys (164–166), and lungs (167–

169), indicating its broad therapeutic potential for treating cardiovascular, liver, renal, neurodegenerative, and pulmonary diseases. Notably, SalB's cardiovascular protective effects are strongly supported by extensive preclinical animal data, with some indications advancing to clinical trials (Table 1). For example, intravenous administration of SalB for angina pectoris and coronary artery disease has entered Phase I clinical trials (CTR20192236). Cheng et al. assessed the safety, tolerability, and pharmacokinetic profile of SalB in healthy subjects (170), revealing no serious adverse events across all dose groups, with favorable safety and tolerability (170), supporting its potential application in CVD. Additionally, SalB has shown promising results in other clinical settings. A study of 42 patients with oral submucous fibrosis reported that combining triamcinolone acetonide with SalB significantly improved mouth opening and reduced burning sensations, with no adverse effects observed (171). In another clinical trial involving 60 patients with chronic hepatitis B-related liver fibrosis, six months of oral SalB tablets significantly improved liver fibrosis markers without side effects (172). Furthermore, multiple patents covering SalB's extraction methods and therapeutic strategies for CVD further validate its clinical and methodological value (Table 2). In conclusion, SalB holds substantial promise for clinical translation in cardiovascular therapeutics. With growing clinical evidence, it may become a safe and effective treatment option, opening new pathways for patient care.

7 Conclusions and prospects

SalB, a polyphenolic compound extracted from *S. miltiorrhiza* Bunge, exhibits remarkable cardiovascular protective potential. Its multi-target mechanism includes a range of biological effects such as antioxidant, anti-inflammatory, anti-fibrotic, anti-thrombotic,

TABLE 1 Preclinical and clinical trial studies on the cardiovascular therapeutic effects of SalB.

Research category	Drug	Disease	Mode of administration	Target	Reference
Preclinical study	SalB	Atrial fbrillation	Tail vein injection	AMPK	(36)
Preclinical study	SalB	MI/RI	Intravenous injection	TRIM8	(38)
Preclinical study	SalB	MI/RI	Intravenous injection	GPX4	(43)
Preclinical study	SalB	Atherosclerosis	Intraperitoneal injection	NF-κB	(48)
Preclinical study	SalB	Atherosclerosis	Intraperitoneal injection	MAPKs	(50)
Preclinical study	SalB	TAC	Gavage	ERK1/2	(66)
Preclinical study	SalB	MI/RI	Intraperitoneal injection	PI3K	(68)
Preclinical study	SalB	MI	Tail vein injection	MMP-9	(95)
Preclinical study	SalB-MSC	MI	Spot injection	VEGF	(97)
Preclinical study	SalB	MI	Intraperitoneal injection	AMPK	(98)
Preclinical study	SalB	AMI	Intravenous injection	/	(99)
Preclinical study	SalB	AMI	Tail vein injection	SIRT1	(102)
Preclinical study	SalB	MI	Intraperitoneal injection	Nrf2	(103)
Preclinical study	SalB+ginsenoside Rg1 (60 mg/kg)	AMI	Gavage	/	(104)
Preclinical study	RGD-S/P-LPNs	AMI	Intravenous injection	/	(105)
Preclinical study	SalB-PDA/pre-EMH	MI	Intramuscular injection	/	(107)
Preclinical study	SalB	MI/RI	Gavage	/	(109)
Preclinical study	SalB	MI/RI	Perfusion	/	(110)
Preclinical study	SalB	MI/RI	Intravenous administration	/	(111)
Preclinical study	SalB	MI/RI	Gavage	RagD	(112)
Preclinical study	SalB+ginsenoside Rg1 (10 mg/kg)	MI/RI	Reperfusion time	/	(115)
Preclinical study	SalB	Diabetic cardiomyopathy	Intraperitoneal injection	IGFBP3	(121)

(Continued)

TABLE 1 Continued

Research category	Drug	Disease	Mode of administration	Target	Reference
Preclinical study	SalB	Diabetic cardiomyopathy	Gavage	Smad7	(122)
Preclinical study	SalB	Doxorubicin (DOX)-induced cardiotoxicity	Intravenous injection	TRPC3/6	(135)
Preclinical study	SalB	Septic cardiomyopathy	Intraperitoneal injection	ATF5	(126)
Preclinical study	SalB	Uremic cardiomyopathy	Intraperitoneal injection	/	(130)
Preclinical study	SalB	Cisplatin-induced cardiac injury	Gavage	Nrf2	(139)
Preclinical study	SalB	Atherosclerosis	Intraperitoneal injection	Piezo1	(80)
Preclinical study	SalB	Atherosclerosis	Per os	/	(83)
Preclinical study	SalB+Astragaloside IV	Atherosclerosis	Intraperitoneal injection	/	(141)
Preclinical study	SalB+ginsenoside Rg1 (30 mg/kg)	MI	Intraperitoneal injection	MMP-9	(143)
Preclinical study	SMND-309	MI	Tail vein injection	Bcl-2	(173)
Preclinical study	CD/GO-SalB/ADSC	AMI	Intramuscular injection	CD31	(174)
Preclinical study	SalB	MI/RI	Intravenous administration	SIRT3	(175)
Preclinical study	SalB	Hypertension	Gavage	AT1	(176)
Preclinical study	SalB	Portal hypertension	Perfusion	iNOS	(177)
Preclinical study	SalB	Portal Pressure	Gavage	RhoA	(178)
Preclinical study	SalB	Atherosclerosis	Per os	MMP-2/9	(179)
Phase I clinical trial	SalB	Angina pectoris; Coronary artery disease	Intravenous injection	/	CTR20192236

TABLE 2 The relevant patents of SalB in cardiovascular diseases.

Patent name	Publication number	Application	Publication date
Application of SalB in the preparation of protective and synergistic antitumor drugs for cardiotoxicity induced by arsenic trioxide	CN103230390B	Cardiotoxicity	2016-01-13
A time-delay controlled-release tablet for the treatment of coronary heart disease and its preparation method	CN109453132A	Coronary heart disease	2019-03-12
A drug composition for the treatment of myocardial injury in Kawasaki disease and its application	CN111617088A	Kawasaki disease myocardial injury	2020.09.04
SalB-supported 3D printing degrades intravascular stents	CN114470344A	Injured vessel	2022-05-13
SalB complex and its preparation and application	CN113082014B	Ischemic heart disease	2022-05-17
Application of SalB in the preparation of drugs for myocardial protection in patients with myocardial infarction during perioperative PCI	CN115998727A	Myocardial infarction	2023-04-25
Application of SalB in the preparation of drugs for diseases with lymphatic hypogenesis	CN117462529A	Dilated cardiomyopathy	2024-01-30
A long-acting sustained-release salvianolic acid B injectable hydrogel for heart failure treatment and its preparation method	CN115554235B	Heart failure	2023-08-25
Nickel-titanium alloy surface chitosan-SalB coating, preparation method and application thereof	CN117379602B	Thrombus	2024-03-15
SalB or total saponin of notoginseng and its application	CN117100733B	Lung cancer heart disease	2024-04-05
SalB is used to prepare drugs for the prevention and treatment of cardiotoxic-related diseases caused by PD-1/PD-L1 targeted inhibitors	CN118021786A	Cardiotoxicity	2024-05-14

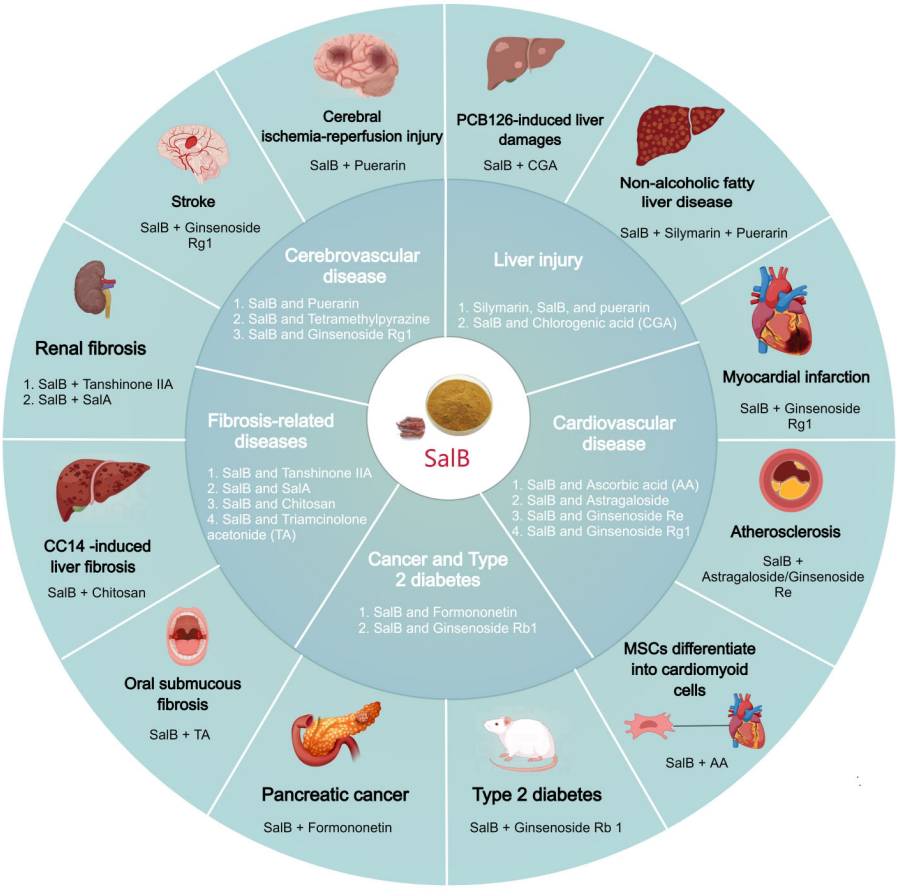

FIGURE 5
The combination therapy of SalB. SalB can be combined with ascorbic acid, astragaloside IV, ginsenoside Re, ginsenoside Rg1, puerarin, and tetramethylpyrazine for cardiocerebrovascular diseases; with puerarin and chlorogenic acid for hepatic injury; with tanshinone IIA, SalA, chitosan, and triamcinolone acetonide for fibrosis-related disorders; with formononetin for cancer; and with ginsenoside Rb1 for type 2 diabetes.

and anti-apoptotic activities, along with promoting angiogenesis, making it highly applicable for treating CVD such as MI, MI/R injury, DCM, drug-induced cardiomyopathy, and atherosclerosis. Notably, SalB monomer preparations (injection) have entered clinical trials for CVD, marking a shift from an "active ingredient" in traditional Chinese medicine formulations to a modern "single chemical drug," signifying a critical advancement in the modernization of traditional Chinese medicine. Therefore, SalB is well-positioned to become a key clinical treatment for CVD. Given this potential, future research should focus on several key areas: In basic research, efforts should be directed toward developing personalized treatment strategies based on SalB's multi-target mechanisms for various cardiovascular conditions. In applied research, optimizing drug carrier design and formulating new dosage forms is essential to improve SalB's stability, bioavailability, and clinical efficacy, with the aim of advancing SalB monomer preparations toward market release. In clinical translation, large-scale, multicenter trials are necessary to validate SalB's safety and efficacy while exploring potential combination therapies with other agents. In conclusion, with continued progress in basic research, drug development, and clinical translation, SalB—an agent with multiple mechanisms of action targeting diverse pathological processes—has the potential to become a mainstream clinical drug for CVD in the form of monomer preparations.

Author contributions

YS: Writing – original draft, Conceptualization. LZ: Validation, Writing – review & editing. SJ: Validation, Writing – review & editing. FS: Conceptualization, Validation, Writing – review & editing. XL: Conceptualization, Validation, Writing – review & editing.

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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.

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