



OPEN ACCESS

EDITED BY

Sushil Kumar Chaudhary,
SVKM's Narsee Moonjee Institute of
Management & Studies (NMIMS), India

REVIEWED BY

Jijun Li,
Shanghai Jiao Tong University, China
Nan Zhang,
School of Design, Shanghai Jiao Tong
University, China

*CORRESPONDENCE

Han Deng,
✉ denghan1234@163.com
Ning Weng,
✉ Wengning36@outlook.com

RECEIVED 12 December 2025

REVISED 27 February 2026

ACCEPTED 27 February 2026

PUBLISHED 20 March 2026

CITATION

Deng H, Li B, Mu Y, Xia W and Weng N
(2026) Molecular mechanisms and
therapeutic potential of natural products
and traditional Chinese medicine formulas
in ADHD: a review of preclinical evidence.
Front. Pharmacol. 17:1766222.
doi: 10.3389/fphar.2026.1766222

COPYRIGHT

© 2026 Deng, Li, Mu, Xia and Weng. This is
an open-access article distributed under
the terms of the [Creative Commons
Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use,
distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication
in this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Molecular mechanisms and therapeutic potential of natural products and traditional Chinese medicine formulas in ADHD: a review of preclinical evidence

Han Deng^{1*}, Bo Li¹, Yuze Mu², Weili Xia¹ and Ning Weng^{3*}

¹Shandong Provincial Key Medical and Health Laboratory of Shandong Mental Health Center, Shandong University, Jinan, Shandong, China, ²Department of Public Health, The First Affiliated Hospital of Shandong First Medical University, Jinan, Shandong, China, ³Department of Chinese Medicine, Shandong Mental Health Center, Shandong University, Jinan, China

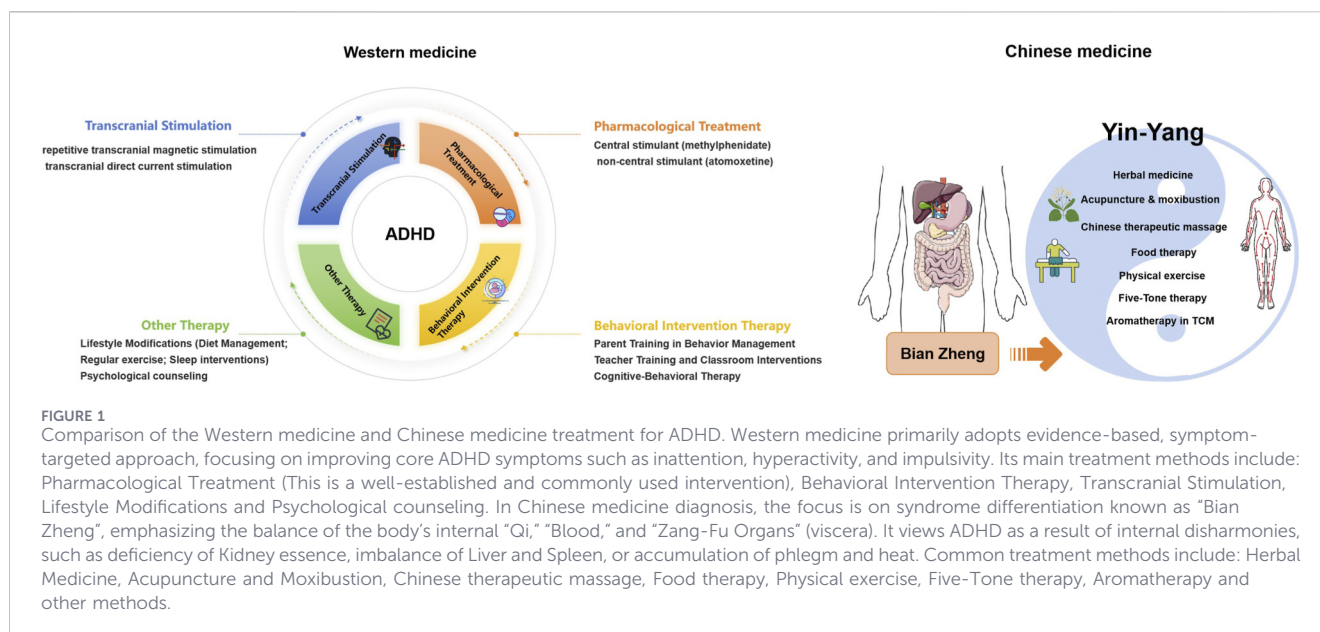
Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental condition marked by inattention, hyperactivity, and impulsivity. Although current pharmacotherapies are effective for many patients, their clinical utility is frequently limited by insufficient efficacy, adverse effects, and concerns regarding long-term tolerability or patient acceptance. Accordingly, increasing research attention has been directed toward the therapeutic potential of traditional Chinese medicine (TCM) formulas and other natural products, which are thought to offer multi-target mechanisms and holistic regulatory effects. This review provides a critical synthesis of recent preclinical studies, focusing on the molecular mechanisms by which specific TCM formulas and natural products ameliorate ADHD-like behaviors. We delineate these actions across several biological scales, including the modulation of catecholamine neurotransmission, enhancement of neurodevelopment and synaptic plasticity, attenuation of neuroinflammation, and regulation of the gut–brain axis. In addition, this review highlights current limitations, including the overreliance on single animal models and the insufficient integration of pharmacokinetic and translational data. Finally, we discuss future research directions and aim to provide new perspectives for the development of natural product-derived interventions in ADHD management.

KEYWORDS

attention-deficit/hyperactivity disorder, gut–brain axis, molecular mechanisms, natural products, neurotransmitters, synaptic plasticity, traditional Chinese medicine formulas

1 Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsive behavior. Symptoms typically manifest in early childhood and may persist into adulthood (Koirala et al., 2024). The global prevalence among children is estimated to range from 5% to 10%, with a significantly higher diagnostic rate in males than in females (Mowlem et al., 2019). Current diagnostic criteria are based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD), which define ADHD as a chronic pattern of symptoms present in multiple settings and not better explained by other disorders (Drechsler et al., 2020). Standard treatment guidelines advocate for



psychoeducation, behavioral interventions, and pharmacotherapy with either stimulant or non-stimulant medications as the primary approaches (Popit et al., 2024; Posner et al., 2020; Solmi et al., 2025). Although these drugs are effective for many patients, their use may be limited by incomplete response, adverse effects and concerns about long-term safety or acceptability among families (Faraone et al., 2015; Goetz et al., 2007; Kotsopoulos and Spivak, 2001), highlighting the need for alternative therapeutic strategies.

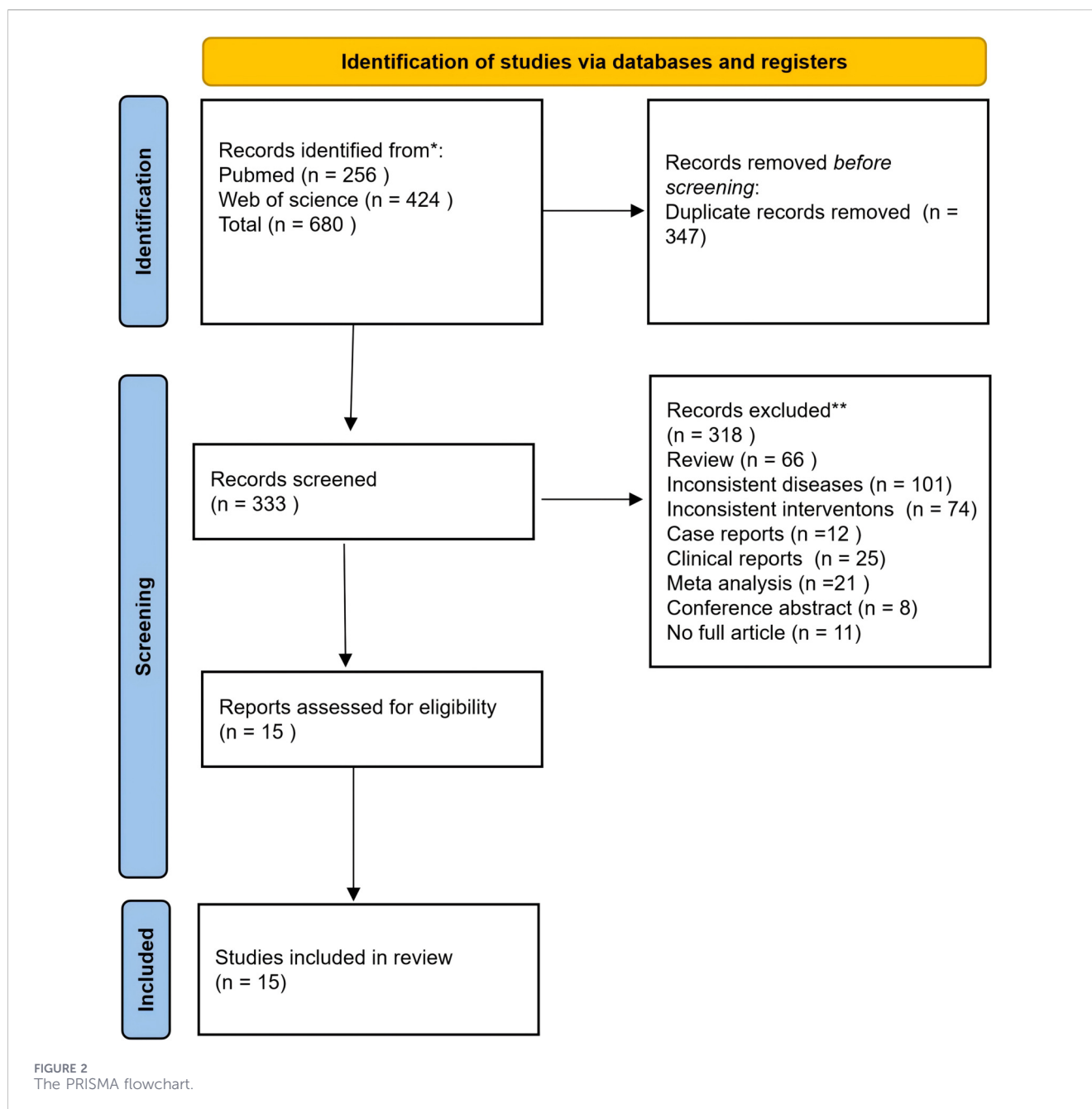
Traditional Chinese medicine (TCM) is a widely practiced system of medicine that posits human health is characterized by the dual forces of "yin" and "yang," along with five organ systems. "Yin" represents calmness and tranquility, while "yang" symbolizes activity and impatience. The balance of these forces and organ systems is essential for physical and mental health, whereas imbalance can lead to conditions such as ADHD (Figure 1). Based on its clinical characteristics, ADHD is classified into the categories of "restlessness," "deficiency and irritability" or "amnesia". Its etiology primarily involves congenital deficiency, acquired improper care, trauma, illness, emotional disorders and other factors. Pathologically, it is primarily associated with dysfunction of the heart, liver, spleen, and kidney. Deficiency of both the heart and spleen leads to a loss of nourishment to the mind, resulting in inattention; exuberant liver yang can cause emotional fluctuations and impulsive behavior; liver and kidney yin deficiency often leads to insufficient essence and blood, resulting in hyperactivity; phlegm-heat disturbing the heart, arising from internal phlegm dampness, leads to restlessness and distractibility. Additionally, congenital insufficiency, such as kidney essence deficiency, may also be a contributing factor. In terms of treatment, TCM emphasizes syndrome differentiation to improve symptoms by regulating organ function and harmonizing qi and blood (Yuan H. et al., 2018). Depending on the source of the imbalance, various herbal formulations can be developed to address deficiencies and restore harmony (Liang et al., 2020).

TCM, which includes herbal medicine, acupuncture, dietary therapy, and physical exercise, is widely used for the treatment of

various diseases, with herbal medicine being the most commonly applied modality, as illustrated in Figure 1 (Guo et al., 2024; Li W. et al., 2023). Modern neurobiology conceptualizes ADHD as a heterogeneous disorder involving dysregulation of catecholamine neurotransmission, alterations in cortical and subcortical development, disrupted synaptic plasticity and connectivity, and low-grade neuroinflammatory and metabolic changes (Posner et al., 2020). Preclinical studies in animal models have demonstrated that botanical formulations and their bioactive metabolites regulate dopamine and norepinephrine pathways, enhance neuroprotective signals, improve synaptic structure, reduce inflammatory cascades and oxidative stress, and modulate the gut-brain axis (Liang et al., 2020; Ni et al., 2015; Yuan H. et al., 2018). These findings suggest that such multi-target mechanisms may effectively address the complex symptomatology of ADHD. However, the existing evidence remains fragmented across disparate metabolites and models, and a systematic synthesis of these mechanistic insights is lacking. Therefore, this review aims to summarize preclinical studies of TCM formulas, single botanical drugs, and their active metabolites in the treatment of ADHD. By elucidating their complex molecular mechanisms of action, this review aims to provide a rigorous scientific basis for their future translation into clinical applications.

2 Literature search and methods

Although this manuscript was designed as a narrative rather than a systematic review, a structured literature search was undertaken to enhance completeness and transparency. We searched PubMed and Web of Science from database inception to February 2026. We used the following keywords to search for relevant articles ("Attention-Deficit/Hyperactivity Disorder" OR "ADHD" OR "hyperactivity") AND ("botanical drug" OR "herbal medicine" OR "herbal formula" OR "natural



product” OR “metabolite”). Articles were restricted to those with full text available in English. The inclusion criteria focused on preclinical studies (*in vivo* and *in vitro*) investigating the modulation of ADHD-related pathways by TCM formulas, botanical drugs, or their isolated metabolites. We excluded studies not directly related to ADHD pathophysiology; conference abstracts, reviews, news articles, and non-research commentaries; and studies with incomplete data or those where full text was unavailable.

To ensure taxonomic and pharmacological rigor, studies were further screened for the inclusion of essential experimental details, such as dose ranges, specific models used, and chemical

characterization of the material under investigation. The selection process and study flow are detailed in the PRISMA flowchart shown in Figure 2.

3 Molecular mechanisms of botanical interventions in ADHD

Preclinical evidence indicates that TCM formulas, botanical drugs, and their active metabolites alleviate ADHD symptomatology through pleiotropic mechanisms, including the modulation of neurotransmitter systems, enhancement of

TABLE 1 Pharmacological mechanisms of natural products and TCM formulas for the treatment of ADHD.

Natural products/TCM formulas	Constituents/source	Experimental model	Dosage	Main target	Main signaling pathways	Efficacy	Ref.
Jingning Granules	<i>Pseudostellaria heterophylla</i> (Miq.) Pax. (Taizishen) <i>Rehmannia glutinosa</i> (Gaertn.) Libosch. ex DC. (Shudihuang), <i>Lycium barbarum</i> L. (Gouqizi), <i>Schisandra chinensis</i> (Turcz.) Baill. (Wuweizi), <i>Polygala tenuifolia</i> Willd. (Yuanzhi) <i>Acorus verus</i> (L.) Raf. (Shichangpu), and <i>Poria cocos</i> (Schw.) Wolf (Fuling)	SHR	(1) Low/medium/high dose: 5.785, 11.57, and 23.14 g/kg (2) 10.14 g/kg	(1) the number of neurons in the hippocampal CA1 area ↑; D1R and D2R in the striatum and hippocampus↑; cAMP↓; Ca2+↓; CaM↓; CaMKII ↑ (2) kynurenic/quinolinic acid ratio↑; The abundance and diversity of intestinal microorganisms, the beneficial bacteria in the intestine ↑	(1) cAMP/PKA pathway Ca2+/CaM-CaMKII pathway (2) tryptophan metabolic pathway; microbiota-gut-brain axis	(1) Promote the production of neurotransmitters (DA) (2) Restore the balance of the intestinal microbiota and correct the dysfunction of tryptophan metabolism through the gut-brain axis	Ding et al. (2022), Yang et al. (2026)
An Shen Ding Zhi Ling	<i>Bupleurum chinense</i> DC. (Chaihu), <i>Scutellaria baicalensis</i> Georgi (Huangqin), <i>Forsythia suspensa</i> (Thunb.) Vahl. (Lianqiao), <i>Polygala tenuifolia</i> Willd. (Yuanzhi), <i>Acorus verus</i> (L.) Raf. (Shichangpu), <i>Bambusa textilis</i> McClurei (Tianzhuhuang) <i>Curcuma longa</i> L. (Yujin), <i>Senna tora</i> (L.) Roxb. (Juemingzi), <i>Uncaria rhynchophylla</i> (Miq.) Miq. (Gouteng), <i>Angelica sinensis</i> (Oliv.) Diels (Danggui), <i>Alpinia oxyphylla</i> Miq. (Yizhiren) and <i>Rehmannia glutinosa</i> (Gaertn.) Libosch. ex DC. (Shengdihuang)	SHR	(1) 27.4 g/kg (2) 21.25 g/kg	(1) BDNF, TrkB, p75, JNK1, and NF-κB in the PFC and hippocampus↑ (2) IL-1β, IL-4, IL-6, TNF-α and MCP-1↓; IL-10↑; microglia, astrocytes and mast cells in the PFC and hippocampus; p-p38 MAPK, p-JNK, p-IκBα and p-p65 NF-κB↓	(1) BDNF/TrkB pathway BDNF/p75/JNK1/NF-κB pathway (2) MAPK signaling pathway; NF-κB signaling pathway	(1) Increase DA concentration in the synaptic cleft (2) Inhibit inflammatory responses	Song et al. (2020), Yaquin et al. (2022)
Long Mu Qing Xin Mixture	<i>Rehmannia glutinosa</i> (Gaertn.) Libosch. ex DC. (Shudihuang) <i>Paeonia lactiflora</i> Pall. (Baishao), <i>Ostrya draconis</i> (Longgu), <i>Ostrea gigas</i> Thunberg (Muli), <i>Uncaria rhynchophylla</i> (Miq.) Miq. (Gouteng)	SHR	Low/medium/high dose: 5.28 mL/kg/d; 10.56 mL/kg/d; 21.12 mL/kg/d	DA, NE, AC, cAMP, PKA, p-CREB, BDNF, D1, Gas, Gaolf ↑	D1/cAMP/PKA- CREB signaling pathway	Increase catecholamine neurotransmitters	Li X. et al. (2024)

(Continued)

TABLE 1 Continued

Natural products/TCM formulas	Constituents/ source	Experimental model	Dosage	Main target	Main signaling pathways	Efficacy	Ref.
Xiaoer Huanglong Pellets	<i>Rehmannia glutinosa</i> (Gaertn.) Libosch. ex DC. (Shudihuang) <i>Paeonia lactiflora</i> Pall. (Baishao), <i>Ophiopogon japonicus</i> (Thunb.) Ker Gawl. (Maidong), <i>Anemarrhena asphodeloides</i> Bunge. (Zhimu), <i>Schisandra chinensis</i> (Turcz.) Bail. (Wuweizi), <i>Codonopsis pilosula</i> (Franch.) Nannf. (Dangshen), and <i>Acorus verus</i> (L.) Raf. (Shichangpu)	SHR	5.76 g/kg (WR_HL), 7.20 g/kg (CR_HL), 7.20 g/kg (JCR_HL)	BDNF, TH, DAT, and TPH2 ↑ Claudin-1, occludin, and ZO-1 ↑ TNF-α, IL-6 and IL-1β ↓ The abundance and diversity of intestinal microorganisms, the beneficial bacteria in the intestine ↑ Glu, His, Tyr, Trp, Ach, 5-HT, DA, NE, SCFAs ↑	microbiota-gut-brain axis	Optimize the bacterial community structure, restore the barrier function, regulate amino acid metabolism and SCFAs, ultimately improving neuroinflammation and neurotransmitter disorders	You et al. (2025)
Dimu Ningshen	<i>Rehmannia glutinosa</i> (Gaertn.) Libosch. ex DC. (Shudihuang), <i>Lycium barbarum</i> L. (Gouqizi), <i>Ligustrum lucidum</i> W.T.Aiton (Nv Zhenzi) <i>Cornus officinalis</i> Siebold & Zucc. (Shanzhuyu), <i>Schisandra chinensis</i> (Turcz.) Baill. (Wuweizi) <i>Dioscorea polystachya</i> Turcz. (Shanyao), <i>Anemarrhena asphodeloides</i> Bunge. (Zhimu), <i>Scrophularia ningpoensis</i> Hemsl. (Xuanshen), <i>Glycyrrhiza glabra</i> L. (Gancao), <i>Ostrea gigas</i> Thunberg (Muli)	SHR	4.05 mg/kg	ALT, TBA, LDH-L, Cre, TG (No change); Ruminococcaceae_NK4A214_group, Ruminococcus_2, Eubacterium_nodatum_group ↑; peripheral monoamine neurotransmitter precursors ↑; peripheral fatty acid amides ↓	. Microbiota-gut-brain axis	Improve the structural composition of the gut microbiota and, at the same time, increase the circulating levels of peripheral polyamine neurotransmitter precursors (such as phenylalanine) and decrease the circulating levels of peripheral fatty acid amides (such as oleamides)	Tang et al. (2022)
Sansoninto	<i>Ziziphus jujuba</i> Mill.var. <i>spinosa</i> (Bunge) Hu ex H.F.Chou, <i>Poria cocos</i> (Schw.) Wolf (Fuling), <i>Glycyrrhiza glabra</i> L. (Gancao), <i>Anemarrhena asphodeloides</i> Bunge. (Zhimu)	Social isolation mice	800 and 2400 mg/kg	Egr-1 ↑	Egr-1 signaling pathway	Promote neural synaptic plasticity	Fujiwara et al. (2018)

(Continued)

TABLE 1 Continued

Natural products/TCM formulas	Constituents/ source	Experimental model	Dosage	Main target	Main signaling pathways	Efficacy	Ref.
Rehmanniae Radix Preparata	the root tuber of the plant <i>Rehmannia glutinosa</i>	SHR	2.4 g/kg	The structure of the hippocampal region ↑; The number of hippocampal neurons in the CA1 region ↑; The number of TUNEL-positive cells ↓; Synaptic plasticity of the hippocampal DG ↑; neurogenesis in the hippocampus ↑; TrkB, Cdk5, FGFR1 ↑	BDNF/TrkB pathway; FGF/FGFR pathway	Reduce neuronal loss and increased the number of hippocampal stem cells, and promoted synaptic plasticity	Sun et al. (2024)
Baicalin	<i>Scutellaria baicalensis</i> Georgi	SHR	(1) Low/medium/high dose: 50 mg/kg; 100 mg/kg; 150 mg/kg (2) 150 mg/kg	(1) TH, SNAP25, VMAT2, and syntaxin 1a ↑; DA ↑ (2) 8-OHdG ↓; CAT, GSH, and T-AOC ↑; Nrf2, Keap-1, and HO-1 ↑; TNF-α ↓; DAT ↓; VMAT2 ↑; p-NF-κB P65 ↓; HSC70 ↑	(1) SNAP25/syntaxin 1a (2) Nrf2/Keap-1/HO-1 pathway	(1) Promote DA synthesis and release (2) Activation of the Nrf2/Keap-1/HO-1 signaling pathway restored the balance of DAT and VMAT2 transport, and inhibited inflammatory responses, as well as reshaping the dopamine homeostasis in the brain	Ding et al. (2025), Zhou et al. (2019)
Saikosaponin A	<i>Bupleurum chinense</i> DC	SHR	25 and 50 mg/kg	DA ↑; DAT ↓; BDNF ↑	–	Increase neurotransmitters	Jichao et al. (2017)
Gastrodin	<i>Gastrodia elata</i> Blume	bisphenol A	30 and 60 mg/kg	GSH, MAO activity, and DA ↓; GFAP-positive cells in the cerebral cortex and hippocampus ↓	–	Increase neurotransmitters, Inhibition of lipid peroxidation and inhibition of astrocyte activation	Saifi et al. (2025)
Catalpol	<i>Rehmannia glutinosa</i> (Gaertn.) Libosch. ex DC.	SHR	50 mg/kg	MBP and NeuN expression in PFC and striatum ↑; BDNF ↑; Cdk5/p35 activity ↑; FGF21 and FGFR1 ↑	Cdk5/p35 FGF/FGFR pathway	Inhibit lipid peroxidation, reduce inflammatory response	Yuan et al. (2019)
Rhynchophylline	<i>Uncaria rhynchophylla</i> (Miq.) Miq	<i>In vivo</i> : Male DAT-KO Mice <i>In vitro</i> : LPS-Treated Microglia and Astrocytes	30 mg/kg; 20 mM	GFAP and CD11b-positive cells ↓ TNF-α, IL-1β, iNOS, and COX-2 in microglia and astrocytes ↓ TNF-α and IL-1β in cortical homogenates ↓	–	Promote neural development	Li J. et al. (2024)

neurodevelopment and synaptic plasticity, regulation of neuroinflammation, and modulation of the gut–brain axis (Table 1).

3.1 Neurotransmitter system

Imbalances in catecholamine neurotransmitters, particularly dopamine (DA) and norepinephrine (NE), play a crucial role in the pathophysiology of ADHD (Li X. et al., 2024). The hydroxylation of DA is essential for NE production, and both neurotransmitters are critical for executive function through their neuromodulatory effects on frontal-striato-cerebellar circuits (Del Campo et al., 2011). Reduced concentrations of DA and NE have been observed in the serum of children with ADHD, potentially reflecting a disrupted central catecholaminergic state (Xiong et al., 2021). Rectifying this abnormal catecholaminergic neurotransmission is a crucial aim in

treating ADHD. Spontaneously hypertensive rats (SHR) serve as a well-validated animal model for ADHD research, exhibiting key features of ADHD at 4–10 weeks of age, including inattention, impulsivity, and hyperactivity (Regan et al., 2022). A large number of experiments have confirmed that various botanical metabolites have demonstrated significant modulatory effects in ADHD models (Figure 3). For instance, Saikosaponin A (SSA), the primary triterpene saponin isolated from *Bupleurum chinense* DC., has been shown to increase DA concentrations and brain-derived neurotrophic factor (BDNF) levels in the prefrontal cortex (PFC) and striatum of SHR (Jichao et al., 2017). The DA transporter (DAT) facilitates extracellular DA reuptake, ultimately leading to DA degradation (German et al., 2015; Omiattek et al., 2013). The study has confirmed that elevated DA may be associated with reduced DAT (Jichao et al., 2017). Baicalin is a flavonoid purified

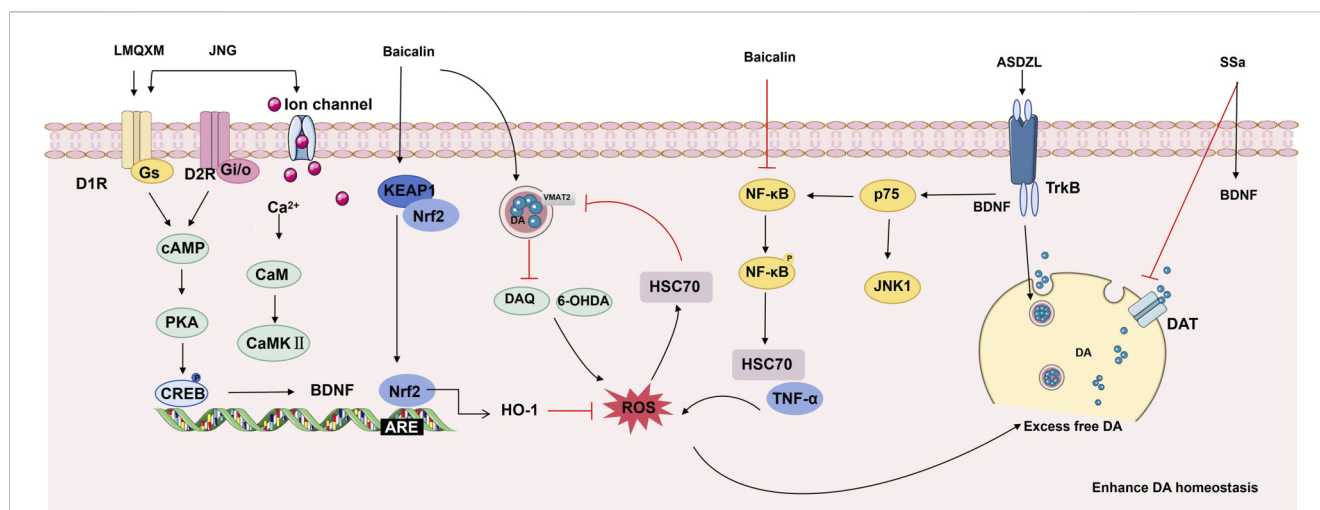


FIGURE 3

TCM ameliorates ADHD by promoting neurotransmitters. TCM (formulas and their isolated metabolites) alleviates ADHD symptoms by modulating neurotransmitter levels in the brain. LMQXM improves hyperactivity and learning/memory deficits in SHR by activating the DRD1/cAMP/PKA-CREB signaling pathway and increasing catecholamine neurotransmitter levels. JNG coordinates the balance between D1- and D2-like receptors, as well as their downstream cAMP/PKA and Ca^{2+} /CaM/CaMKII signaling cascades, ultimately improving impulsivity, learning, and cognitive functions. ASDZL attenuates hyperactivity in SHR by regulating the balance between the BDNF/TrkB pathway (promoting vesicle cycling) and the BDNF/p75/JNK1/NF- κ B pathway (inhibiting vesicle cycling) within synaptic compartments, thereby increasing dopamine concentration in the synaptic cleft. By activating the Nrf2/Keap-1/HO-1 pathway, baicalin significantly reduces oxidative stress and neuroinflammation, thereby restoring the DAT-VMAT2 transport equilibrium and enhancing DA stability. SSa promotes brain BDNF expression and simultaneously inhibits DAT-mediated dopamine reuptake, raising synaptic dopamine concentrations and alleviating ADHD-like symptoms. (Abbreviations: cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; CREB, cAMP response element-binding protein; CaMKII, Ca^{2+} /calmodulin-dependent protein kinase II; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; JNK1, c-Jun N-terminal kinase 1; LMQXM, Long Mu Qing Xin Mixture; JNG, Jingning Granules; ASDZL, An Shen Ding Zhi Ling; SSA, Saikosaponin A.)

from the plant *Scutellaria baicalensis* Georgi. Zhou et al. demonstrated that baicalin targeted the striatum and increased DA levels only in the striatum (Zhou et al., 2019). Furthermore, baicalin was found to enhance DA homeostasis by restoring DAT-vesicular monoamine transporter 2 (VMAT2) transport balance and reducing oxidative stress and inflammation by activating the nuclear factor erythroid 2-related factor (Nrf2)/kelch-like ECH-associated protein 1 (Keap-1)/heme oxygenase-1 (HO-1) pathway (Ding et al., 2025).

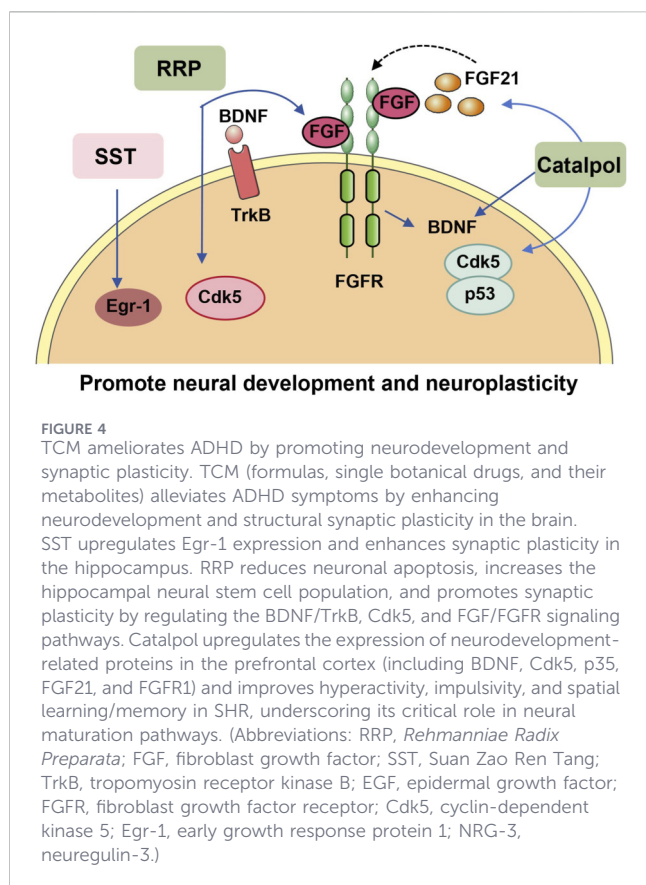
Beyond isolated metabolites, the complex pharmacological mechanisms of multi-herb TCM formulas have garnered considerable research attention. Jingning granules (JNG), a potent TCM formula developed from years of clinical expertise in treating ADHD, has been recognized with a national invention patent (Patent No. ZL201510303541.6). JNG can effectively improve the dysfunction of dopaminergic neurons in SHR. The mechanism may be through reducing the excessive function of D1-like receptors and promoting cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) and Ca^{2+} /calmodulin (CaM)-dependent protein kinase II (CaMKII) signaling pathway (Ding et al., 2022). An shen ding zhi ling (ASDZL), a TCM formula, has been extensively utilized for the treatment of ADHD within the province of Jiangsu in China. ASDZL has been shown to alleviate ADHD symptoms in SHR rats by modulating the balance between the BDNF/tropomyosin receptor kinase B (TrkB) (which promotes vesicle circulation) and BDNF/p75/C-Jun N-terminal kinases 1 (JNK1)/nuclear factor kappa B (NF- κ B) signalling pathway (which inhibits vesicle circulation) within the PFC and the hippocampus synaptosome, consequently increasing DA concentration in the synaptic cleft (Yaqun et al., 2022). Additionally, Longmu Qingxin Mixture

(LMQXM), a TCM formula specifically designed for ADHD, has been demonstrated to elevate brain DA and NE levels via the D1/cAMP/PKA-cAMP response element-binding protein (CREB) signaling pathway (Li X. et al., 2024; Li X. et al., 2023).

3.2 Neural development and plasticity

ADHD arises from a multifactorial etiology, and neuroimaging investigations have revealed that multiple critical brain regions in individuals with ADHD exhibit reduced volume or delayed maturation, as documented in prior research (Ming and Song, 2011; Song et al., 2016). Accumulating evidence has confirmed that restoring neuroplasticity in ADHD model rats effectively mitigates ADHD-related symptoms, with recent findings consistently supporting this therapeutic effect (Anderson et al., 2024; Marques et al., 2023; Sun et al., 2024). Neurogenesis persists throughout the mammalian lifespan, with the dentate gyrus (DG) of the hippocampus identified as its primary site (Ming and Song, 2011). In pediatric populations, the hippocampus is particularly notable, as it undergoes the most significant volume reductions and maturational delays compared to other brain regions (Hoogman et al., 2017) (Figure 4).

This link between hippocampal dysfunction and ADHD has directed attention to botanical drug interventions, with a data mining analysis identifying *Rehmanniae radix* preparata (RRP) as the most frequently utilized botanical drug remedy for ADHD treatment (Jia et al., 2023). Subsequent experimental validation confirmed that RRP exerts neuroprotective effects by reducing neuronal loss, expanding the population of hippocampal stem cells, and enhancing synaptic plasticity. The underlying



mechanism may involve upregulation of the fibroblast growth factor (FGF)/fibroblast growth factor receptor (FGFR) signaling pathway (Sun et al., 2024). Beyond the hippocampus, abnormal neurodevelopment of prefrontal-striatal circuits is also recognized as a key contributor to ADHD pathogenesis. Studies have found that RRP may improve spontaneous and impulsive behaviors by upregulating BDNF/TrkB and Neuregulin 3 (NRG3) expression in the prefrontal cortex and striatum, thereby improving neuronal growth and maturation in SHR (Yuan H. et al., 2018; Yuan H. X. et al., 2018). In addition, catalpol, the active metabolite of RRP, has been shown to be involved in the upregulation of several regulatory proteins in PFC development, such as BDNF, cyclin-dependent kinase 5 (Cdk5), p35, FGF21 and its receptor (FGFR) 1 (Yuan et al., 2019).

Regarding animal models of ADHD, early post-weaning social isolation (SI) in rodents has emerged as a viable approach, as it induces behavioral abnormalities analogous to those observed in human ADHD—including heightened aggressive responses, attention-deficit-like behaviors, and hyperactivity (Abu-Elfotuh et al., 2023; Fujiwara et al., 2018). SI stress in mice was recently found to cause not only impaired social competence and spatial attention, but also cognitive deficits in fear conditioning tests. Suan Zao Ren Tang (SST, also known as Sansoninto), a TCM formula historically used to treat insomnia, depression, and neuropathy in adults, has shown therapeutic potential. Daily administration of SST was found to alleviate SI-induced impairments in episodic and auditory fear memory, while also reversing the downregulation of early growth responsive gene-1 (Egr-1) expression in the

hippocampus and cortex of SI-exposed animals (Fujiwara et al., 2018).

3.3 Inflammation and immune regulation

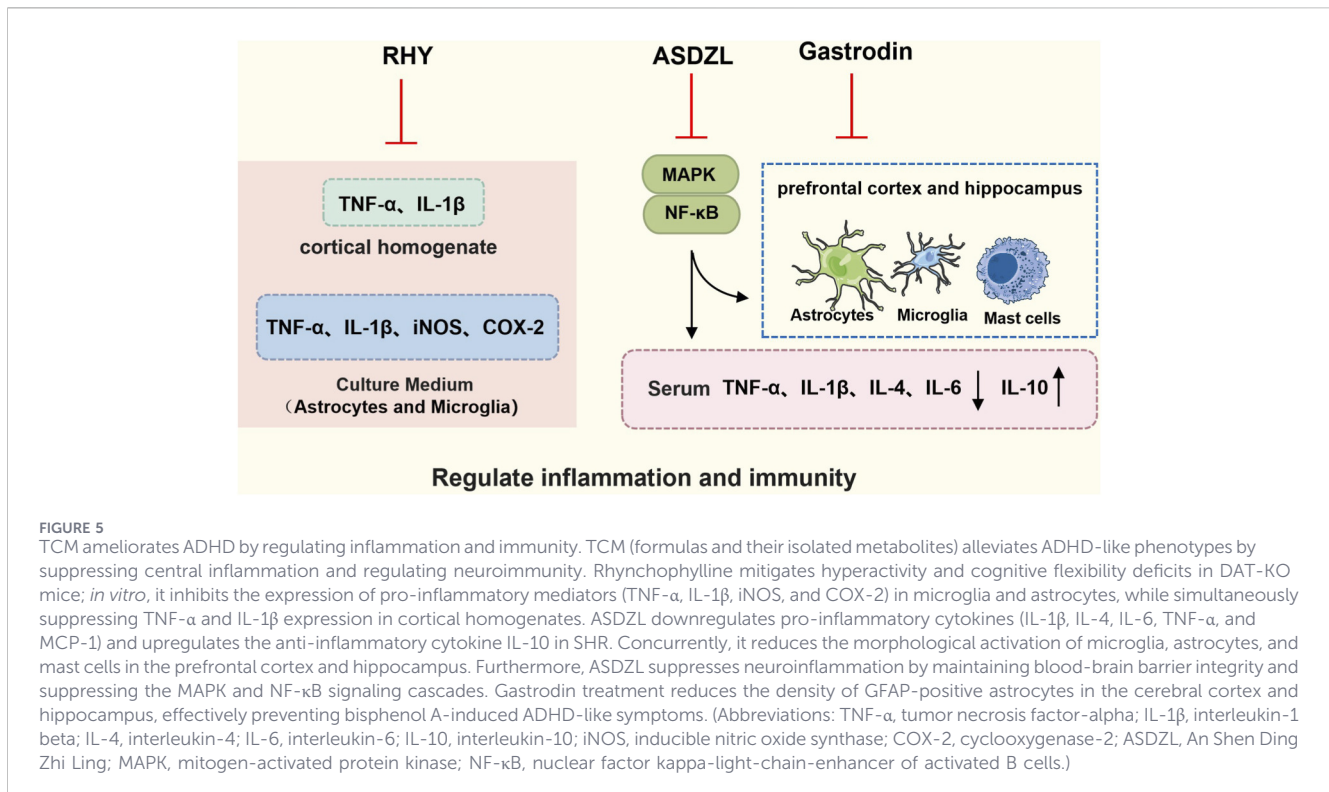
Neuroinflammation can lead to brain dysfunction and is evident in both neurological and psychiatric disorders (Bauer and Teixeira, 2019; Jeon et al., 2019). Research indicates that ADHD patients exhibit elevated concentrations of proinflammatory cytokines and reduced levels of anti-inflammatory cytokines as well as brain BDNF (Cortese et al., 2019; Darwish et al., 2019; Dunn et al., 2019; Elsadek et al., 2020). High concentrations of cytokines, chemokines, and oxidative stress markers have been identified in the serum of SHR (Kozłowska et al., 2019). Therefore, inhibiting neuroinflammation may represent an effective therapeutic strategy for ADHD (Figure 5).

ASDZL has been shown to significantly increase DA levels in SHR in previous studies, while recent studies have found that ASDZL effectively downregulates pro-inflammatory cytokines (IL-1 β , IL-4, IL-6, TNF- α , MCP-1) while upregulating the anti-inflammatory cytokine IL-10. It concurrently reduces activation of microglia, astrocytes, and mast cells in the PFC and hippocampus. This anti-neuroinflammatory action likely involves suppression of the mitogen-activated protein kinase (MAPK) and NF- κ B signaling pathways (Song et al., 2020). As a TCM formula, Ningdong granule (NDG) has been used to treat ADHD for several years in China. Clinical studies found that NDG improved ADHD symptoms after 8 weeks of drug treatment with fewer side effects compared to methylphenidate. NDG was safe and tolerable in children with ADHD as determined by blood, urine, and stool analysis and liver and kidney function monitoring for 8 weeks (Li et al., 2011). Subsequent preclinical studies extended these insights by identifying rhynchophylline, a major alkaloid constituent of NDG, as a key bioactive agent responsible for ameliorating hyperactivity and cognitive flexibility deficits in a DAT knockout (DAT-KO) mice model (Li J. et al., 2024). These effects were mechanistically linked to suppression of neuroinflammatory signaling pathways.

Gastrodin (GAS) is a bioactive pharmaceutical metabolite extracted from the dried roots of *Gastrodia elata* Blume. Network pharmacological analysis suggested that neuroactive ligand-receptor interaction, cholinergic synapses, and dopaminergic synapses may be the core pathways through which GAS exerts its therapeutic effects in ADHD (Song et al., 2022). In the latest study, Saifi et al. used Bisphenol A (BPA) to establish an ADHD rat model. After GAS treatment, it reduced lipid peroxidation, enhanced the monoamine oxidase (MAO) activity, and reduced the number of GFAP-positive cells in the cerebral cortex and hippocampus (Saifi et al., 2025).

3.4 Gut-brain axis interaction

The gut microbiota can directly or indirectly influence neurotransmitter production through the host's biosynthetic pathways. Imbalance in this process can lead to disorders in neurotransmitters and neural development functions (Sittipo et al., 2022; Ullah et al., 2023). In recent years, the role of intestinal flora imbalance in the pathological mechanism of ADHD has gradually attracted attention (Gandhi et al., 2024;



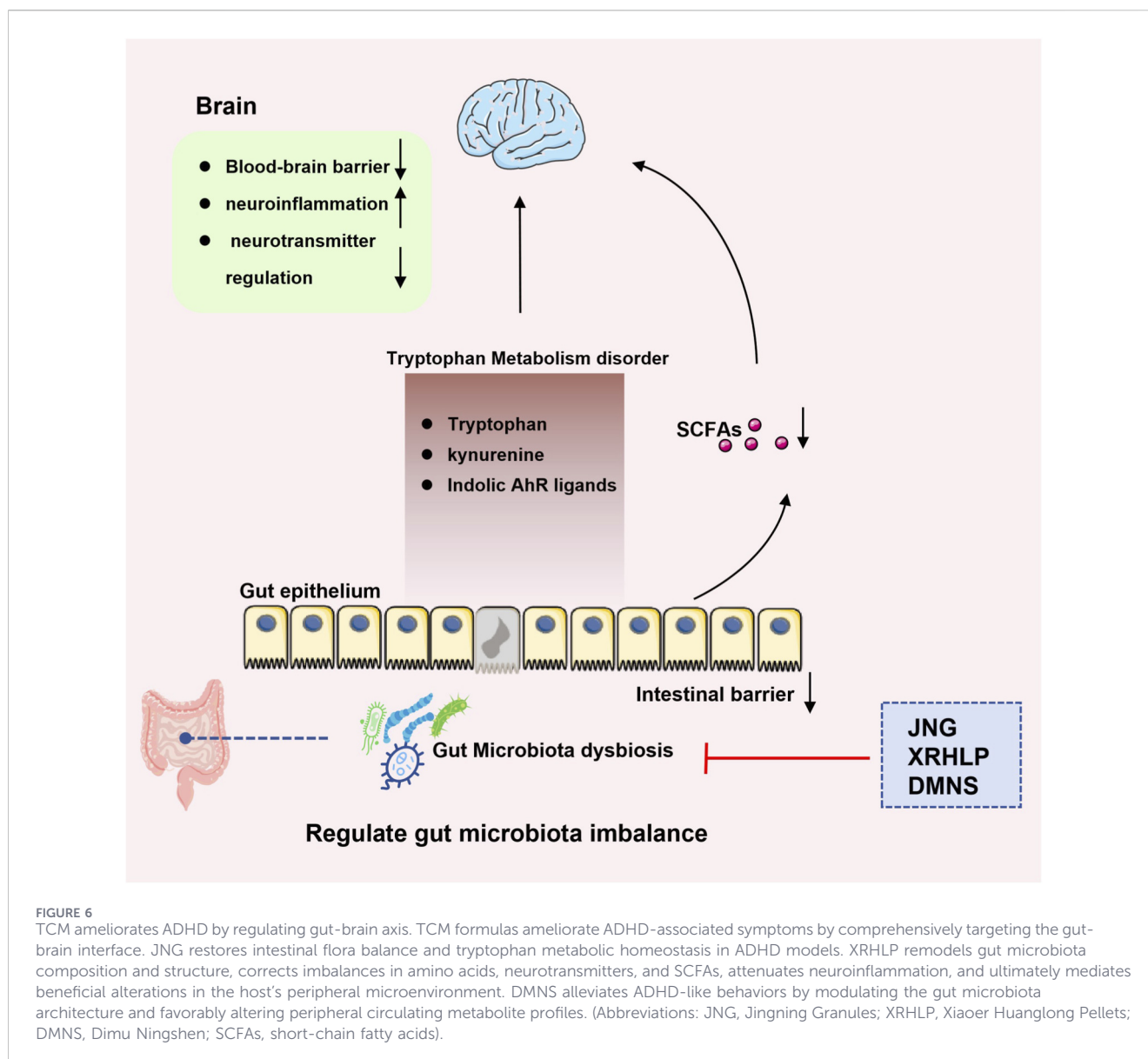
Han et al., 2025; Harigai et al., 2025; Leng et al., 2025; Lewis et al., 2025; Liu et al., 2025; Novau-Ferré et al., 2025; Steckler et al., 2024; Yin et al., 2024; You et al., 2025). Existing studies have confirmed that intestinal flora imbalance can contribute to ADHD-related pathological processes through multiple mechanisms. On the one hand, it can induce chronic intestinal inflammation, promote the accumulation of harmful metabolites, and directly damage the integrity of the intestinal epithelial barrier (Braniste et al., 2014; Kelly et al., 2015). On the other hand, neuroactive substances produced by microbial metabolism can cross the blood-brain barrier (BBB) through the blood circulation, interfere with the dynamic balance of neurotransmitters by regulating the synthesis, release and reuptake of neurotransmitters, and subsequently affect central nervous system function (Asano et al., 2012; Liu et al., 2025). More importantly, the bidirectional regulation mechanism of gut-brain axis plays a key role in this process (Checa-Ros et al., 2021; Gershon and Margolis, 2021).

Several TCM formulas appear to act on ADHD through this gut-brain interface (Figure 6). A targeted-release formulation of Xiaoeer Huanglong Pellets (XRHLP), designed for delivery to the stomach, intestine and colon, has been shown in SHR to restore microbial homeostasis, suppress excessive inflammatory cascades and repair both intestinal barrier and BBB structure, suggesting multi-level regulation of flora balance, inflammation, and barrier integrity (You et al., 2025). Notably, Tang et al. further validated the regulatory role of CM in the gut-brain axis of ADHD through a study on Dimu Ningshen (DMNS), an oral TCM formula. The study showed that DMNS could significantly modulate the gut microbiota structure of SHR, which reduced the abundance of ADHD-associated pathogenic microbiota such as Ruminococcaceae_NK4A214_group, Ruminococcus_2, Eubacterium_nodatatum_group, and

Christensenellaceae (which were highly abundant in the SHR group), and increased the proportion of beneficial bacteria including Bacteroidetes and Patensibacteria. Simultaneously, it increases circulating precursors of monoamine neurotransmitters and decreases fatty acid amides linked to ADHD, indicating coordinated modulation of microbiota-metabolite networks (Tang et al., 2022). These findings suggest that DMNS may exert its therapeutic effects in ADHD by regulating the interaction between gut microbiota and metabolites, thereby modulating the gut-brain axis. In addition, the commonly used drug JNG has been shown to increase the overall quantity and diversity of microorganisms, selectively promote the growth of beneficial intestinal bacteria, and increase the ratio of kynurenic/quinolinic acid. Such changes are generally considered to have neuroprotective effects (Yang et al., 2026).

4 Discussion

ADHD is a multifactorial neurodevelopmental disorder involving dysregulation of monoaminergic neurotransmission, impaired synaptic plasticity, neuroimmune activation, and disturbances in the gut-brain axis (Ding et al., 2025; Song et al., 2020; Sun et al., 2024; Yang et al., 2026). Although pharmacological interventions such as the stimulant methylphenidate (MPH) and the non-stimulant atomoxetine remain first-line treatments, their long-term tolerability, risk of adverse reactions, and incomplete symptom remission in a subset of patients underscore the need for complementary therapeutic strategies. In this review, botanical drugs and plant-derived bioactive metabolites have attracted increasing attention due to their multi-target regulatory



characteristics. The studies summarized in this review suggest that botanical interventions may modulate dopaminergic and noradrenergic signaling, enhance plasticity-related pathways such as BDNF, attenuate microglial activation and inflammatory cascades, and restore gut microbiota balance. These findings collectively support the concept that botanical interventions exert systems-level modulation across interconnected pathological domains of ADHD.

Importantly, neurotransmission, synaptic plasticity, neuroinflammation, and the gut-brain axis are not independent domains but components of a dynamically interacting system. Pro-inflammatory cytokines can alter dopamine synthesis and transporter activity, thereby influencing executive function circuits in the prefrontal cortex (Yan et al., 2015). Conversely, dopaminergic signaling can modulate microglial activation states and immune tone (Yan et al., 2015). Gut microbiota-derived metabolites, including short-chain fatty acids and tryptophan metabolites, may further regulate both central neurotransmission

and inflammatory responses through immune, endocrine, and neural pathways (Liu et al., 2024; Qiu et al., 2022). Within this integrative framework, the multi-target properties of botanical formulations appear theoretically aligned with the complex pathophysiology of ADHD. However, while conceptual coherence exists, direct experimental evidence demonstrating coordinated and causal interactions among these axes remains limited.

Despite encouraging mechanistic findings, the preclinical literature presents notable limitations. First, the majority of mechanistic investigations have been conducted using the SHR model. While SHR exhibit hyperactivity and certain catecholaminergic alterations, they represent only one ADHD-relevant phenotype. Very few botanical drugs have been evaluated in DAT-KO mice or neonatal 6-hydroxydopamine (6-OHDA) lesion models, which represent distinct pathophysiological mechanisms. The near-exclusive reliance on SHR restricts external validity and raises concerns about model-specific effects. Cross-model validation is essential to determine whether reported

pharmacological actions generalize across ADHD subtypes. Second, pharmacokinetic profiling is rarely conducted. Consequently, brain exposure levels, dose–response relationships, and minimal effective concentrations often remain undefined. Third, the chemical standardization of plant extracts is frequently inadequate, with insufficient reporting on drug-to-extract ratios, metabolite quantification, or voucher specimen documentation. Fourth, the inclusion of positive control benchmarks is inconsistent, complicating the interpretation of pharmacodynamic outcomes. Collectively, these limitations constrain both reproducibility and the strength of translational inferences.

In addition to preclinical evidence, emerging clinical data also suggest that botanical treatment of ADHD may bring benefits (Ni et al., 2015; Qi et al., 2025). For example, a randomized controlled trial of Jingling Oral solution (Liaoning Oriyuan Pharmaceutical Co., LTD.) reported that the formulation improved total scores and hyperactivity/impulsivity subscale scores in children with ADHD, with good short-term safety (Qi et al., 2025). This study employed centralized randomization and a placebo-controlled parallel design, which reduces selection bias and enhances internal validity. However, despite these strengths, several methodological issues warrant careful consideration. Although the study was described as double-blind, botanical formulations inherently pose challenges in placebo matching due to their distinctive taste, color, and odor. The adequacy of blinding integrity was not formally tested, and no assessment of blinding success was reported, leaving potential performance and detection bias insufficiently addressed. Second, while the trial included a relatively larger sample compared with previous botanical drug studies, detailed justification of sample size calculation and power estimation for secondary outcomes was limited, raising questions about statistical robustness beyond primary endpoints. This represents a common limitation of current randomized controlled trials (RCTs) investigating botanical drugs for ADHD treatment. Furthermore, all available studies have been conducted exclusively in China, which constrains their generalizability due to regional and ethnic specificities. Consequently, while botanical drugs show promising therapeutic potential, high-quality, multicenter clinical trials involving diverse populations are urgently needed before their widespread application on a global scale can be justified.

Integrated traditional Chinese and Western medicine (ICWM) is an important approach in ADHD clinical practice in China (Wang and Zhang, 2017). In ICWM, Western medicine can quickly control the core symptoms through standardized drugs, while TCM can regulate the function of viscera, improve comorbidities (such as anxiety and sleep disorders) and reduce the side effects of Western medicine. For example, Huanglian Wen Dan Tang, a classical formula traditionally used to “clear heat and resolve phlegm” has been shown in pharmacological studies to modulate γ -aminobutyric acid type A (GABA_A) receptor activity, suggesting a potential role in ameliorating insomnia (Klein-Schwartz, 2002; Li L. et al., 2024; Shi et al., 2025). Given that MPH treatment is frequently associated with sleep disturbances and irritability, it is theoretically plausible that such formulas may mitigate these adverse effects. However, it must be emphasized that these assumptions are primarily based on pharmacological inference rather than direct clinical evidence in ADHD populations. Although several clinical studies have explored ICWM approaches, standardized, evidence-based protocols have yet to

be established. An early RCT by Lin et al. examined a 12-week course of combined MPH and Ningshen Oral Liquid in children with ADHD. The overall response rate in the combination group (83.76%) exceeded that of the Western medicine group (72.30%) and the TCM-only group (70.98%). Moreover, the incidence of adverse reactions was lower than in the MPH monotherapy group, although still higher than in the TCM-only group (Lin Yuin et al., 2007). These findings suggest potential benefits of integrative therapy, but fall short of defining a standardized, evidence-based ICWM regimen.

5 Conclusion and prospects

In recent years, the adjuvant treatment of ADHD with botanical drugs has attracted attention due to their favorable safety profiles and multi-target treatment characteristics. This comprehensive review systematically outlines the substantial preclinical progress achieved in elucidating the molecular mechanisms underlying botanical formulations in ADHD management. However, to maintain absolute scientific objectivity, the profound limitations of the current literature base must be explicitly acknowledged. These include the predominant use of a single animal model (SHR), substantial variability in botanical formulations, extraction methods, and dosing regimens across studies, as well as clinical investigations characterized by small sample sizes, geographic restriction to China, and a paucity of rigorous RCTs.

Future research should prioritize more in-depth mechanistic studies employing diverse experimental animal models to elucidate the complex “multi-component–multi-target–multi-pathway” network of actions underlying botanical interventions. At the preclinical level, cross-model validation using DAT-KO mice, neonatal 6-OHDA lesion models, and other ADHD-relevant models is essential to establish generalizability of findings. Additionally, pharmacokinetic profiling and standardized chemical characterization of botanical extracts should become mandatory components of preclinical investigations. At the clinical level, beyond increasing sample sizes and extending follow-up durations, more rigorous study designs are required, including the use of blinding and placebo controls, incorporation of objective biomarkers as adjunctive efficacy measures, and systematic assessment of quality of life and long-term functional outcomes.

Ultimately, advancing the standardization and individualization of integrative Chinese and Western medicine for ADHD is of great importance. Evidence-based treatment guidelines grounded in both pattern differentiation and disease diagnosis should be established to clarify the optimal timing, target populations, and regimens for combination therapy, with the aim of enhancing efficacy, reducing toxicity, and achieving both symptomatic relief and root-cause resolution, thereby offering more comprehensive and personalized treatment options for patients with ADHD worldwide.

Author contributions

HD: Funding acquisition, Writing – original draft, Writing – review and editing. BL: Formal Analysis, Writing – review and editing. YM: Formal Analysis, Writing – review and editing. WX: Formal Analysis,

Writing – review and editing. NW: Funding acquisition, Writing – review and editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was supported by Shandong Province Traditional Chinese Medicine Science & Technology Project (No. M-20243301 and M-2022198). Doctoral Research Initiation Project of Shandong Mental Health Center (2024KYQD0009).

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- Abu-Elfotuh, K., Darwish, A., Elsanhory, H. M. A., Alharthi, H. H., Hamdan, A. M. E., Hamdan, A. M., et al. (2023). *In silico* and *in vivo* analysis of the relationship between ADHD and social isolation in pups rat model: implication of redox mechanisms, and the neuroprotective impact of punicalagin. *Life Sciences* 335, 122252. doi:10.1016/j.lfs.2023.122252
- Anderson, L. G., Vogiatzoglou, E., Tang, S., Luiz, S., Duque, T., Ghaly, J. P., et al. (2024). Memory deficits and hippocampal cytokine expression in a rat model of ADHD. *Brain, Behavior, & Immunity - Health* 35, 100700. doi:10.1016/j.bbih.2023.100700
- Asano, Y., Hiramoto, T., Nishino, R., Aiba, Y., Kimura, T., Yoshihara, K., et al. (2012). Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice. *Am. Journal Physiology. Gastrointest. Liver Physiology* 303, G1288–G1295. doi:10.1152/ajpgi.00341.2012
- Bauer, M. E., and Teixeira, A. L. (2019). Inflammation in psychiatric disorders: what comes first? *Ann. N. Y. Acad. Sci.* 1437, 57–67. doi:10.1111/nyas.13712
- Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Tóth, M., et al. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Sci. Translational Medicine* 6, 263ra158. doi:10.1126/scitranslmed.3009759
- Checa-Ros, A., Jerez-Calero, A., Molina-Carballo, A., Campoy, C., and Muñoz-Hoyos, A. (2021). Current evidence on the role of the gut microbiome in ADHD pathophysiology and therapeutic implications. *Nutrients* 13, 249. doi:10.3390/nu13010249
- Cortese, S., Angriman, M., Comencini, E., Vincenzi, B., and Maffei, C. (2019). Association between inflammatory cytokines and ADHD symptoms in children and adolescents with obesity: a pilot study. *Psychiatry Research* 278, 7–11. doi:10.1016/j.psychres.2019.05.030
- Darwish, A. H., Elgohary, T. M., and Nosair, N. A. (2019). Serum Interleukin-6 level in children with attention-deficit hyperactivity disorder (ADHD). *J. Child Neurology* 34, 61–67. doi:10.1177/0883073818809831
- Del Campo, N., Chamberlain, S. R., Sahakian, B. J., and Robbins, T. W. (2011). The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 69, e145–e157. doi:10.1016/j.biopsych.2011.02.036
- Ding, J., Ding, Y., Wu, J., Deng, J., Yu, Q., and Wang, J. (2022). Jing-ning granules can alleviate attention deficit hyperactivity disorder in rats by modulating dopaminergic D2/D1-like receptor-mediated signaling pathways. Evidence-based complementary and alternative medicine. *eCAM* 2022, 9139841. doi:10.1155/2022/9139841
- Ding, X., Ma, B., Zhou, R., Zhang, Y., Zhang, Y., Xie, X., et al. (2025). Baicalin restores dopamine homeostasis in the ADHD model by regulating DAT-VMAT2 transport imbalance through activation of the Nrf2/Keap-1/HO-1 pathway. *Free Radical Biology & Medicine* 232, 107–127. doi:10.1016/j.freeradbiomed.2025.02.032
- Drechsler, R., Brem, S., Brandeis, D., Grünblatt, E., Berger, G., and Walitz, S. (2020). ADHD: current concepts and treatments in children and adolescents. *Neuropediatrics* 51, 315–335. doi:10.1055/s-0040-1701658

Generative AI statement

The author(s) declared that generative AI was not 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.

- Dunn, G. A., Nigg, J. T., and Sullivan, E. L. (2019). Neuroinflammation as a risk factor for attention deficit hyperactivity disorder. *Pharmacol. Biochemistry, Behavior* 182, 22–34. doi:10.1016/j.pbb.2019.05.005
- Elsadek, A. E., Al-Shokary, A. H., Abdelghani, W. E., Kamal, N. M., Ibrahim, A. O., El-Shorbagy, H. H., et al. (2020). Serum levels of Interleukin-6 and tumor necrosis factor alpha in children with attention-deficit hyperactivity disorder. *J. Pediatric Neurosciences* 15, 402–408. doi:10.4103/jpn.JPN_1_20
- Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., et al. (2015). Attention-deficit/hyperactivity disorder. *Nat. Reviews. Dis. Primers* 1, 15020. doi:10.1038/nrdp.2015.20
- Fujiwara, H., Tsushima, R., Okada, R., Awale, S., Araki, R., Yabe, T., et al. (2018). Sansoninto, a traditional herbal medicine, ameliorates behavioral abnormalities and down-regulation of early growth response-1 expression in mice exposed to social isolation stress. *J. Traditional Complementary Medicine* 8, 81–88. doi:10.1016/j.jtcm.2017.03.004
- Gandhi, D. N., Pande, D. N., Harikrishna, A., Advilkar, A., Basavan, I., and Ansari, R. (2024). Beyond the brain: attention deficit/hyperactivity disorder and the gut-brain axis. *Cureus* 16, e76291. doi:10.7759/cureus.76291
- German, C. L., Baladi, M. G., McFadden, L. M., Hanson, G. R., and Fleckenstein, A. E. (2015). Regulation of the dopamine and vesicular monoamine transporters: pharmacological targets and implications for disease. *Pharmacol. Reviews* 67, 1005–1024. doi:10.1124/pr.114.010397
- Gershon, M. D., and Margolis, K. G. (2021). The gut, its microbiome, and the brain: connections and communications. *J. Clinical Investigation* 131, e143768. doi:10.1172/JCI143768
- Goez, H., Back-Bennet, O., and Zelnik, N. (2007). Differential stimulant response on attention in children with comorbid anxiety and oppositional defiant disorder. *J. Child Neurology* 22, 538–542. doi:10.1177/0883073807303221
- Guo, J., Chen, X., Wu, M., Wang, D., Zhao, Y., Li, Q., et al. (2024). Traditional Chinese medicine FYTF-919 (zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial. *Lancet London, Engl.* 404, 2187–2196. doi:10.1016/S0140-6736(24)02261-X
- Han, D., Zhang, Y., Liu, W., Wan, R., Hu, J., Pan, F., et al. (2025). Disruption of gut microbiome and metabolome in treatment-naïve children with attention deficit hyperactivity disorder. *BMC Microbiology* 25, 381. doi:10.1186/s12866-025-04048-7
- Harigai, W., Mikami, K., Choudhury, M. E., Yamauchi, H., Yajima, C., Shimizu, S., et al. (2025). Effects of fecal microbiota transplantation on behavioral abnormality in attention deficit hyperactivity disorder-like model rats. *J. Pharmacological Sciences* 157, 189–198. doi:10.1016/j.jpsh.2025.01.007
- Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schwenen, L. S. J., et al. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis. *Lancet Psychiatry* 4, 310–319. doi:10.1016/S2215-0366(17)30049-4

- Jeon, S. W., Yoon, H. K., and Kim, Y. K. (2019). Role of inflammation in psychiatric disorders. *Adv. Experimental Medicine Biology* 1192, 491–501. doi:10.1007/978-981-32-9721-0_24
- Jia, J., Chen, J., Wang, G., Li, M., Zheng, Q., and Li, D. (2023). Progress of research into the pharmacological effect and clinical application of the traditional Chinese medicine Rehmannia Radix. *Biomed. & Pharmacotherapy = Biomedecine & Pharmacotherapie* 168, 115809. doi:10.1016/j.biopha.2023.115809
- Jichao, S., Xinmin, H., Xianguo, R., Dongqi, Y., Rongyi, Z., Shuang, L., et al. (2017). Saikosaponin A alleviates symptoms of attention deficit hyperactivity disorder through downregulation of DAT and enhancing BDNF expression in spontaneous hypertensive rats. *Evidence-based Complementary Alternative Medicine eCAM* 2017, 2695903. doi:10.1155/2017/2695903
- Kelly, J. R., Kennedy, P. J., Cryan, J. F., Dinan, T. G., Clarke, G., and Hyland, N. P. (2015). Breaking Down the Barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front. Cellular Neuroscience* 9, 392. doi:10.3389/fncel.2015.00392
- Klein-Schwartz, W. (2002). Abuse and toxicity of methylphenidate. *Curr. Opinion Pediatrics* 14, 219–223. doi:10.1097/00008480-200204000-00013
- Koirala, S., Grimsrud, G., Mooney, M. A., Larsen, B., Feczko, E., Elison, J. T., et al. (2024). Neurobiology of attention-deficit hyperactivity disorder: historical challenges and emerging frontiers. *Nat. Reviews. Neurosci.* 25, 759–775. doi:10.1038/s41583-024-00869-z
- Kotsopoulos, S., and Spivak, M. (2001). Obsessive-compulsive symptoms secondary to methylphenidate treatment. *Can. J. psychiatry. Revue Can. De psychiatrie* 46, 89.
- Kozłowska, A., Wojtacha, P., Równiak, M., Kolenkiewicz, M., and Huang, A. C. W. (2019). ADHD pathogenesis in the immune, endocrine and nervous systems of juvenile and maturing SHR and WKY rats. *Psychopharmacology* 236, 2937–2958. doi:10.1007/s00213-019-5180-0
- Leng, Y., Wu, N., Wang, J., Geng, L., Yue, Y., and Zhang, Q. (2025). Astaxanthin mitigates ADHD symptoms in spontaneously hypertensive rats via dopaminergic modulation and brain-gut axis regulation. *Mol. Basel, Switz.* 30, 1637. doi:10.3390/molecules30071637
- Lewis, N., Lagopoulos, J., and Villani, A. (2025). Gut-brain inflammatory pathways in attention-Deficit/Hyperactivity disorder: the role and therapeutic potential of diet. *Metabolites* 15, 335. doi:10.3390/metabo15050335
- Li, J. J., Li, Z. W., Wang, S. Z., Qi, F. H., Zhao, L., Lv, H., et al. (2011). Ningdong granule: a complementary and alternative therapy in the treatment of attention deficit/hyperactivity disorder. *Psychopharmacology* 216, 501–509. doi:10.1007/s00213-011-2238-z
- Li, W., Yu, L., Li, W., Ge, G., Ma, Y., Xiao, L., et al. (2023). Prevention and treatment of inflammatory arthritis with traditional Chinese medicine: underlying mechanisms based on cell and molecular targets. *Ageing Research Reviews* 89, 101981. doi:10.1016/j.arr.2023.101981
- Li, X., Xiao, Z., Pu, W., Jiang, Z., Wang, S., and Zhang, Y. (2023). Network pharmacology, molecular docking, and experimental validation to explore the potential mechanism of Long Mu Qing Xin mixture for the treatment of attention deficit hyperactivity disorder. *Front. Pharmacology* 14, 1144907. doi:10.3389/fphar.2023.1144907
- Li, J., Chen, B., Li, Z. W., Wang, Y., Alberts, I., Sun, K., et al. (2024). Rhynchophylline alleviates hyperactivity and cognitive flexibility impairment associated with inhibition of inflammatory responses in mice that partly lack the dopamine transporter protein. *Brain Behavior* 14, e70121. doi:10.1002/brb3.70121
- Li, L., Wu, X., Gong, J., Wang, Z., Dai, W., Qiu, L., et al. (2024). Activation of GABA type A receptor is involved in the anti-insomnia effect of Huanglian Wendan Decoction. *Front. Pharmacology* 15, 1389768. doi:10.3389/fphar.2024.1389768
- Li, X., Xiao, Z., Jiang, Z., Pu, W., Chen, X., Wang, S., et al. (2024). Long Mu Qing Xin mixture improves behavioral performance in spontaneously hypertensive rats (SHR/NCrI) by upregulating catecholamine neurotransmitters in prefrontal cortex and striatum via DRD1/cAMP/PKA-CREB signaling pathway. *Front. Pharmacology* 15, 1387359. doi:10.3389/fphar.2024.1387359
- Liang, Z. W., Ong, S. H., Xie, Y. H., Lim, C. G., and Fung, D. (2020). The effects of a traditional Chinese medication on children with Attention-Deficit/Hyperactivity disorder. *J. Alternative Complementary Medicine (New York, N.Y.)* 26, 473–481. doi:10.1089/acm.2020.0009
- Lin, Y., Wang, Z., and zhijian, L. (2007). Observation on the effect of methylphenidate combined with Chinese medicine Ningshen Kou f u Ye on attention-deficit hyperactivity disorder. *World J. Integr. Traditional West. Med.* 12, 722–725. doi:10.13935/j.cnki.sjzx.2007.12.022
- Liu, P., Liu, Z., Wang, J., Wang, J., Gao, M., Zhang, Y., et al. (2024). Immunoregulatory role of the gut microbiota in inflammatory depression. *Nat. Communications* 15, 3003. doi:10.1038/s41467-024-47273-w
- Liu, Y., Zhang, P., and Sun, H. (2025). A narrative review of research advances in gut microbiota and microecological agents in children with attention deficit hyperactivity disorder (ADHD). *Front. Psychiatry* 16, 1588135. doi:10.3389/fpsy.2025.1588135
- Marques, D. M., Almeida, A. S., Oliveira, C. B. A., Machado, A. C. L., Lara, M. V. S., and Porciúncula, L. O. (2023). Delayed outgrowth in response to the BDNF and altered synaptic proteins in neurons from SHR rats. *Neurochem. Research* 48, 2424–2435. doi:10.1007/s11064-023-03917-9
- Ming, G. L., and Song, H. (2011). Adult neurogenesis in the Mammalian brain: significant answers and significant questions. *Neuron* 70, 687–702. doi:10.1016/j.neuron.2011.05.001
- Mowlem, F. D., Rosenqvist, M. A., Martin, J., Lichtenstein, P., Asherson, P., and Larsson, H. (2019). Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment. *Eur. Child & Adolescent Psychiatry* 28, 481–489. doi:10.1007/s00787-018-1211-3
- Ni, X. Q., Han, X. M., Yin, D. Q., and Liu, C. Q. (2015). Study on medication regularity of traditional Chinese medicines in treating attention deficit hyperactivity disorder based on data mining. *Zhongguo Zhong Yao Za Zhi* 40, 1185–1191.
- Novau-Ferré, N., Papandreou, C., Rojo-Marticella, M., Canals-Sans, J., and Bulló, M. (2025). Gut microbiome differences in children with attention deficit hyperactivity disorder and autism spectrum disorder and effects of probiotic supplementation: a randomized controlled trial. *Res. Developmental Disabilities* 161, 105003. doi:10.1016/j.ridd.2025.105003
- Omiatek, D. M., Bressler, A. J., Cans, A. S., Andrews, A. M., Heien, M. L., and Ewing, A. G. (2013). The real catecholamine content of secretory vesicles in the CNS revealed by electrochemical cytometry. *Sci. Reports* 3, 1447. doi:10.1038/srep01447
- Popit, S., Serod, K., Locatelli, I., and Stuhc, M. (2024). Prevalence of attention-deficit hyperactivity disorder (ADHD): systematic review and meta-analysis. *Eur. Psychiatry The Journal Assoc. Eur. Psychiatrists* 67, e68. doi:10.1192/j.eurpsy.2024.1786
- Posner, J., Polaczyk, G. V., and Sonuga-Barke, E. (2020). Attention-deficit hyperactivity disorder. *Lancet London, Engl.* 395, 450–462. doi:10.1016/S0140-6736(19)33004-1
- Qi, Y., Luo, X., Liu, Y., Zhang, J., Chen, X., and Zheng, Y. (2025). Efficacy and safety of jingling oral liquid for children with ADHD: a multicenter, randomized, double-blind, placebo-controlled clinical trial. *J. Attention Disorders* 29, 1345–1354. doi:10.1177/10870547251365676
- Qiu, P., Ishimoto, T., Fu, L., Zhang, J., Zhang, Z., and Liu, Y. (2022). The gut microbiota in inflammatory bowel disease. *Front. Cell Infect. Microbiol.* 12, 733992. doi:10.3389/fcimb.2022.733992
- Regan, S. L., Williams, M. T., and Vorhees, C. V. (2022). Review of rodent models of attention deficit hyperactivity disorder. *Neurosci. Biobehavioral Reviews* 132, 621–637. doi:10.1016/j.neubiorev.2021.11.041
- Saifi, M. A., Khan, H., Javed, M., Ahmad, S., Khan, Z., Mangla, A., et al. (2025). Neuroprotective effects of gastrodin against bisphenol A induced-ADHD-like symptoms in rats. *Drug Chemical Toxicology* 48, 1–14. doi:10.1080/01480545.2025.2473472
- Shi, M., Yang, J., Liu, Y., Zhao, H., Li, M., Yang, D., et al. (2025). Huanglian wendan decoction improves insomnia in rats by regulating BDNF/TrkB signaling pathway through gut microbiota-mediated SCFAs and affecting microglia polarization. *Mol. Neurobiology* 62, 1047–1066. doi:10.1007/s12035-024-04330-1
- Sittipo, P., Choi, J., Lee, S., and Lee, Y. K. (2022). The function of gut microbiota in immune-related neurological disorders: a review. *J. Neuroinflammation* 19, 154. doi:10.1186/s12974-022-02510-1
- Solmi, M., Basadonne, I., Bodini, L., Rosenbaum, S., Schuch, F. B., Smith, L., et al. (2025). Exercise as a transdiagnostic intervention for improving mental health: an umbrella review. *J. Psychiatric Research* 184, 91–101. doi:10.1016/j.jpsychires.2025.02.024
- Song, N. N., Jia, Y. F., Zhang, L., Zhang, Q., Huang, Y., Liu, X. Z., et al. (2016). Reducing central serotonin in adulthood promotes hippocampal neurogenesis. *Sci. Reports* 6, 20338. doi:10.1038/srep20338
- Song, Y., Yuan, H., Chen, T., Lu, M., Lei, S., and Han, X. (2020). An shen ding zhi ling alleviates symptoms of attention deficit hyperactivity disorder via anti-inflammatory effects in spontaneous hypertensive rats. *Front. Pharmacology* 11, 617581. doi:10.3389/fphar.2020.617581
- Song, Z., Luo, G., Han, C., Jia, G., and Zhang, B. (2022). Potential targets and action mechanism of gastrodin in the treatment of attention-deficit/hyperactivity disorder: bioinformatics and network pharmacology analysis. Evidence-based complementary and alternative medicine. *eCAM* 2022, 3607053. doi:10.1155/2022/3607053
- Steckler, R., Magzal, F., Kokot, M., Walkowiak, J., and Tamir, S. (2024). Disrupted gut harmony in attention-deficit/hyperactivity disorder: dysbiosis and decreased short-chain fatty acids. *Brain, Behavior, & Immunity - Health* 40, 100829. doi:10.1016/j.bbih.2024.100829
- Sun, R., Yuan, H., Wang, J., Zhu, K., Xiong, Y., Zheng, Y., et al. (2024). Rehmannia Radix Preparata ameliorates behavioral deficits and hippocampal neurodevelopmental abnormalities in ADHD rat model. *Front. Neuroscience* 18, 1402056. doi:10.3389/fnins.2024.1402056
- Tang, K., Hao, W., Mo, X., Chen, Y., Guo, X., He, L., et al. (2022). Analysis of the therapeutic effect of dimu ningshen (TCM formula) on attention deficit hyperactivity disorder based on gut microbiota and serum metabolomics. *BMC Complementary Medicine Therapies* 22, 24. doi:10.1186/s12906-022-03512-5
- Ullah, H., Arbab, S., Tian, Y., Liu, C. Q., Chen, Y., Qijie, L., et al. (2023). The gut microbiota-brain axis in neurological disorder. *Front. Neuroscience* 17, 1225875. doi:10.3389/fnins.2023.1225875
- Wang, W. J., and Zhang, T. (2017). Integration of traditional Chinese medicine and Western medicine in the era of precision medicine. *J. Integrative Medicine* 15, 1–7. doi:10.1016/S2095-4964(17)60314-5

- Xiong, Z., Yan, J., and Shi, S. (2021). Val158Met polymorphisms of COMT gene and serum concentrations of catecholaminergic neurotransmitters of ADHD in Chinese children and adolescents. *Medicine* 100, e27867. doi:10.1097/MD.00000000000027867
- Yan, Y., Jiang, W., Liu, L., Wang, X., Ding, C., Tian, Z., et al. (2015). Dopamine controls systemic inflammation through inhibition of NLRP3 inflammasome. *Cell* 160, 62–73. doi:10.1016/j.cell.2014.11.047
- Yang, C., Bao, L., Shi, Z., Xv, X., Li, J., Jiang, D., et al. (2026). Jingning formula alleviates ADHD by restoring gut microbiota dysbiosis and tryptophan metabolic dysfunction. *J. Pharmaceutical Biomedical Analysis* 269, 117256. doi:10.1016/j.jpba.2025.117256
- Yaqu, L., Haixia, Y., Yuchen, S., Mingxin, Z., Manqi, L., Yunlong, T., et al. (2022). An shen ding Zhi ling ameliorates the symptoms of attention deficit hyperactivity disorder via modulating brain-derived neurotrophic factor-related signaling pathways. Evidence-based complementary and alternative medicine. *eCAM* 2022, 5471586. doi:10.1155/2022/5471586
- Yin, X., Liu, W., Feng, H., Huang, J., Wang, Q., Zhang, Q., et al. (2024). *Bifidobacterium animalis* subsp. *lactis* A6 attenuates hippocampal damage and memory impairments in an ADHD rat model. *Food & Function* 15, 2668–2678. doi:10.1039/d3fo04665f
- You, L., Peng, H., Liu, J., Sai, N., Zhao, W., Li, X., et al. (2025). Xiaoe Huanglong pellets remodels the periphery microenvironment to improve attention deficit hyperactivity disorder based on the microbiota-gut-brain axis. *Phytomedicine International Journal Phytotherapy Phytopharmacology* 145, 157007. doi:10.1016/j.phymed.2025.157007
- Yuan, H., Yang, M., Han, X., and Ni, X. (2018). The therapeutic effect of the Chinese herbal medicine, *rehmanniae radix* preparata, in attention deficit hyperactivity disorder via reversal of structural abnormalities in the cortex. *Evidence-based Complementary Alternative Medicine eCAM* 2018, 3052058. doi:10.1155/2018/3052058
- Yuan, H. X., Ni, X. Q., Wu, Z. Z., Han, X. M., Xu, D. G., Song, Y. C., et al. (2018). Regulatory effect of shudihuang on expressions of BDNF/trkB and NRG-3 in prefrontal cortex and striatum of ADHD model rats. *Zhongguo Zhong Yao Za Zhi* 43, 3539–3544. doi:10.19540/j.cnki.cjcmm.20180522.004
- Yuan, H., Ni, X., Zheng, M., Han, X., Song, Y., and Yu, M. (2019). Effect of catalpol on behavior and neurodevelopment in an ADHD rat model. *Biomed. & Pharmacotherapy* 118, 109033. doi:10.1016/j.biopha.2019.109033
- Zhou, R., Wang, J., Han, X., Ma, B., Yuan, H., and Song, Y. (2019). Baicalin regulates the dopamine system to control the core symptoms of ADHD. *Mol. Brain* 12, 11. doi:10.1186/s13041-019-0428-5

Glossary

ADHD	Attention-Deficit/Hyperactivity Disorder	XRHLP	Xiaoer Huanglong Pellets
DSM	Diagnostic and Statistical Manual of Mental Disorders	DMNS	Dimu Ningshen
ICD	International Classification of Diseases	ICWM	Integrated traditional Chinese and Western medicine
TCM	Traditional Chinese medicine	6-OHDA	6-hydroxydopamine
CM	Chinese medicine	RCT	Randomized controlled trial
DA	dopamine		
NE	norepinephrine		
SHR	Spontaneously hypertensive rats		
SSa	Saikosaponin a		
BDNF	brain-derived neurotrophic factor		
PFC	prefrontal cortex		
DAT	DA transporter		
VMAT2	vesicular monoamine transporter 2		
Nrf2	nuclear factor erythroid 2-related factor		
Keap-1	kelch-like ECH-associated protein 1		
HO-1	heme oxygenase-1		
GAS	Gastrodin		
BPA	Bisphenol A		
MAO	monoamine oxidase		
JNG	Jing ning granules		
cAMP	cyclic adenosine monophosphate		
PKA	protein kinase A		
CaM	calmodulin		
CaMKII	CaM-dependent protein kinase II		
ASDZL	An shen ding zhi ling		
TrkB	tropomyosin receptor kinase B		
JNK1	C-Jun N-terminal kinases 1		
NF- κ B	nuclear factor kappa B		
LMQXM	Longmu Qingxin Mixture		
CREB	cAMP response element-binding protein		
DG	dentate gyrus		
FGF	fibroblast growth factor		
FGFR	fibroblast growth factor receptor		
SI	Social isolation		
Cdk5	cyclin-dependent kinase 5		
SST	Suan Zao Ren Tang		
early growth responsive gene-1	early growth responsive gene-1		
mitogen-activated protein kinase	mitogen-activated protein kinase		
NDG	Ningdong granule		
RHY	Rhynchophylline		
BBB	blood-brain barrier		