Mechanisms of Xiaoyao San in Treating Depression: A Comprehensive Review of Pharmacological Actions and Clinical Evidence

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Abstract. Xiaoyao San (XYS), a classic Traditional Chinese Medicine (TCM) formula, is widely used for treating depression by addressing "liver stagnation and spleen deficiency" syndrome. Despite its clinical efficacy, the underlying mechanisms of XYS in depression treatment remain multifaceted and require systematic elucidation. Advances in network pharmacology, metabolomics, and molecular biology have enabled deeper investigations into XYS's pharmacological actions. This comprehensive review synthesizes preclinical and clinical research spanning over two decades (2000–2025), highlighting the XYS's critical role in modulating neurotransmitter systems (e.g., 5-HT, DA, GABA/glutamate balance), neuroinflammation (e.g., microglial polarization, NLRP3 inflammasome), HPA axis regulation, gut-brain axis interactions, and neuroplasticity (e.g., BDNF, mTOR signaling). Key pathways such as PI3K/AKT, MAPK, and TLR4/NF-κB are implicated in its antidepressant effects. Additionally, this review explores the active components of XYS, including *paeoniflorin, quercetin*, and *atractylenolide III*, which target multiple biological processes. Clinical evidence supports the safety and efficacy of XYS for treating depression, both as monotherapy and as an adjunctive therapy, including in special populations. (e.g., post-stroke depression, perimenopausal women). This review provides a foundation for further research on XYS-based therapies, integrating TCM theory with modern pharmacology.

Keywords: Xiaoyao San, Depression, Neurotransmitter modulation, Neuroinflammation, Gut-brain axis, HPA axis, Neuroplasticity.

1. Introduction

Depression, a debilitating mental disorder affecting over 300 million people globally, ranks as a leading cause of disability worldwide (WHO, 2023). Conventional antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), face significant limitations including delayed efficacy (2–6 weeks), suboptimal response rates (50%), and adverse effects (e.g., sexual dysfunction, weight gain). These challenges underscore the urgent need for alternative therapeutic strategies with improved safety profiles.

XYS, addresses the TCM syndrome of "liver qi stagnation with spleen deficiency" –a pathological state mirroring depression's core manifestations. Its eight herbal components (*Mentha haplocalyx*, et al.) synergistically regulate neuroendocrine-immune networks, with modern applications spanning depression, premenstrual syndrome, and irritable bowel syndrome.

The therapeutic potential of XYS in depression is grounded in robust evidence spanning molecular mechanisms, clinical efficacy, and chemical characterization. First, XYS exhibits multi-target mechanisms, modulating key pathways implicated in depression, including neurotransmitter systems (5-HT, DA, NE) [1, 2], neuroinflammation (NLRP3, IL-6, TNF-α) [3, 4], gut-brain axis interactions (microbiota, SCFAs) [5, 6], and HPA axis regulation (corticosterone, GR) [7; 8]. Second, clinical validation from randomized controlled trials (RCTs) demonstrates XYS's non-inferiority to SSRIs in reducing HAMD scores, coupled with a favorable safety profile [9, 10]. Third, advanced analytical

techniques have identified bioactive compounds (e.g., *paeoniflorin, saikosaponins*), providing a molecular foundation for its antidepressant effects. Together, these pillars substantiate XYS as a promising integrative therapy for depression, bridging traditional medicine with modern pharmacotherapy.

This review synthesizes recent advances (2020–2025) in XYS depression research, bridging TCM theory with translational evidence to inform integrative treatment paradigms.

2. Chemical Composition of Xiaoyao San

2.1. Key Bioactive Components

XYS and its modified formulations exert antidepressant effects through a diverse array of bioactive compounds with distinct pharmacological actions. Advanced analytical techniques, including LC-Q-TOF/MS, have identified 108 constituents in Jiawei Xiaoyao Wan (JXW), such as saikosaponins (e.g., saikosaponin A/D) and paeoniflorin, which collectively regulate inflammation and monoamine neurotransmitter systems in depression models. Notably, Modified Danzhi Xiaoyao San (MDZXYS) contains 81 compounds, of which 13—including senkyunolide A and atractylenolide III—cross the blood-brain barrier to directly activate ERK1/2-AKT signaling and restore synaptic plasticity [11]. Core components like paeoniflorin (from *Paeonia*), liquiritin (from *Glycyrrhiza*), and ferulic acid (from *Angelica*) further target key proteins (TP53, EGFR, PTGS2) to modulate PI3K-AKT/MAPK pathways, thereby inhibiting neuronal apoptosis and neuroinflammation [12].

These compounds exhibit multifaceted mechanisms: saikosaponins suppress neuroinflammation via NLRP3 inhibition and normalize HPA axis dysfunction; paeoniflorin upregulates BDNF to promote hippocampal neurogenesis; quercetin attenuates neuronal pyroptosis by targeting PTGS2. Together, these bioactive constituents underpin XYS's holistic antidepressant effects through synergistic modulation of neurochemical, inflammatory, and neuroplasticity pathways.

2.2. Analytical Techniques

Advanced analytical platforms enable comprehensive characterization of XYS compounds. Integrated UPLC-Q-Orbitrap-MS et al. identified 299 constituents (198 non-volatile, 101 volatile) in Xiaoyao Wan, establishing a quality marker system with 14 quantified compounds[13]. For brain bioavailability studies, LC-Q-TOF/MS detected 10 prototype compounds and 16 metabolites in brain tissues, confirming blood-brain barrier penetration of key agents (e.g., paeoniflorin, atractylenolide III) [12]. These techniques validate XYS’s multi-component synergy and provide quality control benchmarks.

3. Pharmacological Mechanisms

3.1. Neurotransmitter Regulation

3.1.1. Monoaminergic Modulation

XYS and its derivatives significantly enhance monoaminergic neurotransmission. Quercetin—a key flavonoid in modified XYS formulations—elevates hippocampal 5-HT, DA, and NE levels in breast cancer-related depression (BCRD) models by targeting the PTGS2-mediated ferroptosis pathway. Molecular docking confirms quercetin-PTGS2 binding, and PTGS2 overexpression abolishes these effects[2]. Similarly, Danzhi Xiaoyao San (DZXYS) alleviates depressive symptoms by normalizing monoamine deficits and dampening HPA axis hyperactivity, with minimal adverse effects [1].

3.1.2. Tryptophan Metabolic Pathway

XYS restores tryptophan metabolism homeostasis by inhibiting hepatic tryptophan 2,3-dioxygenase (TDO). LC-MS/MS analyses reveal that XYS increases the 5-HT/KYN ratio and

decreases the KYN/TRP ratio in the blood, liver, and brain of stress-induced depressive mice, though its TDO-inhibitory efficacy is less pronounced than Chaihu Shugan San [14]. This modulation shifts tryptophan metabolism toward serotonin synthesis rather than the neurotoxic kynurenine pathway.

3.2. Anti-inflammatory and Neuroprotective Effects

3.2.1. Microglial Polarization (M1→M2)

XYS derivatives suppress neuroinflammation by reprogramming microglial activation states. In breast cancer-related depression (BCRD), Xiaoyao Kangai Jieyu Recipe (XKJR) inhibits hippocampal microglial activation (↓CD11b) and downregulates IL-1β, IL-18, and COX-2, reducing neuronal damage and tumor growth by 48.83%. Similarly, Modified Danzhi Xiaoyao San (MDZXYS) promotes TRIM31-mediated ubiquitin-proteasomal degradation of the NLRP3 inflammasome in CUMS rats, reversing anhedonia and neuronal injury [3]. Notably, Danzhi Xiaoyao San (DZXYS) shifts microglia from pro-inflammatory M1 to anti-inflammatory M2 phenotypes in post-stroke depression by activating the PKCγ/p38/NF-κB axis, improving cerebral blood flow and reducing infarct volume [15].

3.2.2. Astrocyte Protection

XYS enhances astrocyte-mediated neuroprotection through multiple signaling pathways. Xiaoyao Pills (XYW) upregulate the PIK3CA-AKT1-NFE2L2/BDNF axis in olfactory-bulbectomized rats, increasing antioxidant markers (SOD1, GPX3, HMOX1) and reducing oxidative stress (↓malondialdehyde, ↓ROS). In LPS-induced neuroinflammation, XYW elevates neurotrophic factors (BDNF, NGF), synaptic proteins (SYP), and neurogenesis markers (BrdU/$NeuN^+$ cells) while suppressing IL-6 and TNF-α [16].

3.2.3. Pyroptosis and Oxidative Stress

Key XYS components inhibit neuronal pyroptosis. Quercetin (in XYS formulations) downregulates ASC/NLRP3/caspase-1 in BCRD, reversing pyroptosis-induced neuronal death and restoring monoamine levels (5-HT/DA/NE) [17].

3.2.4. Systemic Inflammation Regulation

XYS modulates systemic inflammatory networks. Network pharmacology analyses identify IL-6, TNF-α, and IL-4 as core targets of XYS in treating depression and comorbidities (e.g., breast hyperplasia), with kaempferol and quercetin showing high binding affinity to these cytokines [18]. Additionally, XYS alleviates postmenopausal osteoporosis via the IL-17 pathway, demonstrating its broad anti-inflammatory role beyond neurological disorders [19].

3.3. HPA Axis Regulation

3.3.1. Corticosterone and Glucocorticoid Receptor (GR)

XYS attenuates hyperactivity of the HPA axis in depression models. Paeoniflorin—a core component of XYS—reduces serum corticosterone (CORT, a primary glucocorticoid in rodents) levels, mitigates glucocorticoid receptor (GR) dysregulation, and elevates hippocampal brain-derived neurotrophic factor (BDNF), thereby counteracting stress-induced neurotoxicity [7]. In rats subjected to chronic unpredictable mild stress (CUMS), XYS suppresses hippocampal damage and serum CORT elevation by upregulating GR phosphorylation (p-GR) and connexin 43 (Cx43). This interaction forms a Cx43/GR/BDNF neuroprotective axis that inhibits stress-induced neuronal apoptosis.

3.3.2. Estrogen-like Effects

XYS exerts estrogen-mimetic actions via ERα signaling. In ovariectomized (OVX) ApoE-/- mice, XYS inhibits hepatic steatosis by activating estrogen receptor α (ERα), downregulating lipogenic genes (LXRα, SREBP-1c), and reducing triglyceride accumulation. These effects are partially reversed by the ER antagonist ICI 182,780[20]. Although not directly studied in XYS, the related

formula Chaigui Granule (containing XYS herbs) increases serum and hippocampal estradiol (E2) by upregulating CYP19A1 (aromatase) and activating the CYP19A1-E2-ERK pathway, suggesting a conserved mechanism for XYS in gender-specific depression treatment.

3.4. Gut-Brain Axis Modulation

3.4.1. Gut Microbiota Remodeling

XYS formulations exert antidepressant effects by reshaping gut microbial ecology. In chronic stress models, JWXYP increase the abundance of *Lactobacillus* and elevate short-chain fatty acids (SCFAs), correlating with increased brain 5-HT/VIP levels. Similarly, Danzhi Xiaoyao San (DZXYS) combined with SSRIs in depressed patients enriches beneficial *Bacteroides coprophilus* while reducing pathogenic *Ruminococcus gnavus*, concomitant with the normalization of 39 serum metabolites (e.g., lysophosphatidic acid) linked to neuroinflammation [6]. Network pharmacology analyses further identify quercetin and luteolin in XYS as key modulators of gut-brain signaling through AVPR2 and EGFR targeting (ibid).

3.4.2. Gut Barrier Protection

XYS enhances intestinal integrity to mitigate neuroinflammation. In high-fat diet (HFD)-induced obesity with depression, XYS increases Faecalibaculum rodentium and its SCFA metabolites, which activate dopamine D2 receptors (DRD2) in the medial prefrontal cortex [4]. For comorbid irritable bowel syndrome (IBS) and depression, XYS repairs intestinal villi and upregulates zonula occludens-1 (ZO-1) to fortify the mucosal barrier. Mechanistically, it inhibits the colonic ACT1/TRAF6/p38MAPK/AP-1 pro-inflammatory pathway while activating the cerebral DRD2/tyrosine hydroxylase axis to boost dopamine synthesis [21].

3.5. Neuroplasticity and Mitochondrial Function

3.5.1. Synaptic Plasticity (PSD95/mTOR)

Contemporary research demonstrates that modified Xiaoyao San formulations promote hippocampal synaptic remodeling through multiple rapid mechanisms: (1) The refined GMA formula (*Gardeniae Fructus-Moutan Cortex-Atractylodis Rhizoma combination*) exhibits dual regulatory effects by simultaneously inhibiting microglial activation (Iba-1/NF-κB↓) to reduce neuroinflammation while activating mTOR-BDNF signaling and normalizing NMDA receptor subunits (GluN1/GluN2B), with therapeutic effects lasting 5 days [22]; (2) Jiawei Danzhi Xiaoyao San (JWDZXYS) enhances neuronal structural stability by promoting ERK1/2 phosphorylation and upregulating neurofilament proteins (NEFL/NEFM) expression [23]. These findings systematically elucidate how different modified Xiaoyao San formulations collectively enhance synaptic plasticity through distinct molecular mechanisms, providing a theoretical foundation for developing fast-acting antidepressant herbal medicines.

3.5.2. Mitochondrial Energy Metabolism

Emerging evidence demonstrates that XYS comprehensively ameliorates mitochondrial dysfunction in depression through a cascade of coordinated metabolic interventions. At the enzymatic level, XYS restores TCA cycle flux by upregulating key metabolic enzymes including pyruvate dehydrogenase (PDH) et al, with troxerutin identified as a principal bioactive component mediating these effects [24].

The therapeutic effects extend to hepatic mitochondria, where XYS normalizes the profile of nine critical metabolites involved in AGE-RAGE and HIF-1 signaling pathways, resulting in measurable improvements in physical exercise capacity [8]. Importantly, these organ-specific effects culminate in systemic metabolic normalization, as evidenced by correction of plasma metabolic abnormalities including phenylalanine and arachidonic acid metabolism [25].

This hierarchical regulation- from enzymatic activity to cellular ultrastructure, organ function and systemic metabolism- demonstrates XYS's unique capacity to target mitochondrial dysfunction at

multiple biological levels. The coordinated action across these levels provides a comprehensive and integrated approach to metabolic regulation in depression, offering new insights into the therapeutic potential of traditional herbal medicine for metabolic aspects of mood disorders.

4. Conclusion

XYS exemplifies a sophisticated multi-target therapeutic approach that harmonizes the traditional Chinese medicine principle of "*soothing liver qi stagnation and fortifying the spleen*" with contemporary neurobiological understanding. This botanical formula orchestrates four synergistic mechanisms of action: (1) Comprehensive neurotransmitter regulation through monoamine (5-HT/DA/NE) modulation, GABA/glutamate rebalancing, and hepatic tryptophan metabolism control via TDO inhibition [2, 14]; (2) Advanced immunomodulation by reprogramming microglial polarization (M1→M2) through dual NLRP3/TRIM31 ubiquitination and TLR4/NF-κB pathway suppression [3, 4]; (3) Gut-brain axis optimization via microbiota remodeling (notably *Faecalibaculum rodentium* enrichment) and SCFA-mediated enhancement of intestinal barrier function, which subsequently activates central DRD2 signaling [4, 6]; and (4) Systemic neuroendocrine restoration through HPA axis normalization (corticosterone/GR regulation) coupled with structural neuroplasticity enhancement via BDNF/mTOR/PSD95 pathways. This multidimensional therapeutic architecture positions XYS as a unique integrative intervention that simultaneously addresses the neurotransmitter, inflammatory, metabolic, and structural dimensions of depression pathophysiology.

Clinically, XYS demonstrates non-inferior efficacy to SSRIs/SNRIs in reducing HAMD scores with superior safety (↓sexual dysfunction)[9,26]; particularly in special populations (e.g., post-stroke and perimenopausal depression).

While XYS has demonstrated promising clinical efficacy, several key challenges must be addressed to advance its therapeutic application. Mechanistic studies should employ cutting-edge metabolomic and epigenomic approaches to establish definitive causal relationships between specific bioactive components (e.g., paeoniflorin, saikosaponins) and clinical outcomes. Clinical translation requires rigorous large-scale RCTs comparing XYS efficacy against emerging antidepressants (e.g., ketamine) in treatment-resistant populations [9]. Formulation optimization could leverage nanocarrier technology to improve blood-brain barrier penetration of critical compounds [11]. These strategic research directions will be essential for transforming XYS from an empirically-used herbal formula into a mechanistically-validated, precision-targeted antidepressant therapy.

Integrating XYS into mainstream depression management offers a promising "disease-syndrome" combined approach, exemplifying how TCM-derived multi-target strategies address the complexity of neuropsychiatric disorders beyond monoamine-centric therapies. Develop a deep learning model of 'herbal components - biological targets - signaling pathways - clinical phenotypes' to predict the efficacy of XYS on depression subtypes.Further studies should validate XYS's multi-target effects using omics approaches and standardized clinical protocols.

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References

[1] Xie Z, Xie H, Peng X et al. (2023). The antidepressant-like effects of Danzhi Xiaoyao San and its active ingredients. [Journal Article; Review]. *Phytomedicine*, 119, 155015.

[2] Zhu Q, Han Y, He Y et al. (2024). Quercetin inhibits neuronal Ferroptosis and promotes immune response by targeting lipid metabolism-related gene PTGS2 to alleviate breast cancer-related depression. [Journal Article]. *Phytomedicine*, 130, 155560.

[3] Wang B, Tian L, Wu M et al. (2024). Modified Danzhi XiaoyaoSan inhibits neuroinflammation via regulating TRIM31/NLRP3 inflammasome in the treatment of CUMS depression. [Journal Article]. *Exp Gerontol*, 192, 112451.

[4] Yang Y, Zhong Z, Wang B et al. (2022). Xiaoyao San ameliorates high-fat diet-induced anxiety and depression via regulating gut microbiota in mice. [Journal Article]. *Biomed Pharmacother*, 156, 113902.

[5] Li Z, Zhao Y, Cheng J et al. (2022). Integrated Plasma Metabolomics and Gut Microbiota Analysis: The Intervention Effect of Jiawei Xiaoyao San on Liver Depression and Spleen Deficiency Liver Cancer Rats. [Journal Article]. *Front Pharmacol*, 13, 906256.

[6] Zhu X, Wu S, Zhou Y et al. (2024). The pharmacological actions of Danzhi-xiaoyao-San on depression involve lysophosphatidic acid and microbiota-gut-brain axis: novel insights from a systems pharmacology analysis of a double-blind, randomized, placebo-controlled clinical trial. [Journal Article; Randomized Controlled Trial]. *J Biomol Struct Dyn*, 42 (18), 9309 - 9324.

[7] Guo W, Yao X, Cui R et al. (2022). Mechanisms of paeoniaceae action as an antidepressant. [Journal Article; Review]. *Front Pharmacol*, 13, 934199.

[8] Zhao W, Ji C, Zheng J et al. (2024). Effects of Xiaoyao San on exercise capacity and liver mitochondrial metabolomics in rat depression model. [Journal Article]. *Chin Herb Med*, 16 (1), 132 - 142.

[9] Dang C, Wang Q, Li Q et al. (2024). Chinese herbal medicines for the treatment of depression: a systematic review and network meta-analysis. [Journal Article; Systematic Review]. *Front Pharmacol*, 15, 1295564.

[10] Wang X, Feng S, Wang Y et al. (2022). Canonical Chinese medicine formula Danzhi-Xiaoyao-San for treating depression: A systematic review and meta-analysis. [Journal Article; Meta-Analysis; Systematic Review]. *J Ethnopharmacol*, 287, 114960.

[11] Wu M, Yan X, Huang H et al. (2025). Integration of network pharmacology and experimental verification to reveal the active components and molecular mechanism of modified Danzhi Xiaoyao San in the treatment of depression. [Journal Article]. *J Ethnopharmacol*, 336, 118739.

[12] Zhou S, Wang Y, Xie M et al. (2025). Uncovering the antidepressant active ingredients and related molecular mechanisms of Xiaoyao Pill using integrated pharmacological strategy. [Journal Article]. *J Chromatogr B Analyt Technol Biomed Life Sci*, 1255, 124502.

[13] Yin J, Wu T, Zhu B et al. (2024). Comprehensive multicomponent characterization and quality assessment of Xiaoyao Wan by UPLC-Q-Orbitrap-MS, HS-SPME-GC-MS and HS-GC-IMS. [Journal Article]. *J Pharm Biomed Anal*, 239, 115910.

[14] Cong M, Liang X, Chen F et al. (2021). [Antidepressant mechanism of Shugan Lipi recipe in regulating tryptophan metabolism and its common pharmacodynamic substances]. [Journal Article]. *Zhongguo Zhong Yao Za Zhi*, 46 (14), 3633 - 3642.

[15] Zeng J, Xie Z, Xie H et al. (2025). Reducing neuroinflammation through PKCgamma/p38/NF-kappaB signaling pathway: the mechanism of Danzhi Xiaoyaosan in improving post-stroke depression. [Journal Article]. *J Ethnopharmacol*, 352, 120151.

[16] Fang Y, Shi B, Liu X et al. (2020). Xiaoyao Pills Attenuate Inflammation and Nerve Injury Induced by Lipopolysaccharide in Hippocampal Neurons In Vitro. [Journal Article; Research Support, Non-U.S. Gov't]. *Neural Plast*, 2020, 8841332.

[17] Zhu Q, Yang L, Yang H et al. (2022). Quercetin Alleviates the Progression of Breast Cancer-Related Depression via Inhibiting the Pyroptosis and Promoting the Immune Response. [Journal Article]. *Mediators Inflamm*, 2022, 8011988.

[18] Wei F, Liu H, Fan Y et al. (2021). [Mechanism of Xiaoyao San in treatment of depression, breast hyperplasia, and functional dyspepsia based on network pharmacology]. [Journal Article]. *Zhongguo Zhong Yao Za Zhi*, 46 (16), 4230 - 4237.

[19] Yang Y, Zhang Y, Kuang S et al. (2024). Studies on the Anti-Inflammatory Effect of Xiaoyao Pills in The Treatment of Postmenopausal Osteoporosis in Mice. [Journal Article; Video-Audio Media]. *J Vis Exp* (210).

[20] Hu T, Wei M, Hong G et al. (2022). Xiaoyao San attenuates hepatic steatosis through estrogen receptor alpha pathway in ovariectomized ApoE-/- mice. [Journal Article]. *J Ethnopharmacol*, 282, 114612.

[21] Yu J, Li X, Sun Y et al. (2025). Transcriptomic analysis and experiment to verify the mechanism of Xiaoyao san in the treatment of irritable bowel syndrome with depression. [Journal Article]. *J Ethnopharmacol*, 347, 119732.

[22] Wu Z, Yin Y, Liu R et al. (2024). A refined formula derived from Jiawei-Xiaoyao pill exerts rapid antidepressant-like effects in LPS-induced depression by reducing neuroinflammation and restoring neuroplasticity signaling. [Journal Article]. *J Ethnopharmacol*, 335, 118647.

[23] Yajing L I, Baoying W, Wenxue S et al. (2025). Quantitative proteomic analysis of the brain reveals the potential antidepressant mechanism of Jiawei Danzhi Xiaoyao San in a chronic unpredictable mild stress mouse model of depression. [Journal Article]. *J Tradit Chin Med*, 45 (1), 22 - 31.

[24] Tian J, Wang X, Wu W et al. (2024). Stable Isotope Tracer Technique and Network Pharmacology to Reveal Antidepressant Targets and Active Components of Xiaoyao San. [Journal Article]. *Chem Biodiverse*, 21 (4), e202301736.

[25] Zhu Y, Li S, Zhu C et al. (2020). Metabolomics analysis of the antidepressant prescription Danzhi Xiaoyao Powder in a rat model of Chronic Unpredictable Mild Stress (CUMS). [Journal Article]. *J Ethnopharmacol*, 260, 112832.

[26] Xiyu L I, Yanhong Y, Jian S et al. (2024). Effectiveness and safety of Jiawei Xiaoyao pill in the treatment of premenstrual syndrome (liver depression, spleen deficiency, and blood-heat syndrome): a multi-center, randomized, placebo-controlled trial. [Journal Article; Multicenter Study; Randomized Controlled Trial]. *J Tradit Chin Med*, 44 (2), 373 - 380.