

Research Progress on the Application and Mechanisms of Baihe Dihuang Decoction in Major Depressive Disorder

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Objective: The treatment of major depressive disorder (MDD) is often plagued by inadequate therapeutic efficacy, high relapse rates, and adverse drug effects. Baihe Dihuang Decoction (BDDH, Lily Bulb and Rehmannia Decoction), a classic Traditional Chinese Medicine (TCM) formula, shows promise for depression, but a comprehensive synthesis of modern evidence is warranted. This study aimed to review the clinical efficacy, pharmacological mechanisms, and safety profile of BDDH for MDD to inform its clinical application and guide future research.

Methods: A systematic literature search was conducted in both English (PubMed, Web of Science) and Chinese (CNKI, Wanfang) databases from inception to June 2025. For clinical evidence, the search focused on “Baihe Dihuang Decoction”, “major depressive disorder/depression”, and “randomized controlled trial”. Supplementary searches using terms like “chemical constituents” and “pharmacological action” were performed for mechanistic studies. Relevant literature was subsequently summarized and analyzed.

Results: Current evidence suggests that BDDH, as an adjunct to conventional antidepressants, can improve the overall clinical response rate, reduce Hamilton Depression Rating Scale scores, and potentially alleviate adverse reactions. Its active constituents may exert antidepressant effects via multiple pathways, including monoaminergic neurotransmission modulation, neuroinflammation inhibition, hypothalamic-pituitary-adrenal axis regulation, hippocampal neuron protection, and gut microbiota modulation. However, its efficacy as a monotherapy and long-term safety profile require further validation through high-quality clinical trials.

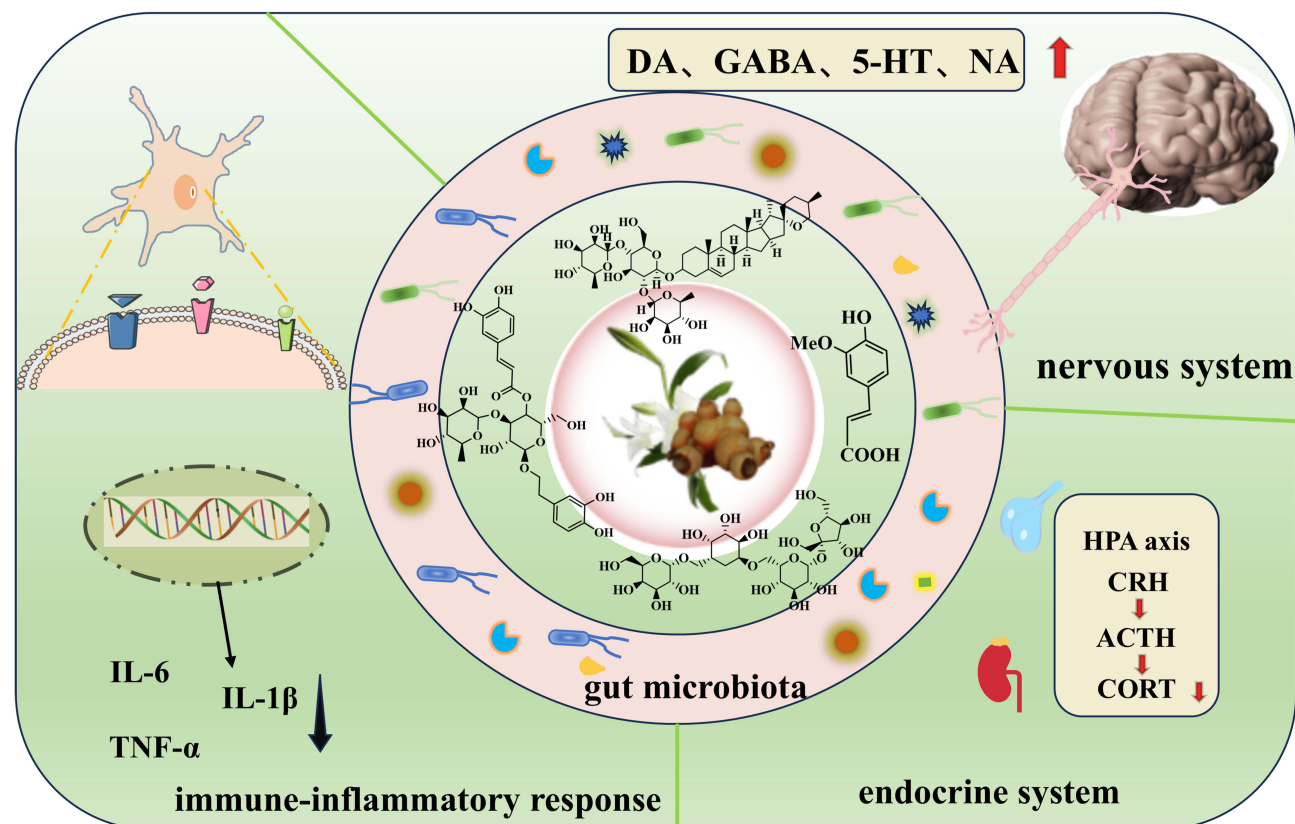
Conclusion: BDDH possesses a multi-target pharmacological basis for antidepressant activity. Existing clinical evidence supports its effectiveness and relative safety as an adjunctive therapy for MDD. To better define its clinical role and advance TCM modernization, future research should prioritize rigorous randomized controlled trials, elucidate its formula compatibility mechanisms, and identify its key bioactive components.

Keywords: Baihe Dihuang decoction, history of development, chemical composition, major depressive disorder, mechanism of action

Introduction

Major depressive disorder (MDD) is primarily characterized by a persistently low mood, often accompanied by a loss of interest, emotional distress, low self-esteem, appetite loss, sleep disturbances, and other clinical manifestations. In severe cases, it may even lead to suicidal tendencies, making it one of the most common types of mental illness. The onset of MDD is complex and results from the interplay of multiple factors, including social, familial, and life circumstances. Individuals who have experienced childhood abuse, severe financial losses, or other adverse events are at a higher risk of developing MDD. Additionally, challenges in school and the workplace can also contribute to its onset.¹ Although psychological therapies and medications are available for

Graphical Abstract



MDD, these treatments are often inaccessible or nonexistent in developing countries and impoverished regions. MDD has become the fourth leading disease worldwide, imposing a significant economic and social burden.²

Currently, several major theories or hypotheses have been proposed, including the monoamine hypothesis, inflammation and oxidative stress response, the hypothalamic-pituitary-adrenal (HPA) axis, reduced synaptic plasticity, secretion disorders of neurotrophic factors, and the microbiota-gut-brain (MGB) axis.³ Among these, the monoamine hypothesis is widely regarded by many scholars as a key mechanism underlying MDD.⁴ It suggests that an abnormal reduction in monoamine neurotransmitters—such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA)—within synapses in the central nervous system is closely associated with the onset of MDD.⁵ Clinically, selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, paroxetine, and sertraline, are commonly prescribed. While these medications provide therapeutic relief to some extent, prolonged use may lead to side effects and even suicidal tendencies in severe cases.⁶ Current clinical studies suggest that TCM formulas may not only help reduce patients' excessive sensitivity to environmental stimuli but also alleviate certain symptoms associated with major depressive disorder. For instance, multiple randomized controlled trials have indicated that specific TCM compound formulations can demonstrate efficacy comparable or complementary to conventional antidepressants in improving particular symptom dimensions or quality-of-life indicators.⁷ Nevertheless, the overall body of evidence still requires further validation and integration. Taking BHDH as an example, the modern clinical and basic research evidence for such classic formulas has yet to be systematically synthesized, which obscures their specific mechanisms of action and clinical positioning. Therefore, this review systematically examines the historical origins, clinical efficacy, pharmacological mechanisms, and safety profile of BHDH, assesses the strengths and limitations of the current evidence, and aims to clarify the existing research landscape while informing future key research priorities.

Baihe Dihuang Decoction Historical Records

Within the theoretical framework of TCM, depression is primarily categorized as “Yu Syndrome”. Its core pathogenesis is considered to be emotional stagnation leading to Qi mechanism obstruction, which may subsequently result in dysfunction of the Zang-fu organs. Guided by TCM principles of syndrome differentiation and treatment, the management of Yu Syndrome typically focuses on key organs such as the liver, heart, and spleen. For instance, the initial stage often presents as liver Qi stagnation, manifesting as emotional depression and a sensation of distension in the chest and hypochondriac regions. If this stagnation persists and transforms into fire, it may disturb the heart spirit, leading to symptoms like irritability and insomnia. Furthermore, if liver stagnation affects the spleen’s transport function, symptoms such as poor appetite, fatigue, and excessive rumination may occur. This holistic perspective, centered on “Zang-fu differentiation”, provides the theoretical rationale for TCM interventions in depression. These interventions aim to soothe the liver and relieve stagnation, nourish the heart to calm the mind, and strengthen the spleen to resolve phlegm.⁸

Guided by this theoretical framework, clinical studies suggest that Chinese herbal formulas may not only help reduce patients’ hypersensitivity to environmental stimuli but also alleviate specific symptoms of major depressive disorder (eg, depressed mood, insomnia, and reduced appetite, which correspond to the manifestations of Yu Syndrome). Multiple studies indicate that certain classic herbal formulas demonstrate efficacy comparable or complementary to conventional antidepressants in improving depressive mood, sleep quality, and quality of life.⁷ Nevertheless, current research is often limited by small sample sizes and methodological shortcomings, making it difficult to fully define the precise role of Chinese herbal medicine within comprehensive depression treatment plans. Therefore, large-scale, high-quality clinical trials are urgently needed to validate these findings.

Among numerous Chinese herbal formulas for treating depression, BHDH has a long history of medicinal use, originating from *Jingui Yaolue* (Essential prescriptions from the golden cabinet), written by Zhang Zhongjing during the Eastern Han dynasty. The text states: “For Baihe disease that has not been treated with emesis, purgation, or diaphoresis and remains unchanged, BHDH decoction is the primary remedy”. Later, during the Tang dynasty, Sun Simiao also documented this formula in *Beiji Qianjin Yaofang* (Essential prescriptions worth a thousand gold), maintaining both its name and therapeutic indications.

Usage of BHDH Decoction

The term “Baihe Disease” first appeared in *Jin Kui Yao Lue* (Synopsis of Prescriptions of the Golden Chamber), a classical text attributed to the Eastern Han dynasty physician Zhang Zhongjing (c. early 3rd century CE), where it was described as a distinct clinical entity. The disease is named after its core therapeutic herb, the lily bulb (Baihe), highlighting the herb’s central role in its treatment. The original text characterizes the condition with symptoms such as: “desiring food but being unable to eat, often remaining silent; wanting to lie down but finding no rest; wishing to move but being unable to walk; at times having an appetite, yet at other times being repelled by the smell of food; a sensation of cold without true cold, and of heat without true heat; a bitter taste in the mouth, and dark-colored urine. as if influenced by a spiritual presence”. According to ancient medical theory, its pathogenesis was attributed to “lingering residual heat after a febrile illness” or “emotional constraint leading to stagnation, which subsequently transforms into fire”. This pathological process results in a state of yin deficiency with internal heat affecting the heart and lungs. The core manifestations of Baihe Disease—persistent dysfunction in emotion, behavior, sensation, and somatic function—exhibit notable overlap with modern diagnostic categories such as MDD, anxiety disorders, and somatic symptom disorders. Consequently, the pathogenesis framework of “yin deficiency with internal heat in the heart and lungs” provides a foundational TCM theoretical model for diagnosing and treating these conditions. The formula BHDH embodies the corresponding therapeutic principle of “nourishing yin, clearing heat, and calming the heart to tranquilize the mind”, standing as the classic prescription exemplar for this specific pattern.

The naming of the formula Baihe Dihuang Decoction (Lily Bulb and Rehmannia Decoction) directly originates from its classical documentation in *Jin Gui Yao Lue* (Essentials from the Golden Cabinet), which specifies “seven lily bulbs” and “fresh rehmannia juice”. This record not only establishes the sovereign herbs but also prescribes a unique preparation process. The key steps include: “seven lily bulbs. wash the lily bulbs with water, soak overnight until white foam appears,

discard the water, then add two sheng of spring water, decoct until one sheng remains, remove the dregs, and add the rehmannia juice". Modern pharmacological research provides a scientific basis for these traditional procedures.^{9–11} First, the white foam that appears after soaking the lily bulbs is related to their colchicine content; this step aims to reduce the level of this component, as while colchicine can be used to treat gout, long-term intake may cause adverse reactions.¹¹ Second, the requirement to use fresh rehmannia juice is due to its rich catalpol content, which is sensitive to pH and can undergo chemical changes in the body. This explains the normal phenomenon of possible darkening of stool after taking the decoction.¹² These findings indicate that the traditional preparation details not only reflect the empirical understanding of medication safety by ancient practitioners but also provide important practical references for modern pharmaceutical research and process optimization.

Functions and Indications

According to ancient texts, BHDH decoction has the effects of clearing heat, nourishing yin, and tonifying the heart and lungs. Lily bulb is known for its functions of clearing the heart, calming the mind, moistening the lungs, and nourishing yin. *R. glutinosa* is recognized for its ability to clear heat, generate fluids, and cool the blood.¹³ When used together, these two herbs work synergistically to nourish yin, tonify the heart and lungs, and clear the heart to calm the mind. In modern clinical practice, this formula is primarily used to treat yin deficiency with internal heat affecting the heart and lungs, presenting symptoms such as restlessness, insomnia, disordered eating, and a bitter taste in the mouth. It is widely applied in the treatment of insomnia, MDD, anxiolytic, antitumor and mood disorders (Figure 1), including menopausal syndrome in women.¹⁴

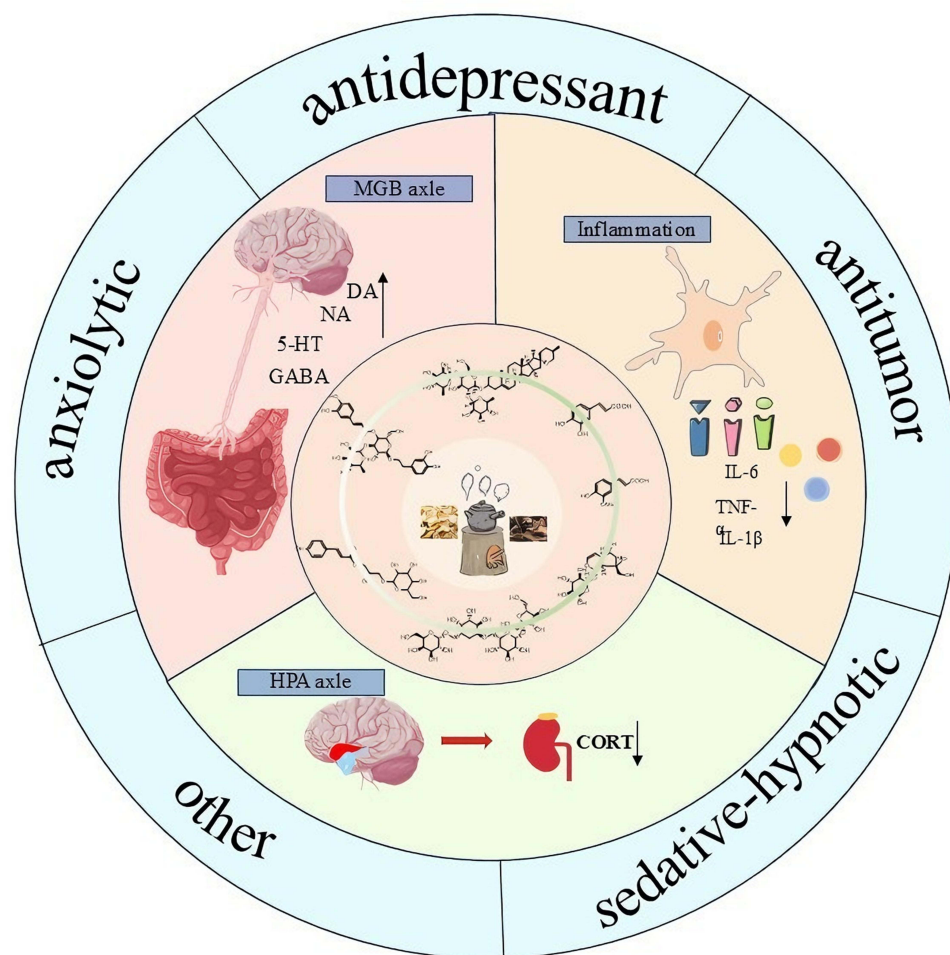


Figure 1 Pharmacological Activity of BHDH.

Chemical Composition of BHDH Decoction

Chemical Components in Lily Bulb

Modern pharmacological studies of TCM have identified a range of active components in lily bulbs. The main components extracted include lily polysaccharides, steroidal saponins, alkaloids, flavonoids, and phenolic compounds. Among these, steroidal saponins are the key active components responsible for the decoction's sedative and hypnotic effects, as well as for regulating gut microbiota and 5-HT, thereby exerting antidepressant properties.¹⁵ Lily polysaccharides, flavonoids, and phenolic compounds also possess antioxidant effects, helping to neutralize free radicals. Additionally, oxidative stress has been widely recognized as a key factor in the development of symptoms such as depression and insomnia.

Polysaccharides

The primary active components in lily bulbs are polysaccharides, which possess biological activities such as immune regulation, antioxidation, blood glucose reduction, anti-aging, and anti-tumor effects.¹⁶

Steroidal Saponins

Currently, all saponins extracted and isolated from lily bulbs are steroidal saponins. A total of 53 types have been identified in the *Lilium* genus ([Supplementary Table 1](#) and [Supplementary Figure 1](#)).

Phenolics

Genus *Lilium* contains abundant phenolic compounds, which represent a major class of bioactive components in this genus ([Supplementary Table 2](#) and [Supplementary Figure 2A](#)).

Flavonoids

Currently, 13 flavonoids have been extracted from lily bulbs, including (+)-catechol, rutin, dihydromyricetin, eriodictyol, myricetin, quercetin, etc. ([Supplementary Table 3](#) and [Supplementary Figure 2B](#)).

Alkaloids and Other Components in Lily Bulb

Alkaloids are also one of the active components in lily bulb. Currently, 11 alkaloids have been extracted (87~101), including 3 steroidal alkaloids ([Supplementary Table 4](#) and [Supplementary Figure 3](#)).

Components From *R. glutinosa*

R. glutinosa here refers to its fresh or dried tuber. Its chemical components include iridoid glycosides, polysaccharides, phenylethanol glycosides, etc. Modern pharmacological studies have shown that *R. glutinosa* has effects such as lowering blood sugar, improving the central nervous, anti-tumor properties, delaying aging, and exhibiting antibacterial activity.⁸⁴

R. glutinosa Polysaccharides

R. glutinosa polysaccharides (RGPs) are one of the primary bioactive components in *R. glutinosa*, demonstrating significant effects in anti-inflammatory, antioxidant, blood sugar-lowering, and neuroregulatory activities, with no reports of significant toxicity.⁸⁵

Iridoids in *R. glutinosa*

Iridoids are the most abundant compounds in *R. glutinosa*, with Catalpols being the main active components ([Supplementary Table 5](#) and [Supplementary Figure 4](#)).

Ionones From *R. glutinosa*

The ionones in *R. glutinosa* are primarily composed of monoterpenes and sesquiterpenes. The hydroxyl group at position 5 can form glycosides with glucose and other sugars ([Supplementary Table 6](#) and [Supplementary Figure 5A](#)).

Phenylethanol From *R. glutinosa*

The phenylethanol compounds in *R. glutinosa* mainly exist as glycosides. Acteoside is a representative compound and serves as a key component in *R. glutinosa* ([Supplementary Table 7](#) and [Supplementary Figure 5B](#)).

Triterpenoids and Flavones From *R. glutinosa*

Triterpenoids and flavones in *R. glutinosa* are primarily found in the leaves. The triterpenoids and flavones that have been isolated and identified from *R. glutinosa* are shown in the figure below ([Supplementary Table 8](#) and [Supplementary Figure 6](#)).

Lignans and Phenolic Acids From *R. glutinosa*

The lignans and phenolic acids from *R. glutinosa* are shown in the table below ([Supplementary Table 9](#) and [Supplementary Figure 7](#)).

Alkaloids and Other Classes From *R. glutinosa*

In addition to the components mentioned above, *R. glutinosa* contains various other types of components, such as alkaloids, amino acids, volatile oils, and inorganic elements ([Supplementary Table 10](#) and [Supplementary Figure 8](#)).

Component Analysis of BHDH Decoction

Regarding the active components of the BHDH decoction, Hu et al Employed “multi-site component profile characterization - multi-index efficacy integration - multi-dimensional data analysis” to identify the intersection of active components with antidepressant effects in the decoction.⁸⁶ The potential pharmacologically active components were confirmed through in vitro cell viability assays, revealing that compounds such as regaloside A, B, C, catalpol, and isoacteoside may be the main active substances underlying its antidepressant effects. Peng et al used the TCMIP database to explore the active components of the BHDH decoction. A total of 12 components from lily bulb were collected, mostly saponins, and 38 components from *R. glutinosa*, including iridoid glycosides and amino acids.⁸⁷ Research findings indicated 10 active components associated with antidepressant activity: 4 from lily bulb, including regaloside D, steroidal saponins, lily glycoside C, and 6-O- β -D-Glucopyranosyl-3 β ,26-dihydroxy- Δ 5-cholesten-16,22-dione-3-O- α -L-mnopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside. In addition, other 6 components from *R. glutinosa* include glutamic acid, L-arginine, xanthostrumarin, adenosine, mannosaccharide, and sucrose. Mao et al used LC-MS to qualitatively analyze the difference in the chemical component between single decoction and combined (BHDH) decoctions.⁸⁸ The results indicated that the decoction of lily bulb contained 35 chemical compounds, while that of fresh *R. glutinosa* contained 36 components. In the BHDH decoction, 69 chemical components were found, including 16 organic acids, 6 sugars and glycosides, 8 amino acids and peptides, and 3 alkaloids ([Table 1](#) and [Supplementary Figure 9](#)).

Understanding of MDD From the Perspective of TCM

From the perspective of TCM, MDD falls under the categories of “emotional disorders” and “stagnation diseases”. Throughout history, TCM literature has documented it under various terms such as “epileptic disorders”, “stagnation disorders”, and “Baihe disease”.⁸⁹ As early as the Spring and Autumn period, the Huangdi Neijing (Yellow Emperor’s Inner Canon) documented the relationship between emotions and the five organs, and based on the Five Elements Theory, it proposed the treatment method of “joy overcoming sadness”. Similarly, in Shennong Bencaojing, herbs such as “Fu Yi” and “He Huan” are noted as treatments for MDD. Later, during the Eastern Han Dynasty, Zhang Zhongjing in the Jingui Yaolue recommended the use of BHDH decoction to treat “Baihe disease”. “Baihe disease”, attributing the main causes of the disease to the heart and lungs. In TCM, the heart is seen as the ruler of the body, governing the blood vessels, while the lungs are considered the assistant, responsible for circulating energy through the vessels. When heat affects both, it causes the vessels to overheat ([Figure 2](#)). Clinically, disturbances in eating, sensory functions, sleep, and behavior are commonly observed, which resemble the clinical symptoms of MDD. Today, BHDH decoction and its modified formulas, or a combination with antidepressant Western drugs, are frequently used to treat MDD triggered by various causes, with significant clinical success.

Summary of Clinical Evidence for BHDH in Treating Depression

Prior to exploring the fundamental pharmacological mechanisms of Baihe BHDH, a systematic evaluation of its clinical evidence is essential to clarify its therapeutic position. This section synthesizes findings from existing randomized controlled trials (RCTs) and meta-analyses, focusing on its efficacy and safety profile as an adjunctive therapy for depression.

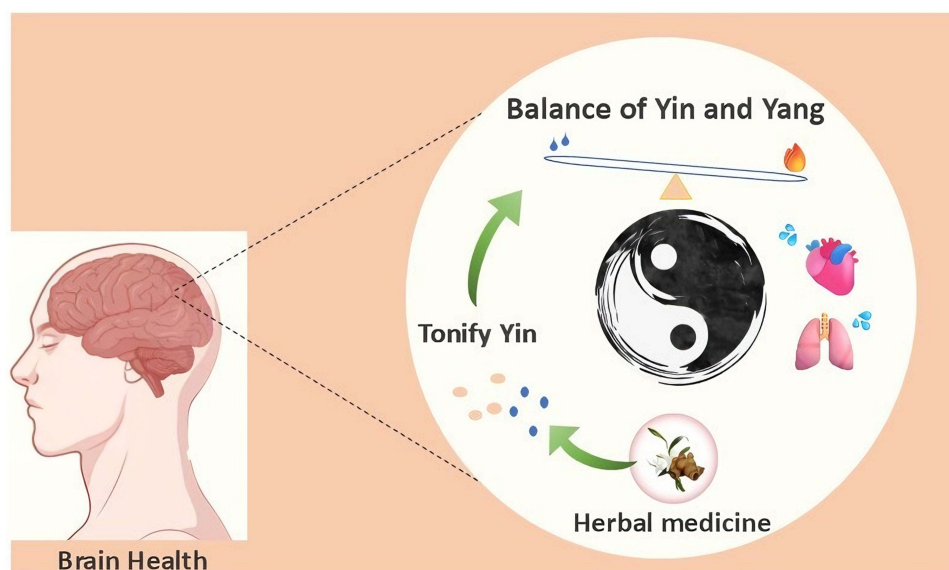


Figure 2 BHDH for depression in Traditional Chinese Medicine Theory.

A 2022 systematic review and meta-analysis, which included 13 RCTs (up to March 2021) involving 878 patients with depression (451 in BHDH combination groups, 427 in control groups), provides the highest level of current evidence.¹⁰⁰ While informative, this analysis acknowledges limitations such as the modest number of studies and heterogeneity among them, underscoring the need for future large-scale trials.

Table I Research on the Mechanisms of Baihe Dihuang Decoction in Treating Depression

Component	Experimental Model	Mechanism of Action	Ref
Acteoside; Isoacteoside; Regaloside B	Chronic unpredictable mild stress (CUMS) depression model in rats	Regulate key targets such as EGFR, ESR1, SRC, GSK3 β , mediating tryptophan and other metabolic pathways	[90]
Regaloside A, B, and C	Adrenal pheochromocytoma cells (PC-12 cells) in rats	Regulate oxidative stress response; protect synaptic structure; increase monoamine neurotransmitters	[91]
Regaloside A, B, and C; Catalpol; isoacteoside	Mice; hippocampal neurons	Inhibit apoptosis of hippocampal neurons; alleviate hippocampal neuron damage and neurotransmitter disorders.	[86]
BHDH decoction	Isolated and CUMS depression model in rats	Modulate gut-brain axis; restore dysregulated gut microbiota	[92]
BHDH decoction	Isolated and CUMS depression model in rats	Modulate metabolism of amino acids, steroid hormones, and glycerophosphates, improving depressive-like behavior in rats	[93]
BHDH decoction	Chronic unpredictable stress (CUS) depression in mice	Inhibit HPA axis hyperactivity under stress; increase hippocampal cAMP	[94]
BHDH decoction	CUMS mice model	Regulate miRNA-144-3p/Gad67/VGAT pathway in the prefrontal cortex to protect GABAergic neurons	[95]
BHDH decoction	CUS mice model	Enhance the expression of hippocampal AMPA receptors GluA1, GluA2, improving synaptic plasticity and repair	[96]
BHDH decoction	Yin deficiency and internal heat depression model in rats	Increase neurotransmitters (5-HT, DA, NE); decrease inflammatory markers (IL-1 β , IL-6, TNF- α); reduce endocrine hormones TRH, TSH, T4, CORT.	[97]
BHDH decoction	Anxiety-depressive model in rats	Inhibit overactivation of NLRP3 inflammasomes; reduce peripheral and central inflammation	[98]
BHDH decoction	Anxiety-depressive model in rats	Alleviate synaptic damage; increase expression of synaptic proteins (synapsin-I, PSD-95, SYP, syn Gap); restore the complexity of the dendritic spine and the number of synapses	[99]

Clinical Efficacy Evidence

As shown in Table 2, available clinical studies consistently report that combining BHDH with conventional antidepressants (eg, SSRIs) is associated with improved therapeutic outcomes compared to antidepressants alone.

Overall Efficacy: Meta-analysis results indicate a significantly higher total effective rate for the combination therapy versus antidepressant monotherapy (OR = 0.33, 95% CI: 0.21–0.53).¹⁰⁰

Core Symptom Improvement: The Hamilton Depression Rating Scale (HAMD) is a primary endpoint for assessing depression severity. The combination regimen demonstrated a greater reduction in HAMD scores (Mean Difference, MD = −2.93), suggesting enhanced efficacy in alleviating core symptoms like depressed mood and anhedonia.¹⁰⁰

Secondary Outcomes and Biomarkers: Some studies evaluated additional scales (eg, for anxiety, somatic symptoms, sleep) and neurochemical indicators. Positive trends were observed for improving comorbid anxiety, sleep disturbances, and quality of life. Notably, combination therapy significantly increased peripheral blood levels of 5-HT and NE, providing a potential biochemical correlate for its clinical effects that aligns with the monoamine hypothesis of depression.¹⁰⁰

Safety Evidence

Safety is a critical consideration in treatment evaluation. Pooled data from meta-analyses suggest that adding BHDH may improve the tolerability profile of antidepressant regimens.

Adverse Event Incidence

A pooled analysis from five studies reporting adverse reactions found a significantly lower overall incidence in the BHDH combination group versus the antidepressant-alone group (OR = 0.47, 95% CI: 0.25–0.91).¹⁰⁰ Common adverse events (eg, nausea, constipation, dizziness, drowsiness) occurred with relatively lower frequency in the combination group.

Analysis of Potential Safety Benefits

This observed safety advantage may be attributed to several factors: (1) The multi-target modulation by BHDH may allow effective treatment with lower doses of concomitant antidepressants, potentially reducing dose-dependent side effects. (2) The TCM actions of BHDH, described as “nourishing yin and clearing heat”, may help counteract certain side effects of Western medicine, such as dryness and agitation. However, the observation period in most included studies was relatively short (2–8 weeks), highlighting the need for long-term safety and follow-up data in future research.

Evidence Summary and Research Prospects

In summary, current clinical evidence supports the use of BHDH as an adjunctive therapy to conventional antidepressants, demonstrating advantages in improving response rates, enhancing core symptom reduction, and potentially lowering the incidence of adverse reactions. These clinical benefits are corroborated by favorable changes in relevant neurochemical biomarkers. These findings establish a clear clinical rationale for investigating BHDH’s pharmacological

Table 2 Summary of Meta-Analysis on Key Clinical Outcome Indicators for Baihe Dihuang Decoction Combined with Conventional Western Medicine in Treating Depression

Outcome Indicator	Number of Included Studies	Sample Size (T/C)	Effect Size (95% CI)	P-value	Conclusion
Total Effective Rate	11	386 / 376	OR = 0.33 (0.21, 0.53)	< 0.00001	Combined therapy is significantly superior to Western medicine alone
HAMD Score	11	383 / 357	MD = −2.93 (−4.56, −1.30)	0.0004	Combined therapy leads to more significant improvement in depressive symptoms
Adverse Reaction Rate	5	180 / 176	OR = 0.47 (0.25, 0.91)	0.02	Combined therapy demonstrates better safety with fewer adverse reactions
5-HT Level	2	81 / 81	MD = 33.80 (15.60, 51.99)	0.0003	Combined therapy can increase serum 5-HT concentration

Abbreviations: T/C, Treatment/Control group; OR, Odds Ratio (<1 favors the treatment group); MD, Mean Difference.

mechanisms, such as neurotransmitter modulation, neuroinflammation inhibition, and hippocampal neuroprotection, which are discussed in subsequent sections.

Future research should prioritize rigorously designed, large-sample, long-term, high-quality RCTs. Key areas of focus should include evaluating BHDH's efficacy across different depression subtypes, its effectiveness as a monotherapy, and its long-term safety profile.

Mechanism of Action of BHDH Decoction in Treating MDD

Currently, the antidepressant effects of BHDH decoction are primarily associated with the nervous system, endocrine system, and immune-inflammatory response. Pan and Pan et al have developed models of MDD characterized by Yin deficiency and internal heat to investigate the therapeutic mechanisms of BHDH decoction. The results indicate that BHDH decoction can significantly improve symptoms of Yin deficiency and internal heat-type MDD, further confirming that its antidepressant action is linked to its ability to regulate pathways in the nervous system, endocrine system, and immune-inflammatory response, contributing to its therapeutic effects.¹⁰¹

Regulation of the Nervous System

Regulation of Amino Acid Metabolism

Small molecule amino acids such as tryptophan (Trp), tyrosine (Tyr), glutamate (Glu), and γ -aminobutyric acid (GABA) are essential neurotransmitters in the human body.¹⁰² Among them, Trp is an indispensable amino acid that cannot be synthesized by the human body and must be obtained through food and produced by the gut microbiota. The metabolism of Trp primarily involves the pathways of 5-HT and kynurenine (KYN). Increasing 5-HT is crucial for treating MDD, as it is predominantly synthesized by chromaffin cells in the intestinal epithelium. Trp is converted into 5-HT by tryptophan hydroxylase (TPH). Additionally, Trp can also follow the KYN pathway, where part of it is converted into neurotoxic quinolinic acid (QA) within microglial cells. An increase in QA can contribute to the onset of MDD. Another portion of Trp is converted into the neuroprotective kynurenic acid (KA) within astrocytes. KA regulates the production of glutamine (Gln), which is then converted into Glu. As an excitatory neurotransmitter in the brain, Glu is further converted into GABA, an inhibitory neurotransmitter, under the action of the rate-limiting enzyme glutamate decarboxylase (GAD). The Glu/GABA ratio, within an optimal range, can enhance learning and memory. However, if this ratio becomes too high, it may cause inhibitory effects and lead to memory impairment and the development of MDD.¹⁰³

Feng et al investigated the effects of BHDH decoction on the serum and fecal metabolomics of depressed rats. The results indicated that amino acid metabolism plays an important role in both the onset and treatment of MDD.⁹² Mou combined network pharmacology and metabolomics and conducted a comprehensive analysis of the mechanisms by which BHDH decoction treats MDD. One of the findings indicated that this mechanism is related to amino acid regulation.⁹⁰ Based on metabolomics, Hu et al explored the mechanisms of BHDH decoction in treating MDD. Their results revealed that the levels of Trp, KYN, and other metabolites were abnormal in the rats of the model group (Figure 3).

The miRNA-144-3p/Gad67/VGAT Pathway in the Protective Effect of BHDH Decoction on GABA Damage in Neurons

Pan investigated the protective effect of BHDH decoction-containing serum on corticosterone (CORT)-induced neuronal damage and explored whether the mechanism was related to correcting the imbalance between excitatory and inhibitory neurotransmitters.⁹⁷ The results showed that BHDH decoction increased the expression of VGAT and Gad67 proteins and genes, promoted GABA synthesis and transport, increased GABA expression, restored the imbalance, and improved GABA damage in CORT-induced Neuro-2a neurons. In addition, Xue conducted experiments in mice to confirm that the antidepressant effects of BHDH decoction were linked to the restoration of GABAergic interneuron dysfunction in the prefrontal cortex. The findings revealed that BHDH decoction reduced the expression of miRNA-144-3p in the prefrontal cortex, increased the expression of Gad67 and VGAT, affected presynaptic GABA synthesis and transport, enhanced GABA release, improved synaptic transmission efficiency, and restored the function of GABAergic neurons in receiving and encoding output information, thereby exerting its antidepressant effect.⁹⁵ Therefore, the miRNA-144-3p/Gad67/VGAT pathway plays a role in the protective effects of BHDH decoction-containing serum against CORT-induced impairment of GABA expression.

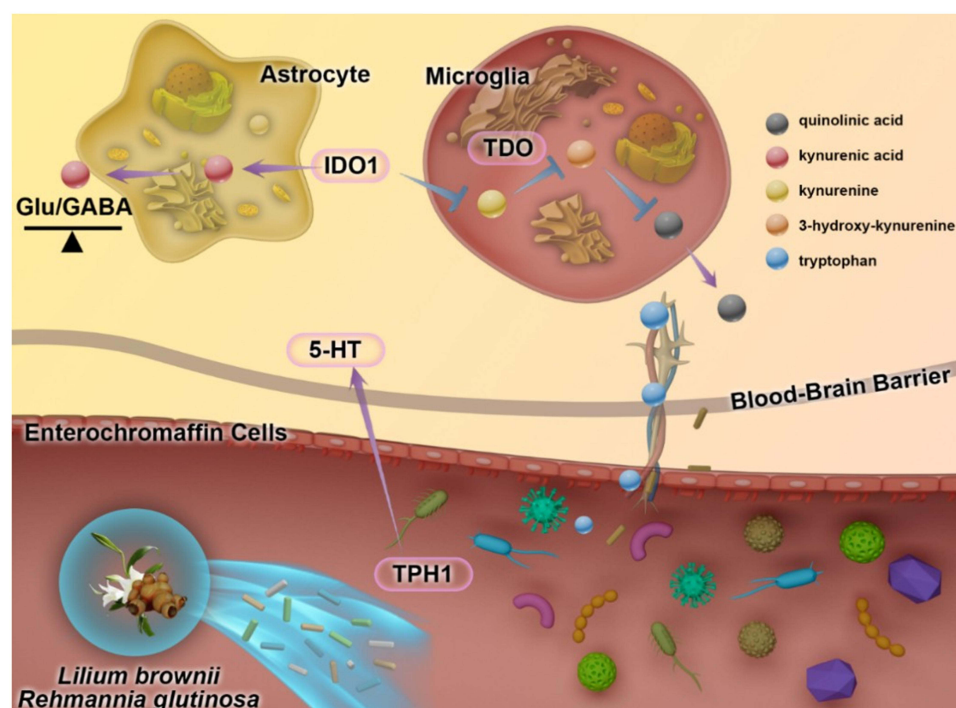


Figure 3 The antidepressant mechanism of BHDH decoction through the regulation of Trp.

Abbreviations: TPH1, Tryptophan hydroxylase; 5-HTP, 5-Hydroxytryptophan; IDO1, Indoleamine 2,3-dioxygenase 1; IDO, Indoleamine 2,3-dioxygenase.

Enhance the Levels of 5-HT, DA, NE, and Other Monoamine Neurotransmitters in the Brain

Studies have shown that monoamine neurotransmitters like DA, 5-HT, and NE are crucial in maintaining the chemical balance within the brain. If these substances are either too high or too low, they can lead to the development of MDD.¹⁰⁴ Xue investigated the antidepressant mechanism of BHDH decoction using CUMS combined with isolation rearing to establish a depression model in rats.¹⁰⁵ The results indicated that the levels of 5-HT, DA, and NE in the hippocampus of the treatment group were significantly higher than those in the model group, while the activity of monoamine oxidase was significantly reduced. This suggests that BHDH decoction regulates the nervous system by reducing the activity of monoamine oxidase in the brain, thereby increasing the levels of monoamine neurotransmitters and exerting antidepressant effects.

Regulation of the Endocrine System

Steroid hormones include two categories: sex hormones and adrenal cortex hormones. Among them, the adrenal cortex hormones involved in the HPA axis play an important role in the pathophysiology of MDD. Studies have shown that in patients with MDD, dysfunction of the HPA axis leads to the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, which then stimulates the release of adrenocorticotrophic hormone (ACTH) from the pituitary. ACTH, carried through the bloodstream, stimulates the adrenal cortex to release cortisol (COR), resulting in elevated levels of CRH, ACTH, and COR in the plasma.¹⁰⁶ As a stress hormone influenced by the HPA axis, COR plays a key role in coordinating various physiological processes. However, excessive levels of COR can lead to cognitive impairments and negative emotions.¹⁰⁷ Guan et al investigated the effects of BHDH decoction on a mouse model of depression induced by social isolation and CUMS. The results revealed that, compared to the model group, both high and low doses of BHDH decoction significantly reduced the levels of CORT and ACTH in the serum of mice, thereby preventing HPA-axis hyperactivity and alleviating depressive symptoms.¹⁰⁸

Regulation of the Immune-Inflammatory Response

Immune-inflammatory response plays a critical role in the pathogenesis of MDD. Experimental and clinical studies have shown that immune-inflammatory responses contribute to MDD by enabling immune cells to release a variety of immune

factors into the blood-brain barrier. This activation triggers an immune response within the brain, causing disruptions in specific brain regions and eventually leading to the development of MDD.¹⁰⁹ Experimental research has demonstrated that many MDD patients, even without other diseases, experience increased levels of inflammatory factors such as IL-1, IL-6, and TNF- β . Additionally, certain pro-inflammatory immunotherapy has been found to induce varying degrees of MDD.¹¹⁰ Jia et al found that elevated levels of IL-2 in MDD patients contribute to the exacerbation of MDD.¹¹¹ Zhao et al discovered that the levels of IL-1 β and IL-6 were elevated in brain regions associated with lipopolysaccharide (LPS) stress in mice.¹¹² Additionally, LPS induced more severe depressive-like behaviors compared to the CUMS model. Therefore, IL-1 β , IL-6, and IL-4 can serve as indicators for assessing the severity of MDD in patients. Liu et al constructed a network of active components and key targets of BHDH decoction, discovering that it may exert therapeutic effects on severe MDD through the release of IL-6.¹¹³ Wang explored the impact of BHDH decoction on changes in IL-4 within the serum of depression model in rats. The results showed that the serum IL-4 in the model group was significantly lower than those in the control group, while the serum IL-4 in the treatment group was significantly higher.¹ Zhou observed the effects of BHDH decoction on CUMS rats and found that BHDH decoction could significantly improve depression-like behaviors in CUMS rats by downregulating serum IL-1 β (Figure 4).

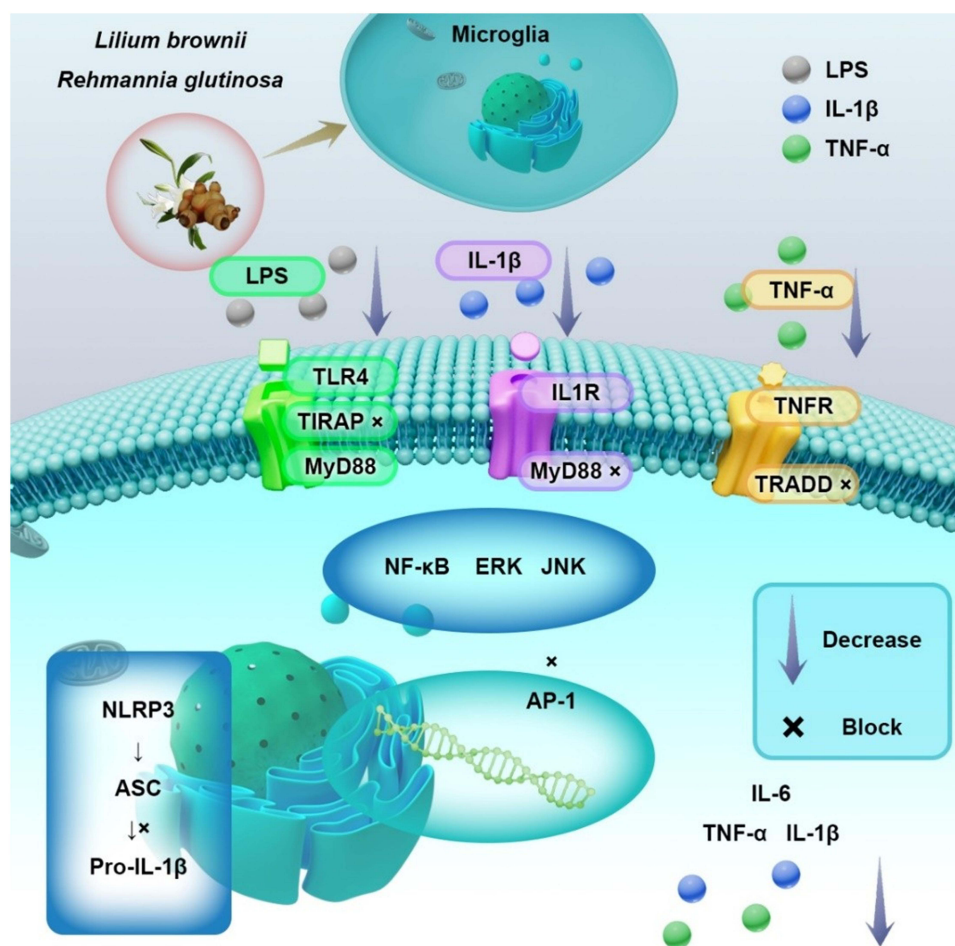


Figure 4 BHDH decoction regulates the immune system for antidepressant effects.

Abbreviations: TLR-4, Toll-like receptor 4; TIRAP, Toll/interleukin-1 receptor (TIR) domain-containing adapter protein; IL1R, Interleukin-1 receptor; MyD88, Myeloid differentiation primary response 88; TNFR, Tumor necrosis factor receptor; TRADD, TNFR-associated death domain protein; ERK, Extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; AP-1, Activator protein-1; NLRP3, NOD-like receptor family pyrin domain-containing 3; ASC, Apoptosis-associated speck-like protein; Pro-IL-1 β , Pro-interleukin-1 β .

Antidepressant Effects by Modulating the MGB Axis

It is well established that MDD is often accompanied by a loss of appetite and gastrointestinal dysfunction, which leads to malnutrition and weakened immunity, thus further exacerbating depressive symptoms. Research has shown a close relationship between the gut microbiota and MDD, with MGB dysfunction being one of the primary causes of the condition. Research progress of microecological food in improving depression by regulating the Gut microbiota.¹¹⁴ Disruption of the gut microbiota results in changes in the diversity and abundance of bacterial species. For example, in MDD patients compared to healthy individuals, the abundance of *Bacteroides* is increased, while the abundance of *Blautia* and *Eubacterium* is reduced, disturbing the balance between symbiotic and pathogenic bacteria.¹¹⁵ This imbalance undermines the integrity of the gut barrier, triggering an inflammatory response that allows harmful substances to enter the bloodstream and, through the vagus nerve, the central nervous system. This, in turn, induces inflammation and neuronal damage and contributes to the development and progression of MDD. Additionally, the metabolic products arising from gut dysbiosis, such as short-chain fatty acids (SCFAs) and 5-HT, affect the brain and can precipitate MDD. Furthermore, the gut microbiota can influence the HPA axis, adding another mechanism through which MDD is triggered.¹¹⁶

Feng et al investigated the relationship between the antidepressant effects of BHDH decoction and the gut microbiota.⁹³ They administered BHDH decoction to rat models of MDD induced by isolation rearing and CUMS. The results revealed that, compared to the model group, the treatment group showed varying degrees of repair in the colon mucosa and also reversed the gut microbiota imbalance, increasing the abundance of *Bacteroides*, *Lactobacillus*, and *Bacillus* species. Through an in vitro study of the antidepressant effects of BHDH decoction based on the gut microbiota and PC12 cells, Wei tested low, medium, and high concentrations of BHDH decoction on healthy rats and rat models of MDD induced by CUMS and isolation rearing.¹¹⁷ The gut microbiota was cultured in vitro and counted. The results showed that, except for the low-dose group, which showed no significant difference, the other BHDH decoction-treated groups suppressed the growth of *Escherichia coli*, *Enterococcus faecalis*, *Bacteroides fragilis*, and *Bifidobacterium*, while promoting the growth of *Lactobacillus* (Figure 5). Ma et al through their research on the mechanisms of BHDH decoction and its active components in the gut-brain axis against MDD, found that the primary ingredient, acteoside, could reverse gut microbiota dysbiosis and inhibit the inflammatory response caused by impaired intestinal permeability or blood-brain barrier leakage, thus achieving therapeutic effects for MDD.¹¹⁸

Conclusion

MDD imposes a substantial burden on individuals and society, for which both modern medicine and TCM offer valuable therapeutic perspectives. The classic formula BHDH, first recorded by Zhang Zhongjing during the Eastern Han Dynasty for treating “Baihe Disease”, aligns closely with modern diagnostic criteria for MDD. This alignment provides a historical and theoretical foundation for its modern application, which is supported by contemporary clinical evidence.

Current pharmacological research indicates that BHDH may intervene in MDD through multiple pathways, including modulation of the nervous, endocrine, and immune-inflammatory systems as well as the gut microbiota (Figure 6). This multi-target action is consistent with TCM’s holistic view of “multi-component, multi-target, multi-pathway” therapy. However, the research landscape reveals significant imbalances: while evidence regarding neurotransmitter regulation and HPA axis modulation is relatively robust, investigations into neuroinflammation and the gut-brain axis remain preliminary and lack conclusive evidence chains.

More critically, fundamental limitations impede the translation of BHDH from potential to definitive application. First, mechanistic studies often remain at the level of correlation, lacking exploration of precise molecular targets and causal pathways. Second, research tends to be fragmented, focusing on individual herbs or compounds rather than elucidating the formula’s synergistic effects. Finally, a major translational gap exists; most mechanistic findings derive from animal models, with insufficient validation using biological samples from MDD patients. This creates considerable uncertainty for clinical application.

Addressing these gaps requires focused future efforts: 1) employing advanced technologies to establish causal mechanisms beyond correlation; 2) adopting systems biology approaches to construct integrated “component-target-pathway-disease” networks that explain the formula’s holistic nature; 3) establishing a translational research framework

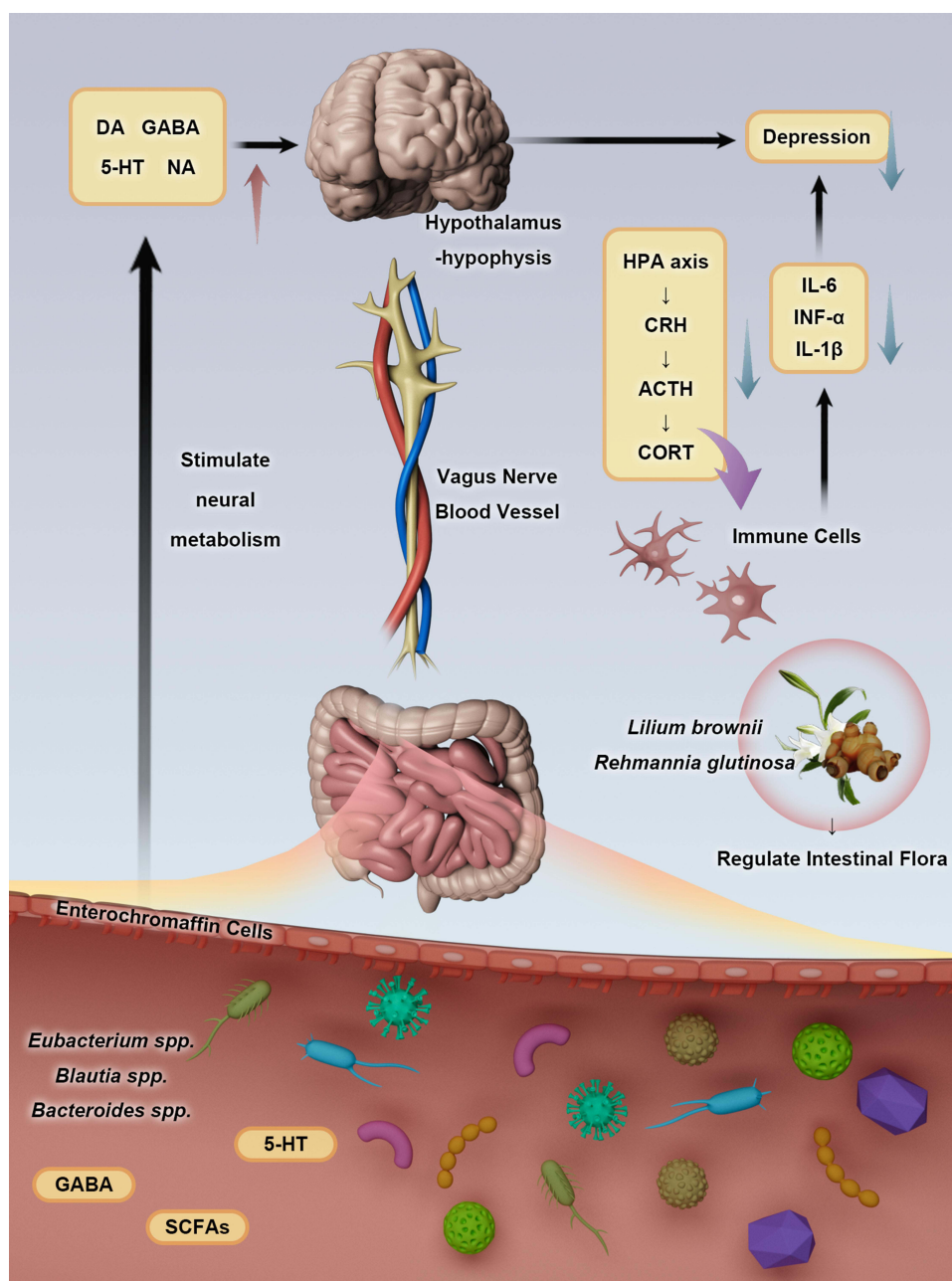


Figure 5 Antidepressant mechanism of BHDH decoction in regulating gut microbiota.

Notes: Microbial taxa annotation: Genus names followed by "spp." indicate representative species within that genus. *Bacteroides* spp. are core commensals involved in polysaccharide metabolism; *Eubacterium* spp. are butyrate producers supporting gut barrier function; *Blautia* spp. are acetate producers linked to metabolic and immune modulation.

Abbreviations: SCFAs, short-chain fatty acids.

that incorporates mechanistic biomarker studies in high-quality clinical trials and validates findings with human-derived models; 4) developing precision application strategies by identifying responder subgroups via biomarkers or TCM syndrome differentiation.

The findings of this study have direct implications for practice and research. Clinically, BHDH could be considered an adjunctive option for patients with inadequate response or intolerance to first-line therapies, particularly those with symptoms like anxiety or insomnia, or with patterns of yin deficiency with internal heat. At the policy level, funding should prioritize translational studies that integrate multi-omics technologies and bridge basic and clinical research, while also promoting the development of TCM-specific evaluation methodologies.

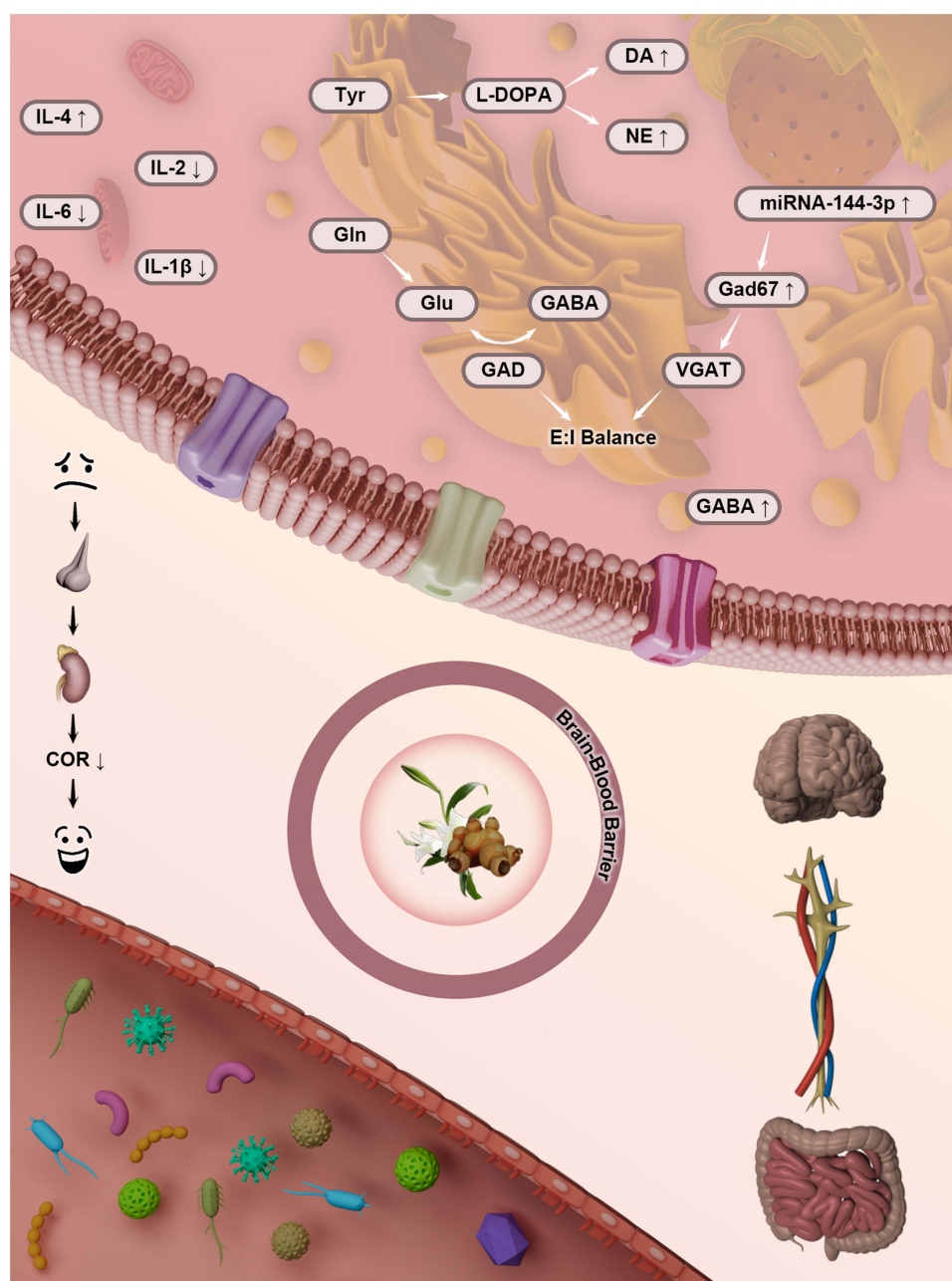


Figure 6 Mechanism of antidepressant action of BHDH decoction.

In conclusion, while BHDH holds notable potential for MDD treatment, its transformation into an evidence-based therapy depends on systematically overcoming the outlined limitations. Future work must achieve deeper mechanistic understanding, a complete scientific elucidation of the formula's synergy, and the construction of robust translational bridges. This process is crucial not only for BHDH but may also provide a generalizable methodological framework for modernizing TCM in the treatment of complex diseases, ultimately benefiting patients with MDD.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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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