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REVIEW

Traditional Chinese Medicine Ameliorates Depression via the Gut-Brain Axis: A Review Focus on NLRP3/TLR4-Mediated Inflammatory Pathways and Gut Microbiota Modulation

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Objective: Depression, a global mental disorder, is linked to gut-brain axis (GBA) dysfunction. This review explores how traditional Chinese medicine (TCM)—including single herbs (eg, Astragalus membranaceus, Lycium barbarum), herbal formulas (eg, Xiaoyaosan, Xiaochaihu Decoction), and acupuncture—alleviates depression via the GBA, focusing on neuroscience-relevant mechanisms (inflammation, neurotrophy).

Methods: A systematic literature search was conducted on PubMed, China National Knowledge Infrastructure (CNKI), and Embase from database inception to July 2025. Keywords included ["Traditional Chinese Medicine" or "TCM" or "herb" or "herbal extracts" or "Chinese herbal formulas"], ["depression" or "Depressive like behavior"], ["immune regulation"], ["inflammatory reaction"], ["neuroregeneration" or "nerve" or "neurotransmitter"]. Including peer-reviewed studies on human/animal models, articles that do not meet the requirements are excluded. A total of 307 eligible studies were included.

Results: TCM regulates gut microbiota composition—eg, increasing Lactobacillus and Bifidobacterium while reducing pathogenic taxa. Mechanistically, TCM inhibits pro-inflammatory pathways: herbs (eg, Astragalus membranaceus) and formulas (eg, Xiaoyaosan) downregulate IL-6, TNF-α, and IL-1β via suppressing NLRP3 inflammasome and TLR4/NF-κB signaling. They also enhance anti-inflammatory IL-10, elevate neurotransmitters (5-HT, DA), and upregulate BDNF. Acupuncture mirrors these effects, reducing plasma IL-6/TNF-α and restoring microbial balance to improve depressive behaviors.

Conclusion: TCM alleviates depression by integrating gut microbiota modulation, inflammatory suppression, and neuroprotection through the GBA. This review highlights TCM's potential as a safe, alternative therapy for depression and identifies directions for standardized, large-scale clinical validation.

Keywords: traditional chinese medicine, Depression, gut microbiota, gut-brain axis, inflammatory reaction, immune regulation, neuroregeneration

Introduction

The Gut-Brain Axis (GBA) refers to a bidirectional communication network between the gut microbiota and the central nervous system, which has gradually gained attention in the research of psychological disorders such as depression.[1] Depression is a global mental health crisis: the World Health Organization (WHO) estimates it affects 280 million people worldwide (3.8% of the global population), with 5% of adults suffering from major depressive disorder (MDD).[2,3] It is the leading cause of disability globally, imposing substantial economic burdens (exceeding $2 trillion annually) and increasing the risk of suicide—accounting for over 700,000 deaths each year.[4,5] Its pathological mechanism is complex,

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involving genetics, environment, neuroinflammation, and neurotransmitter imbalance, with GBA dysfunction emerging as a key contributor.[6]

Conventional treatments for depression primarily rely on pharmacotherapy (eg, selective serotonin reuptake inhibitors, SSRIs) and psychotherapy (eg, cognitive-behavioral therapy, CBT). However, these approaches have notable limitations: SSRIs often cause side effects (gastrointestinal distress, sexual dysfunction, weight gain) that lead to 30–50% of patients discontinuing treatment;[7] approximately 30% of MDD patients are refractory to first-line drugs.[8] Psychotherapy, while effective, is limited by high costs, poor accessibility in low- and middle-income countries, and reliance on trained professionals. Thus, there is an urgent need to explore safe, accessible alternative therapies.

In traditional Chinese medicine (TCM) theory, intestinal health is regarded as an important component of overall health.[9] TCM aims to improve the intestinal environment by regulating visceral functions and balancing yin and yang (A core TCM theory describing two opposing yet complementary forces that maintain bodily homeostasis; TCM treats depression by balancing yin-yang)., thereby influencing mental health.[10] In recent years, a growing number of studies have begun to explore the role of TCM in regulating the gut microbiota, especially in the treatment of depression.[11–13] Zhi-Zi-Chi decoction, a TCM formula consisting of Gardenia jasminoides and fermented soybean, with effects of clearing heat and relieving restlessness. Studies have shown that Zhi-Zi-Chi decoction can increase the production of short-chain fatty acids, which have been proven to exert positive effects on depression.[14] TCM can regulate the gut microbiota through multiple mechanisms, such as improving diet, enhancing the functions of the spleen and stomach, and using specific herbal formulas, thereby affecting the symptoms of depression.[15,16] TCM can regulate the gut microbiota through multiple mechanisms, such as improving diet, enhancing the functions of the spleen and stomach, and using specific herbal formulas, thereby affecting the symptoms of depression.

This review aims to explore the basic concept of the GBA and its significance in depression research, elaborate on the traditional applications and modern research progress of TCM in regulating gut microbiota, and introduce the research objectives and structure of this article. By reviewing relevant literature, it is expected to provide new perspectives and ideas for the application of TCM in the treatment of depression, with a view to offering guidance and references for clinical practice.

Methods

Search Strategy

We searched PubMed, China National Knowledge Infrastructure, and Embase. The search is limited to English or non English articles with published English abstracts since the establishment of the database. Key words include [“Traditional Chinese Medicine” or “TCM” or “herb” or “herbal extracts” or “Chinese herbal formulas”], [“depression” or “Depressive like behavior”], [“immune regulation”], [“inflammatory reaction”], [“neuroregeneration” or “nerve” or “neurotransmitter”]. Preliminary screening is conducted using search engines provided by various databases. Preliminary screening is conducted using search engines provided by various databases. After deleting 256 duplicate records, we identified 712 related articles. Before reading the full text of the selected paper, we use Endnote software to identify references related to the topic. Among them, 87 articles lack full-text abstracts, and 318 articles are unrelated to traditional Chinese medicine and depression. Finally, 307 full-text original research papers related to the topic were included.

Data Extraction and Synthesis

Prior to reading the full text of the given papers, we manually selected topic-related references using Excel software. Eventually, all included articles are peer-reviewed ones relevant to this subject. During the process of writing the paper, one author was responsible for data extraction. Subsequently, other authors cross-checked the extracted data to ensure its completeness and reliability.

Basic Concepts of Gut-Brain Axis

The GBA refers to a bidirectional communication network between the gut and the brain, which transmits information through multiple pathways including the neural, endocrine, and immune systems.[17] The gut microbiota plays a pivotal role in this process, influencing brain function and emotional regulation.[18] Studies have

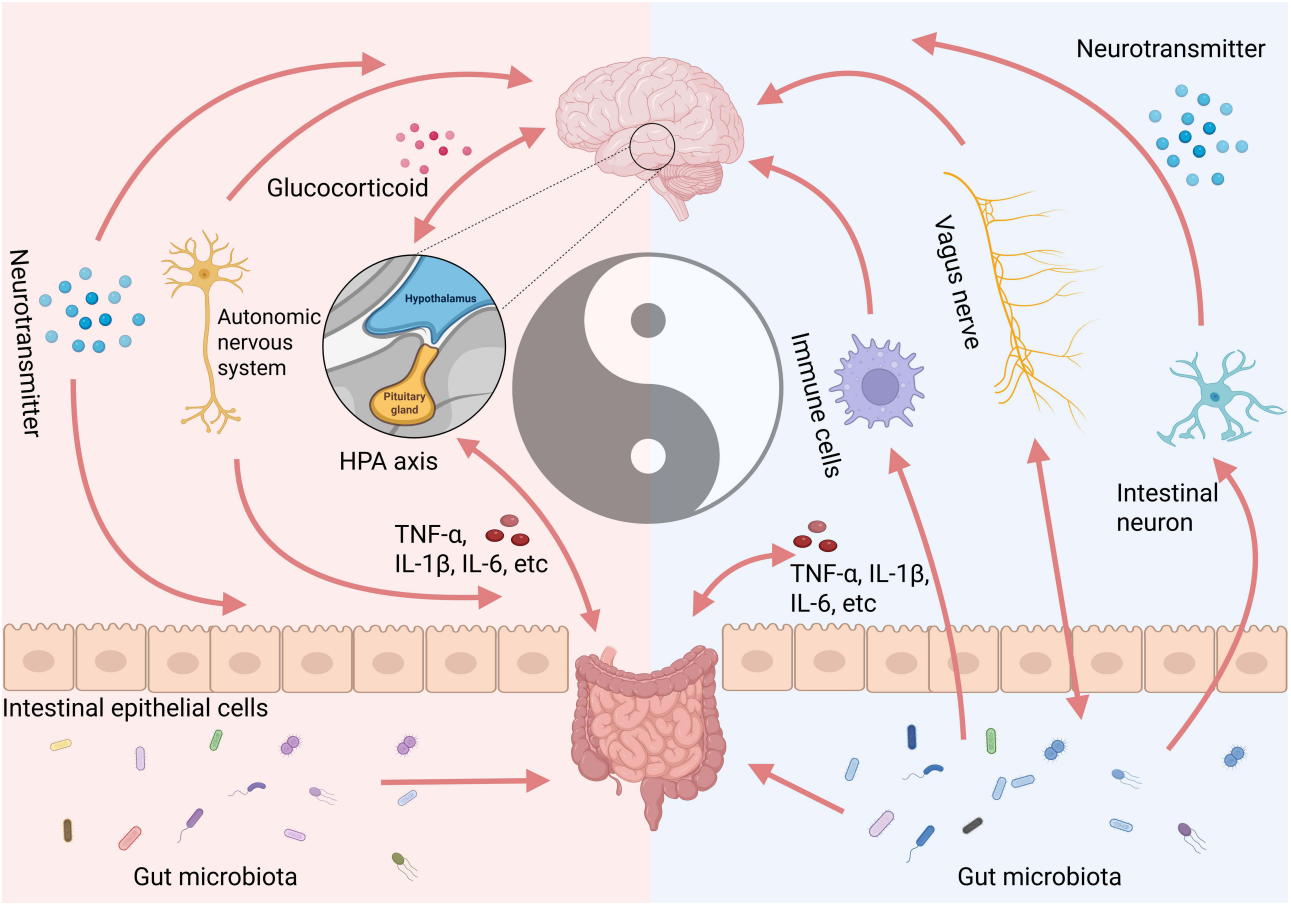

Figure 1 Schematic diagram of gut-brain axis.

demonstrated that alterations in the composition and function of the gut microbiota are closely associated with the pathogenesis of various neuropsychiatric disorders, such as depression and anxiety.[19,20] The functions of the GBA are not limited to the regulation of the digestive system but also include impacts on mental health.[21] By secreting metabolites like short-chain fatty acids and neurotransmitters, the gut microbiota can directly affect neural activity and emotional states in the brain.[22,23] The interaction mechanism of the GBA is illustrated in Figure 1.

The GBA plays a significant role in the regulation of emotions and behaviors. Studies have found that gut microbial dysbiosis (ie, an imbalance of the gut microbiota) may exacerbate mental health issues such as depression and anxiety.[24,25] Specifically, the gut microbiota influences the brain's emotional regulation mechanisms by modulating the synthesis and metabolism of neurotransmitters (eg, serotonin and dopamine).[26] For instance, the gut microbiota can affect the levels of serotonin, a key neurotransmitter closely linked to emotional regulation.[27,28] Agmatine is a substance primarily derived from beneficial gut microbes. Rahangdale et al found that oral administration of agmatine alone or in combination with probiotics significantly reversed antibiotic-induced dysbiosis, restored the gut microbiota, and alleviated depression-like behaviors.[29] Research indicates that dysfunction of the GBA may further exacerbate depressive symptoms by affecting the activity of the hypothalamic-pituitary-adrenal (HPA) axis.[30] Additionally, the gut microbiota regulates brain function and emotional responses through its impacts on the immune and endocrine systems.[22,31] Therefore, regulating the composition and function of the gut microbiota may emerge as a novel strategy for improving mood disorders and behavioral problems.

Pathological Mechanism of Depression

Depression is a complex psychological disorder whose pathological mechanisms involve multiple biological factors. Recent studies have indicated that the occurrence of depression is closely associated with the neurotransmitter system,

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endocrine system, immune system, and genetic factors, among others. In particular, the imbalance of neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA) is regarded as one of the core biological bases of depression.[32] Additionally, chronic stress and neuroinflammation are also recognized as important pathological mechanisms of depression: the former affects the neuroendocrine axis and immune responses, while the latter impacts brain function by activating microglia and releasing inflammatory factors.[33] Studies have also found that structural and functional changes occur in the brains of depressed patients, including hippocampal volume reduction and prefrontal cortex dysfunction, which are correlated with the severity of depressive symptoms.[34]

The microbiota is playing an increasingly important role in the occurrence and development of depression. Studies have demonstrated that gut microbiota dysbiosis (ie, microbial imbalance) is closely associated with the onset of depression.[35] Specifically, gut microbes can influence mental health through multiple mechanisms, including regulating neurotransmitter synthesis, affecting inflammatory responses, and impacting brain function via gut-brain axis signaling.[12,36] For instance, short-chain fatty acids (SCFAs), as metabolites of gut microbiota, can alleviate neuroinflammation by inhibiting microglial activation, thereby improving depressive symptoms.[37] Additionally, changes in microbiota composition are correlated with the severity of depressive symptoms; a reduction in certain beneficial bacteria such as Bifidobacterium and Lactobacillus may be associated with the development of depression.[38] Therefore, regulating the composition of gut microbiota may emerge as a novel strategy for treating depression, and achieving this goal through traditional Chinese medicine has shown promising prospects.[39]

The Relationship Between the Basic Theories of Traditional Chinese Medicine and Depression

Traditional Chinese Medicine's Understanding of Depression

TTCM has a distinct understanding of depression compared to Western medicine. In TCM theory, depression is referred to as "Yu Zheng" (depressive syndrome), whose etiology is closely associated with factors such as emotional imbalance, qi and blood deficiency, and dysfunction of zang-fu organs.[40] TCM holds that emotional fluctuations directly affect the circulation of qi, leading to qi stagnation, which in turn triggers a series of physical and psychological symptoms.[41] For example, liver qi stagnation is regarded as one of the main pathological bases of depression; dysfunction of the liver can result in symptoms such as low mood and anxiety.[42] Additionally, TCM emphasizes the relationship between the health of the spleen and stomach and emotional states: spleen deficiency may cause qi and blood deficiency, thereby affecting mental status.[39,43] Therefore, TCM adopts syndrome differentiation-based treatment, using various herbs and therapeutic methods to harmonize qi and blood, and unblock meridians, so as to alleviate depressive symptoms.[44]

Application Status of Commonly Used Individual Herb or Herbal Extracts in Regulating Gut Microbiota in Depression

In recent years, a growing body of research has indicated that gut microbiota dysbiosis is closely associated with the occurrence of depression. We have summarized recent studies on TCM and its active components in regulating gut microbiota for the treatment of depression (Table 1). TCM exhibits unique advantages in regulating gut microbiota.[45] For example, Chinese herbs such as Astragalus membranaceus, Lycium barbarum, and Angelica sinensis have been found to alleviate depressive symptoms by regulating the gut microbial community.[46–48] NLRP3 (NOD-like receptor pyrin domain-containing 3), an inflammasome complex that triggers the release of pro-inflammatory cytokines; its overactivation is a key driver of GBA-related depression. Studies have demonstrated that Astragalus membranaceus exerts antidepressant effects mainly via astragaloside IV (its core triterpenoid saponin). Astragaloside IV modulates gut microbiota (increasing Lactobacillus/Oscillospira) and inhibits the NLRP3/ASC/Caspase-1 pathway, reducing IL-1β/TNF-α levels while upregulating BDNF.[49] TLR4 (Toll-like receptor 4), a pattern-recognition receptor that mediates gut microbiota-induced inflammation via the NF-κB pathway, contributing to depression pathogenesis. Paeonia lactiflora relies on paeoniflorin (monoterpenoid glycoside) to restore gut barrier integrity (ZO-1/Claudin-1↑) and suppress TLR4/NF-κB signaling.[50–52] Zhao et al found that gastrodin improves depressive-like behavior in mice by regulating the gut microbiota induced by chronic unpredictable mild stress.[53] Active components of TCM herbs such as Salvia miltiorrhiza

Table 1 Summary of Studies on the Use of Single Herb and Its Active Extracts to Regulate Gut Microbiota in the Treatment of Depression

Herb	Extract	Research Model	Changes in Microbiota	Mechanisms	Results	Reference
Soybean	*Genistein*	Depression induced by CUMS in SD rats	Restore the abundance of Firmicutes and Actinobacteriota to normal levels	ACTH↓, CORT↓; 5-HT↑, GAD↑, GABA↑	The antidepressant effect of genistein can be achieved by promoting glutamate metabolism, increasing GAD expression levels, promoting GABA synthesis, and indirectly increasing 5-HT levels.	Ma, 2025[55]
Jasmine tea	Jasmine tea extract	Depression induced by CUMS in SD rats	Increase the abundance of *F*Romboutsia, Blautia, Monoglobus, and decrease the abundance of Bifidobacterium, Clostridium_sensu_stricto_1, Escherichia-Shigella.	TNF-α↓, IL-6↓, IL-1β↓	Jasmine tea extract may alleviate depression by modulating the microbiota-gut-brain axis, highlighting its potential as a dietary intervention for depression management.	Zhou, 2025[56]
Astragalus membranaceus	Astragaloside IV	Depression induced by CUMS in SD rats	Increase the abundances of beneficial bacteria (*Lactobacillus* and *Oscillospira*)	IL-17↓, IL-22↓; IL-10↑, TGF-β↑	Astragaloside IV could function as a promising diet or diet composition to alleviate depressed symptoms.	Liu, 2024[49]
Lilii bulbus and Radix Rehmannia Recens	verbascoside	Depression induced by CUMS in C57BL/6 J mice	Reduce the abundances of Bacteroidetes and Proteobacteria, while increasing the abundance of Firmicutes	TNF-α↓, IL-6↓, IL-1β↓, IL-17A↓; 5-HT↑, DA↑, IL-10↑, GABA↑	Verbascoside inhibits neuroinflammation and intestinal permeability associated with chronic stress-induced depression by regulating the gut microbiota brain axis	Mao, 2024[57]
Citri Reticulatae Pericarpium	Hesperidin	Depression induced by CUMS in SD rats	Increase the abundance of Pseudomonadota and Bacteroidota.	5-HT↑, BDNF↑	The mechanism responsible for the beneficial effects of hesperidin on depressive behavior in rats may be related to inhibition of the expressions of BDNF and 5-HT and preservation of the gut microbiota.	Liang, 2024[58]
Sophora flavescens	Matrine	Depression induced by CUMS in ICR mice	The abundance of lactobacilli increased, while the relative abundance of Helicobacter pylori, Rikenella acidophilus, and Ruminococcus significantly decreased	TNF-α↓, IL-6↓, IL-1β↓; BDNF↑	Matrine can regulate the disturbance of gut microbiota and metabolites, reduce the levels of pro-inflammatory cytokines in peripheral blood circulation and brain regions, and ultimately increase the level of BDNF in the brain.	Zhang, 2023[30]
Paeonia lactiflora Pall.	Paeonia lactiflora Polysaccharide (PLP)	Depression induced by CUMS in C57BL/6 J mice	Restore the abundance of Ruminococcus and Bacteroides to normal levels	TNF-α↓, IL-6↓, IL-1β↓, NLRP3↓; 5-HT↑	PLP modulates depression-related intestinal ecological dysregulation, increases species richness.	Zhou, 2023[52]
Leonuri	Leonurine	Depression induced by CUMS in SD rats	Restore the abundance of *Lactobacillus, Lachnospiraceae_NK4A136_group, Clostridia_UCG-014*, and *Prevotellaceae_Ga6A1_group* to normal levels.	SHH↑, PTCH↑, SMO↑, 5-HT↑, BDNF↑	leonurine regulated hippocampal nerve regeneration in CUMS rats by activating the SHH/GLI signaling pathway and restoring gut microbiota and microbial metabolic homeostasis.	Meng, 2023[59]
Ginkgo biloba	Ginkgo biloba extract (GBE)	Depression induced by CUMS in C57BL/6 J mice	Upregulation of Firmicutes and Verrucous Verruciformes, downregulation of Proteobacteria and Bacteroidetes.	BDNF↑, CaMKIIα↑	GBE acts on gut microbiome-modulated bile acid metabolism to alleviate stress-induced depression.	Zhou, 2023[35]
Angelica sinensis, Maize bran	Ferulic acid, Feruloylated oligosaccharides	Depression induced by CUMS in SD rats	Increase the abundance of *Firmicutes, Solibacillus, Acinetobacter* and *Arthrobacter*, and decrease the abundance of *Parabacteroides, Oscollospira* and *Rummeliibacillus*.	TNF-α↓, IL-6↓, IL-1β↓	Ferulic acid and Feruloylated oligosaccharides mitigated the symptom of depression in mice potentially via changing gut microbiome structure and microbial metabolism.	Deng, 2022[60]
Pueraria Lobelia	Puerarin	Depression induced by CUMS in C57BL/6 J mice	Increase the abundance of Firmicutes, Bacillales, Lactobacillus and decrease the abundance of Proteobacteria, Flexispira, Desulfovibrio	—	The antidepressant mechanism of puerarin may closely interact with restoring beneficial microflora.	Song, 2021[61]
Gardenia jasminoides Ellis	GYP	Depression induced by CUMS in kunming mice	—	GluR1↑, synapsin 1↑, BDNF↑	The antidepressant response induced by GYP depends on the synthesis of synaptic proteins and the elevation of BDNF levels.	Wu, 2016[62]

Notes: ↑: Increased expression/level; ↓: Decreased expression/level.

Abbreviations: GYP, Gardenia yellow pigment; BNDF, Brain-derived neurotrophic factor; CaMKIIα, Calcium–calmodulin (CaM)-dependent protein kinase IIα; GABA, γ-aminobutyric acid; DA, dopamine; 5-HT, hydroxytryptamine; ACTH, adrenocorticotropic hormone; CORT, corticosterone; 5-HT, 5-hydroxytryptamine; GAD, glutamic acid decarboxylase; SHH, sonic hedgehog; PTCH, patched; SMO, smoothened.

and Bupleurum chinense have also been shown to exert antidepressant effects by regulating gut microbial metabolites and promoting neurotransmitter synthesis.[54] Additionally, computer simulations have validated the use of quercetin, luteolin, apigenin, and other components as drugs for the treatment of depression. Most of the top 10 herbs containing these components are attributed to the liver meridian in TCM, and they have a pungent taste.[43] These studies provide a scientific basis for the application of TCM in the treatment of depression.

Application Status of Chinese Herbal Formula in Regulating Gut Microbiota in Depression

Chinese herbal formula preparations have shown favorable efficacy in the treatment of depression.[63] We have summarized recent studies on Chinese herbal formulas in regulating gut microbiota for the treatment of depression (Table 2). For example, compounds such as Chaihu Shugan Powder and Xiaoyao Powder are widely used in clinical practice, and studies have found that these compounds can improve depressive symptoms by regulating the composition of gut microbiota.[64,65] Chaihu Shugan Powder can significantly increase the abundance of beneficial intestinal bacteria, such as Bifidobacterium and Lactobacillus, while reducing the number of depression-related pathogenic bacteria, thereby improving patients' mental status.[66] In addition, Xiaoyao Powder is widely used to treat depression of liver qi stagnation type; its components such as Bupleurum chinense and Paeonia lactiflora (Baishao) have the effects of soothing the liver and relieving depression, as well as harmonizing the spleen and stomach, which can effectively improve patients' mood and quality of life.[67] Xiaoyaosan, a classic TCM formula (composed of Bupleurum chinense, Paeonia lactiflora, etc.) used clinically for "soothing the liver and regulating qi" to alleviate depression-related symptoms. Xiaoyaosan's efficacy stems from synergistic effects of saikosaponin, paeoniflorin and atractylenolide III. Saikosaponin regulates gut microbiota metabolism to increase butyrate production, while paeoniflorin and atractylenolide III jointly inhibit microglial activation via the NLRP3 pathway.[25] Studies have also found that Xiaoyao Powder regulates gut microbial metabolites, inhibits the LPS-mediated TLR4/NLRP3 signaling pathway, increases the level of brain-derived neurotrophic factor (BDNF), thereby promoting neuroplasticity and alleviating depressive symptoms.[25] A multicenter RCT (n=180) showed Xiaoyaosan combined with fluoxetine significantly improved Hamilton Depression Rating Scale (HAMD) scores (mean reduction: 12.3 ± 3.1 vs 8.7 ± 2.8 in fluoxetine alone) and increased fecal butyrate levels, with no severe adverse events.[20] Sun et al found that Xiaochaihu Decoction is a classical TCM formulation that regulates qi, resolves and dissipates stagnation. Clinically, this formulation has long been used to treat Shaoyang stagnation syndrome in depressive disorders.[68] These results indicate that Chinese herbal formula preparations have important clinical significance in regulating gut microbiota and treating depression.

Current Application of Acupuncture in Regulating Intestinal Flora in Depression

Acupuncture, as a TCM therapy, has attracted increasing attention in the treatment of depression in recent years. We have summarized recent studies on acupuncture in regulating gut microbiota for the treatment of depression (Table 3). Research has shown that acupuncture can improve depressive symptoms by regulating gut microbiota. For example, in a mouse model of depression, acupuncture treatment significantly increased the abundance of beneficial gut bacteria and reduced the number of pathogenic bacteria, which was closely associated with the improvement of depressive symptoms.[78] In addition, acupuncture has been found to alleviate depressive symptoms by regulating gut microbial metabolites and reducing inflammatory levels.[79] Notably, in a multicenter, randomized controlled trial, electroacupuncture significantly decreased the levels of inflammatory cytokines such as IL-6, IL-1β, and TNF-α in the plasma of depressed patients, and upregulated BDNF, thereby improving depressive-like behaviors in patients.[80] A multicenter RCT (n=144) demonstrated electroacupuncture (EA) at GV20/EX-HN3 reduced HAMD scores by 10.5 ± 2.4, with serum 5-HT/BDNF elevated and NLRP3 expression reduced.[67] Limitations of current clinical studies include small sample sizes (n<200 in most), short follow-up (≤12 weeks), and lack of microbiota/metabolite monitoring. Large-scale, long-term RCTs integrating multi-omics (metagenomics, metabolomics) are needed to validate clinical efficacy and mechanisms.

Table 2 Summary of Studies on the Use of Chinese Herbal Formula to Regulate Gut Microbiota in the Treatment of Depression

Chinese Herbal Formula	Composition	Research Model	Changes in Microbiota	Mechanisms	Results	Reference
Gan-Mai-Da-Zao decoction (GMDZ)	Wheat, Fructus, Glycyrrhizae Radix et Rhizoma	Depression induced by CUMS in C57BL/6 J mice	Normalize the relative abundance of Bacteroidetes, Proteobacteria, and Actinobacteria	TNF-α↓, IL-6↓, IL-1β↓, NLRP3, ASC↓, Caspase-1↓; 5-HT↑,Occludin↑, Claudin-5↑	GMDZ improves depressive behavior in mice by regulating gut microbiota composition, reducing peripheral and central pro-inflammatory cytokine levels, inhibiting NLRP3 inflammasome pathway activation.	Zhang, 2025[22]
Zhi Zi Chi decoction	Gardenia jasminoides J. Ellis and Glycine max (L). Merr	Depression induced by CUMS in C57BL/6 J mice	Restore the abundance of *Bacteroidetes* and *Firmicutes*; Increased the abundance of *Candidatus, Arthromitus, Corynebacterium, Allobaculum, Lactobacillus, Acinetobacter, Peptostreptococcus*, and *Prevotella*	TNF-α↓, IL-6↓, IL-1β↓; 5-HT↑, DA↑, IL-10↑, GABA↑	Zhi Zi Chi decoction exerts antidepressant effects pleiotropically through modulating the microbiota-gut-brain.	Tian, 2024[69]
Xiaoyaosan (XYS)	Bupleuri radix, Angelicae sinensis radix, Paeoniae radix alba, Atractylodis macrocephalae rhizoma, Poria, Glycyrrhizae radix et rhizoma, Menthae haplocalycis herba and Zingiberis rhizoma.	Depression induced by CUMS in SD rats	Reduce the ratio of Bacteroidetes/ Firmicutes and the abundance of Bacteroidetes and Corynebacterium, while increasing the abundance of Lactobacillus and Acinetobacter.	TLR4↓, NLRP3↓; Claudin 1↑, ZO-1↑	XYS against depression through suppressing LPS mediated TLR4/NLRP3 signaling pathway in "microbiota-gut-brain" axis	Liu, 2024[25]
Gegen Qinlian Decoction	Pueraria lobata (Willd). Ohwi, Coptis chinensis French, Scutellaria baicalensis Georgi, and Glycyrrhiza uralensis Fisch	Depression induced by CUMS in SD rats	Restore the abundance of Ruminococcus and Bacteroides to normal levels	—	GQD treatment effectively alleviated depressive like behavior in CUMS rats.	Peng, 2024[37]
Chaihu-Shugan-San	Dried orange peel, Radix bupleuri, Ligusticum chuanxiong hort, Paeonia lactiflora Pall, Glycyrrhiza uralensis Fisch.	Male rats were subjected to MCAO and to CUMS.	—	TNF-α↓, IL-6↓, IL-1↓, STAT3; IL-10↑, AKT↑, GSK3β↑, PTEN↑	Chaihu-Shugan-San can regulate microglia polarization through the activation of the JAK/STAT3-GSK3β /PTEN/Akt pathway, suggesting that it exerts its effect via the inhibition of neuroinflammation.	Fan, 2023[66]
Shugan Jieyu Capsule	Eleutherococcus senticosus Maxim. and Hypericum perforatum L	Depression induced by CUMS in SD rats	Decrease the abundances of *Firmicutes*, Bifidobacteriaceae and *Actinobacteria*	5-HT↑, GABA↑	Shugan Jieyu Capsule was shown to alleviate depression-like behaviors and could partially rescue the function of the HPA axis.	Tan, 2022[70]
Kai-xin-san (KXS)	Ginseng Radix et Rhizoma, Polygalae Radix, Acori tatarinowii Rhizoma, and Poria	Depression induced by CUMS in mice	—	TNF-α↓, IL-2↓, IL-1β↓, TLR4↓	KXS has antidepressant effects by reducing the expression of pro-inflammatory cytokines in microglia.	Qu, 2021[71]
Xiao-Chai-Hu-Tang	Radix bupleuri, Scutellaria baicalensis, Glycyrrhiza uralensis Fisch., Pinellia ternata, ginger, Jujube, Ginseng Radix et Rhizoma	Depression induced by CUMS in C57BL/6 J mice	Reduce abundances of Parabacteroides, Blautia and Ruminococcaceae bacterium.	TNF-α↓, IL-6↓, IL-1β↓, TLR4↓, MyD88↓; IL-10↑	XCHT can alleviate depression like behavior in CUMS mice by regulating the gut microbiota.	Shao, 2021[72]
Kai-xin-san (KXS)	Ginseng Radix et Rhizoma, Polygalae Radix, Acori tatarinowii Rhizoma, and Poria	Depression induced by CUMS in ICR mice	Reduce the abundances of Coprococcus, Helicobacter, Mucispirillum, Odoribacter, Oscillospira, while increasing the abundance of Allobaculum, Bifidobacterium, and Turicibacter	TNF-α↓, IL-6↓, IL-1β↓; Occludin↑, ZO-1↑	KXS exerted an antidepressant-like effect regulating the gut-brain axis, which included gut micro-environment modification.	Cao, 2020[73]

(*Continued*)

Table 2 (Continued).

Chinese Herbal Formula	Composition	Research Model	Changes in Microbiota	Mechanisms	Results	Reference
Xiaoyaosan (XYS)	Bupleuri radix, Angelicae sinensis radix, Paeoniae radix alba, Atractylodis macrocephalae rhizoma, Poria, Glycyrrhizae radix et rhizoma, Menthae haplocalycis herba and Zingiberis rhizoma.	Depression induced by CUMS in SD rats	Regulate the abundance of Bacteroidetes, Proteobacteria, Firmicutes, Chloroflexi, and Planctomycetes.	—	XYS improves depressive-like behavior in rats with chronic immobilization stress through modulation of the gut microbiota.	Zhu, 2019[74]
Kai-xin-san (KXS)	Ginseng Radix et Rhizoma, Polygalae Radix, Acori tatarinowii Rhizoma, and Poria	Depression induced by CUMS in SD rats	—	BDNF↑, GDNF↑, NT3↑, NT4↑, NT5↑, Trk A↑, Trk B↑, Trk C↑,	The results suggested that the anti-depressant-like action of KXS might be mediated by an increase of neurotransmitters and expression of neurotrophic factors and its corresponding receptors in the brain.	Zhu, 2012[75]
Suanzaoren Decoction	Spina date seed, Liquorice Root, Common Anemarrhena Rhizome, PORIA, Szechuan Lovage Rhizome	Depression induced by CUMS in SD rats	—	BNDF↑, TrKB↑	Suanzaoren Decoction can increase the expression of BDNF and TrKB, promote neuronal survival, and has antidepressant effects.	Tian, 2011[76]
Yueju pill	Nutgrass Galingale Rhizome, Szechuan Lovage Rhizome, Rhizome of Swordlike Atractylodes, Medicated Leaven, Cape Jasmine Fruit	Depression induced by CUMS in kunming mice	—	Plasma cortisol↓; 5-HT↑	Increasing the level of 5-HT of brain tissue in depressive disorder mouse and decreasing the content of plasma cortisol may be the mechanism of Yueju pill.	Yan, 2007[77]

Notes: ↑: Increased expression/level; ↓: Decreased expression/level.

Abbreviations: BNDF, Brain-derived neurotrophic factor; CUMS, chronic unpredictable mild stress; MCAO, middle cerebral artery occlusion; BDNF, brain derived neurotrophic factor; GDNF, glial-cell-line-derived neurotrophic factor; NT3, neurotrophin 3; NT4, neurotrophin 4; NT5, neurotrophin 5; Trk A, tyrosine kinase receptor A; Trk B, tyrosine kinase receptor B; Trk C, tyrosine kinase receptor C; CaMKIIα, Calcium–calmodulin (CaM)-dependent protein kinase IIα; GABA, γ-aminobutyric acid; DA, dopamine; 5-HT, hydroxytryptamine.

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Table 3 Summary of Studies on the Use of Acupuncture to Regulate Gut Microbiota in the Treatment of Depression

	Research Model	Acupoints	Changes in Microbiota	Mechanisms	Results	Reference
EA	Depression induced by CUMS in mice	LI4, LR3	Increase the abundance of Firmicutes, Clostridia and decrease the abundance of Bacteroidetes, Bacteroidia.	—	EA at the "Siguan" acupoints can improve the depression-like behaviors of PSD rats by restoring the physiological structure of the intestinal flora and regulating the function of the intestinal flora.	Li, 2025[81]
MRA	Poststroke depression patients	GV20, EX-HN3, HT7, PC6, LR3	Increase the abundance of Bifidobacterium, Lactobacillus and decrease the abundance of Escherichia	5-HT↑,BDNF↑	MRA effectively treats Post stroke depression, and its mechanism may involve regulating the "microbiota-gut-brain axis", increasing beneficial gut bacteria, and enhancing 5-HT and BDNF levels.	Xie, 2025[82]
Acupuncture	Poststroke depression model rats	GV20, GV24, ST36	Upregulate the abundance of Bifidobacteriaceae and Lactobacillaceae, and decrease the relative abundance of Peptostreptococcaceae, Rikenellaceae, Eggerthellaceae, and Streptococcaceae at family level.	NLRP3↓, ASC↓, caspase-1↓, IL-18↓, IL-1β↓	Acupuncture may reduce depressive-like behaviors of poststroke depression by regulating the gut microbiota and suppressing hyperactivation of NLRP3 inflammasome in the colon.	Cai, 2024[78]
EA	Spared nerve injury induced SD depression rat model	GV20, GV29,	Increase the abundance of Akkermansi, Ruminococcaceae, and Lachnospiraceae,	HDAC2↓; BDNF↑, AcH3↑	The therapeutic effect of EA on depressive like behavior may involve regulation of gut microbiota, leading to changes in histone acetylation and upregulation of BDNF.	Li, 2024[83]
EA	Depression induced by CUMS in SD rats	ST36, ST25	Increase the abundance of Bacteroidetes, Proteobacteria, and Actinobacteria	ATCH↓, SST↓; VIP↑, CGRP↑	EA contributes to the improvement of depression, and gut microbiota may be one of the mechanisms of EA effect.	Wang, 2024[84]
EA	Depression induced by CUMS in SD rats	GV20, EX-HN3	Increase the abundances of Firmicutes, Bacteroidetes and Actinobacteria, and decrease the abundances of Verrucomicrobia and Proteobacteria	DAO↓, D-LA↓, LDH↓; ZO-1↑, claudin4↑, occludin↑	EA has potential antidepressant effects by regulating gut microbiota composition and abundance, subsequently affecting lipid metabolism.	Duan, 2024[85]
EA	Depression induced by CUMS in C57BL/6 mice	GV20	Increase the abundance of Actinobacteria and genus Allobaculum, Bifidobacterium, Dubosiella, Rikenella and Ileibacterium	—	EA improves depressive behavior by regulating the gut microbiota.	Wei, 2024[86]
EA	Depression induced by CUMS in C57BL/6 mice	GV20, GV24	Increase the abundance of Lactobacillus and decrease the abundance of staphylococci.	—	EA may play an antidepressant effect by adjusting the abundance of Lactobacillus and staphylococci.	Qiu, 2023[87]
EA	Poststroke depression model rats	DU20, DU24	Increase the abundance of Lactobacillaceae, Lachnospiraceae and decrease the abundance of Muribaculaceae, Peptostreptococcaceae, Clostridiaceae.	—	Regulation of gut microbiome and lipid metabolism could be one of the potential mechanisms for EA treatment for alleviating the depressive behaviors of PSD.	Cai, 2023[88]
Acupuncture	Depression induced by CUMS in SD rats	GV16, GV23	The abundance of class Gammaproteobacteria, Alphaproteobacteria, order Rhodospirillales, Enterobacteriales, has changed.	NO↓, cGMP↓, NF-κB↓	Acupuncture prevented and attenuated depression-like phenotype induced by CUMS, possibly via regulating the NO/cGMP signaling pathway and thus improving inflammation in serum, LHb and liver, and gut microbiota dysbiosis.	Chen, 2023[89]
EA	Patients with depression	—	—	TNF-α↓, IL-6↓, IL-1β↓; 5-HT↑, BDNF↑	EA treatment is effective and safe for patients with depression.	Cai, 2020[80]

Notes: ↑: Increased expression/level; ↓: Decreased expression/level.

Abbreviations: EA, electroacupuncture; MA, manual acupuncture; MRA, Mind-regulating acupuncture; BNDF, Brain-derived neurotrophic factor; CUMS, chronic unpredictable mild stress; BDNF, brain derived neurotrophic factor; DA, dopamine; 5-HT, hydroxytryptamine;GV16, Fengfu; GV20, Baihu; GV23, Shangxing; GV24, Shenting; ST36, Zusanli; ST25, Tianshu; EX-HN3, Yin tang; HT7, Shen men; PC6, Nei guan; LI4, Hegu; LR3, Tai chong; HDAC2, histone deacetylase2; ATCH, adrenocorticotropic hormone; SST,somatostatin; VIP, vasoactive intestinal peptide;CGRP, calcitonin-gene-related peptide; cGMP, cyclic-guanosine monophosphate; DAO, diamine oxidase; D-LA, D-Lactate; LDH, Lactate Dehydrogenase.

Molecular Mechanisms of Traditional Chinese Medicine Regulating Intestinal Microbiota

Regulation of the Immune System

TCM inhibits NLRP3/TLR4-mediated inflammation via multi-target regulation. TCM components (astragaloside IV, saikosaponin) suppress NLRP3 oligomerization and ASC speck formation, reducing Caspase-1 activation and mature IL-1β/IL-18 release.[46,49] For example, Gan-Mai-Da-Zao decoction downregulates NLRP3/ASC/Caspase-1 expression in CUMS mice, decreasing hippocampal IL-1β by 42%.[22] Xiaoyaosan and Chaihu-Shugan-San downregulate TLR4 and its adapter MyD88, inhibiting NF-κB nuclear translocation and reducing pro-inflammatory cytokines (TNF-α/IL-6).[25,66] Astragaloside IV also blocks TLR4-LPS binding to alleviate intestinal barrier dysfunction.[49] Studies have demonstrated that there is a close interaction between the gut microbiota and the host immune system. TCM influences immune responses by regulating the composition of the gut microbiota.[90] For example, certain TCM components can promote the growth of beneficial bacteria and inhibit the proliferation of harmful bacteria, thereby improving the balance of the intestinal microecology and enhancing the body's immune function.[91] In addition, TCM can improve the immune status of depressed patients by regulating cytokine secretion and reducing inflammatory responses.[92] For instance, studies have found that TCM can significantly reduce the levels of inflammatory factors in depressed patients, such as TNF-αand IL-6, thereby improving their emotional state.[93] This dual effect of regulating the gut microbiota and the immune system provides a new perspective for the application of TCM in the treatment of depression.

Effects on the Neuroendocrine System

TCM plays an important role in the treatment of depression by regulating the neuroendocrine system. Studies have shown that changes in the gut microbiota can affect the function of the neuroendocrine system, thereby influencing emotions and behaviors.[94] Certain components of TCM can regulate the gut microbiota, which in turn affects the activity of the hypothalamic-pituitary-adrenal (HPA) axis, reduces stress responses, and improves depressive symptoms.[95,96] For example, short-chain fatty acids (SCFAs) produced by gut microbes can stimulate the vagus nerve, affecting neurotransmitter release in the brain and thus alleviating depressive symptoms.[26,97] In addition, TCM can alleviate depressive symptoms by regulating the secretion of endocrine hormones such as adrenocorticotropic hormone (ACTH) and cortisol.[98] These findings provide a new biological basis for the application of TCM in the treatment of depression.

The Relationship Between Changes in Neurotransmitters and Depression

Alterations in neurotransmitters play a pivotal role in the occurrence and progression of depression. Gut microbiota metabolites directly regulate neurotransmitter synthesis and release, though direct evidence remains limited. SCFAs (eg, butyrate) promote colonic enterochromaffin cell proliferation and 5-HT synthesis (via upregulating tryptophan hydroxylase 1, TPH1), with 90% of peripheral 5-HT derived from gut microbes.[99] Butyrate also crosses the blood-brain barrier (BBB) to enhance hippocampal 5-HT release.[100] Tryptophan metabolism is another key pathway: gut bacteria (eg, Lactobacillus) convert tryptophan to indole-3-acetic acid, which inhibits the kynurenine pathway (reducing neurotoxic quinolinic acid) and increases hippocampal DA/BDNF levels.[101] However, most studies focus on correlation rather than causation. Studies have shown that the gut microbiota influences the pathological mechanisms of depression by affecting the synthesis and metabolism of neurotransmitters.[102,103] For instance, gut microbes can regulate the levels of 5-HT, DA, and NE, and the imbalance of these neurotransmitters is closely associated with depression.[95] TCM promotes neurotransmitter synthesis and alleviates depressive symptoms by regulating the gut microbiota.[104] For example, certain TCM components can increase the synthesis of 5-HT, thereby improving emotional states.[105] Additionally, studies have found that metabolites produced by gut microbes can further regulate neural transmission function in the brain by influencing the activity of neurotransmitter receptors, thus affecting the development of depression.[100] These studies provide important molecular mechanistic support for the application of TCM in the treatment of depression (As shown in Figure 2).

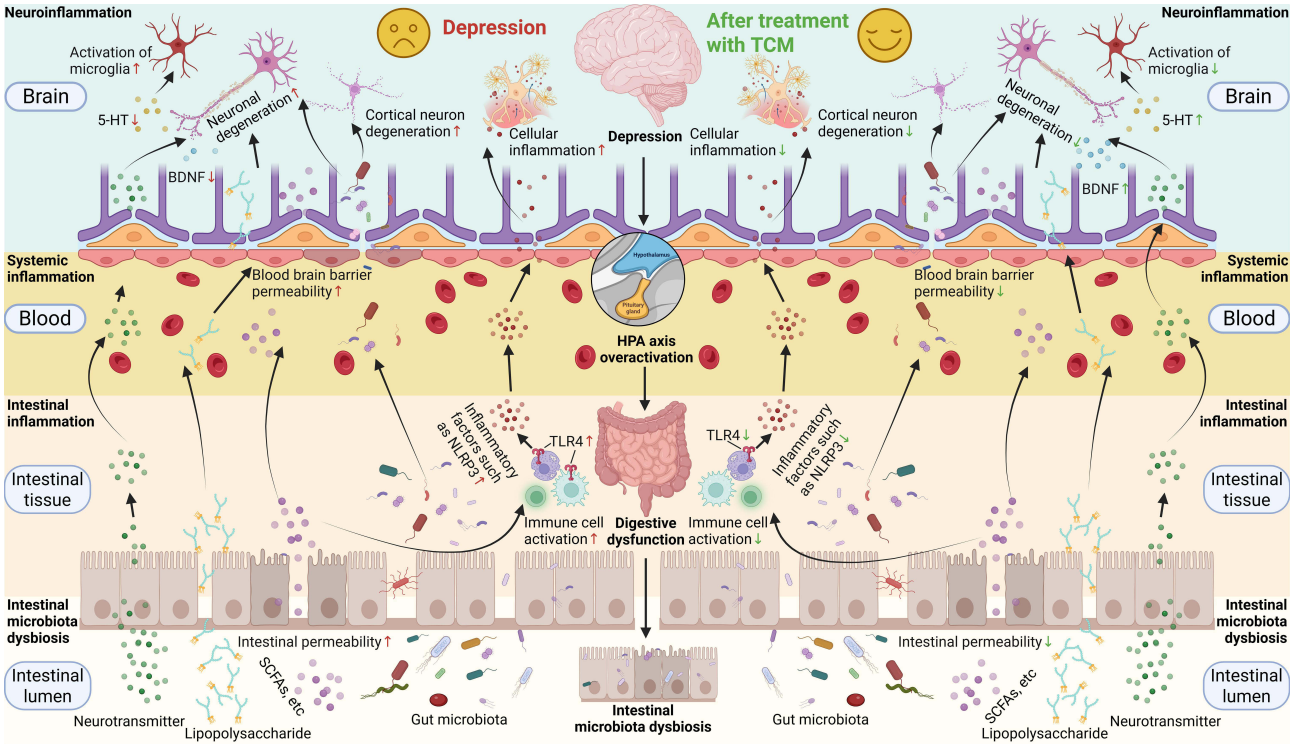

Figure 2 Mechanism diagram of TCM regulating the gut-brain axis in treating depression. Black arrow represents the pathway of regulation and promotion; The red arrow represents the increase or decrease of pro-inflammatory factors; The green arrow represents the increase or decrease of anti-inflammatory factors.

Conclusion

With the increasing depth of the gut-brain axis concept, our understanding of depression is constantly evolving. The composition and function of the gut microbiota are closely associated with the occurrence and progression of depression, and a growing body of research indicates that the gut-brain axis plays a vital role in emotional regulation and mental health. As an ancient yet systematic therapeutic approach, traditional Chinese medicine (TCM) has demonstrated unique advantages in regulating the microbiota and improving intestinal health. Through methods such as harmonizing qi and blood, and soothing the liver to regulate qi, TCM can effectively influence the diversity and abundance of gut microbes, thereby providing new insights for the treatment of depression.

Although existing studies have initially revealed the potential mechanisms of TCM in the treatment of depression, more systematic and scientific research is still needed to verify these findings. Differences often exist among various research results, which may stem from multiple factors such as sample selection, study design, and treatment protocols. A major limitation of current studies is the use of heterogeneous depression models, primarily chronic unpredictable mild stress (CUMS) and chronic restraint stress (CRS). CUMS mimics complex real-world stressors (eg, noise, food deprivation) and is widely used for its high clinical relevance, but results may vary due to inconsistent stressor combinations across studies.[106] In contrast, CRS focuses on single, sustained stress, which simplifies experimental variables but lacks ecological validity.[107] These differences lead to inconsistent findings: for example, Xiaoyaosan significantly increases Lactobacillus abundance in CUMS mice[25] but shows no significant change in CRS models,[75] possibly because CUMS-induced gut microbiota dysbiosis is more severe and responsive to TCM intervention. Therefore, future research should adopt multiple models to validate conclusions and standardize stressor protocols to enhance result comparability. Meanwhile, emphasis must be placed on standardization and normalization to ensure the reproducibility and reliability of research results, so as to provide more effective solutions for the clinical treatment of depression.

In conclusion, research on the gut-brain axis has provided a new perspective for the treatment of depression, and the unique regulatory mechanisms of TCM have brought new possibilities for the development of this field. Future studies

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will require more in-depth exploration to promote the update of gut-brain axis-related theories and the improvement of clinical practices, thereby bringing better quality of life and mental health to patients with depression.

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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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