The Journal of Green Energy and Environmental Engineering

Review Paper

Mechanisms and Therapeutic Potential of Natural Polysaccharides in Alleviating Depression via Microbiota-Gut-Brain Axis

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Abstract. Depression is one of the most burdensome mental disorders worldwide, and its clinical management still faces challenges such as low treatment response rates and frequent adverse effects associated with conventional pharmacological agents. Recent research on the microbiota-gut-brain axis (MGBA) has demonstrated that gut microbiota and their bioactive metabolites play a crucial regulatory role in neurological function by orchestrating neuro-endocrine-immune pathways. These findings provide new potential targets for therapeutic interventions in depression. This review summarizes current research on natural polysaccharides that modulate the gut microbiota and alleviate depression, systematically elucidating the multi-modal antidepressant mechanisms mediated via MGBA, and provides new insights for advancing strategies for the prevention and treatment of depression.

Keywords: *Natural polysaccharides; microbiota-gut-brain axis; depression; gut microbiota; short-chain fatty acids*

Received on 02 July 2025, Accepted on 05 Nov 2025, Published on 15 Dec 2025

1 Introduction

Depression is a complex neuropsychiatric disorder characterized by high disability rates, increased risk of suicide-related death, and premature mortality, making it a major global public health issue [1]. Its core clinical manifestations include persistent anhedonia, cognitive dysfunction, and low mood, often accompanied by somatic symptoms such as appetite disturbances, disrupted sleep architecture, and psychomotor retardation [2]. Beyond neuropsychiatric manifestations, depression can also trigger intestinal barrier damage, neuroimmune dysregulation, and neurodegenerative changes [3]. Although current evidence-based medicine indicates that antidepressant drugs combined with psychotherapy have clinical efficacy for depression, the effectiveness of this comprehensive intervention model is generally at a moderate level, and there is heterogeneity in response among different individuals [4]. The etiological complexity of this disease stems from the convergence of the following pathological mechanisms: (1) imbalance of monoamine neurotransmitters [dopamine, 5-hydroxytryptamine (5-HT), noradrenaline (NE)]; (2) dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis accompanied by hypercortisolemia; (3) microglia-mediated neuroinflammation; (4) mitochondrial oxidative stress cascade; (5) hippocampal neuroplasticity deficits (Fig. 1) [5]. These interconnected pathways form a pathophysiological network, posing challenges to traditional single-target drug therapies. Furthermore, long-term use of synthetic antidepressants may lead to metabolic complications and organ toxicity, prompting research to shift towards natural compounds with multi-target regulatory capabilities and favorable safety profiles.

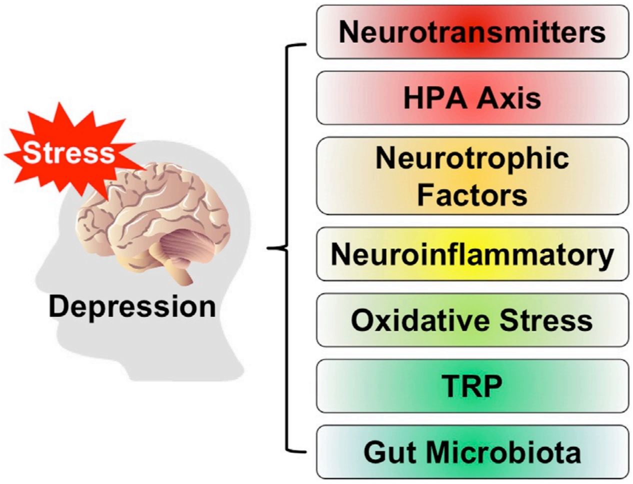


Figure 1 Multidimensional pathological mechanisms involved in depression

Emerging work has pinned down the gut microbiome as a key driver of depressive disorders. This bustling ecosystem of bacteria, archaea, fungi and viruses—dubbed the body's "second genome" [6]—orchestrates far more than digestion. Through the microbiota–gut–brain axis this ever-shifting ecosystem chats bidirectionally with the CNS, reframing the roots of depression in microbial terms. Patient data reveal that depressive subjects carry a dysbiotic gut signature: fewer short-chain fatty acids and a TLR4–NF-κB–driven neuroinflammatory flare [7]. Notably, gut microbes can not only synthesize neuroactive metabolites that directly conduct neural signals but also regulate the expression of brain-derived neurotrophic factor (BDNF) and neurotransmitter receptor profiles [8]. These findings make the MGBA an important target for depression treatment.

Polysaccharides, as ubiquitous natural macromolecules, not only possess biological activities such as anti-inflammatory, immunomodulatory, and antioxidant effects but also exert prebiotic effects by selectively modulating the gut microbiota [9]. Microbial metabolism of polysaccharides produces SCFAs, which enhance intestinal barrier integrity, regulate immune homeostasis, and exert neuroprotective effects via the vagus nerve and circulatory pathways [10]. Existing evidence confirms that polysaccharides can improve depressive behaviors through microbiota-dependent mechanisms, including normalization of HPA axis function, suppression of neuroinflammation, and enhancement of hippocampal neurogenesis [11]. Therefore, this article systematically focuses on natural polysaccharides as a class of substances, aiming to delineate their unique multi-dimensional mechanisms for intervening in depression via the MGBA: (1) polysaccharide-mediated remodeling of the gut microbiota; (2) microbial metabolic transformation of polysaccharides; (3) MGBA-mediated neuropsychiatric effects; (4) clinical applications and existing issues of polysaccharides, providing a theoretical framework for developing microbiota-targeted antidepressant strategies.

2 Overview of the Association between Gut Microbiota and Depression

2.1 Gut Microbiota Microenvironment and Depression

The gut of healthy adults harbors a complex microbial community, including Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, as well as archaea, fungi, viruses, and microeukaryotes. Among these, Firmicutes and Bacteroidetes dominate (approximately 90%), followed by Proteobacteria and Actinobacteria, while Fusobacteriota and Verrucomicrobiota account for about 10% [12]. Core beneficial microbiota crucial for maintaining metabolic, immune, and neurological homeostasis include Bifidobacterium, Lactobacillus, and Bacteroides [13]. Research has identified notable dysbiosis in the gut microbiota of individuals with depression. At the phylum level, there is generally a reduction in the abundance of Firmicutes, accompanied by increased proportions of Bacteroidetes, Proteobacteria, and Actinobacteria. At the family level, Acidaminococcaceae, Rikenellaceae, Porphyromonadaceae, and Enterobacteriaceae are more prevalent compared to healthy controls, whereas Bacteroidaceae, Ruminococcaceae, Lachnospiraceae, Prevotellaceae, and Erysipelotrichaceae are significantly diminished. At the genus level, pro-inflammatory bacteria are overproliferated, while the abundance of anti-inflammatory bacteria is decreased [14] (Fig. 2). Multiple clinical datasets indicate that the microbial signature of depression is characterized by a common pattern of overproliferation of pro-inflammatory/conditionally pathogenic bacteria and depletion of beneficial bacteria. This dysbiosis ultimately leads to neuroinflammation and synaptic plasticity damage through the following mechanisms: impaired SCFA synthesis, exacerbated shift in the tryptophan-kynurenine metabolic pathway, and activation of the TLR4/NF-κB pathway [15].

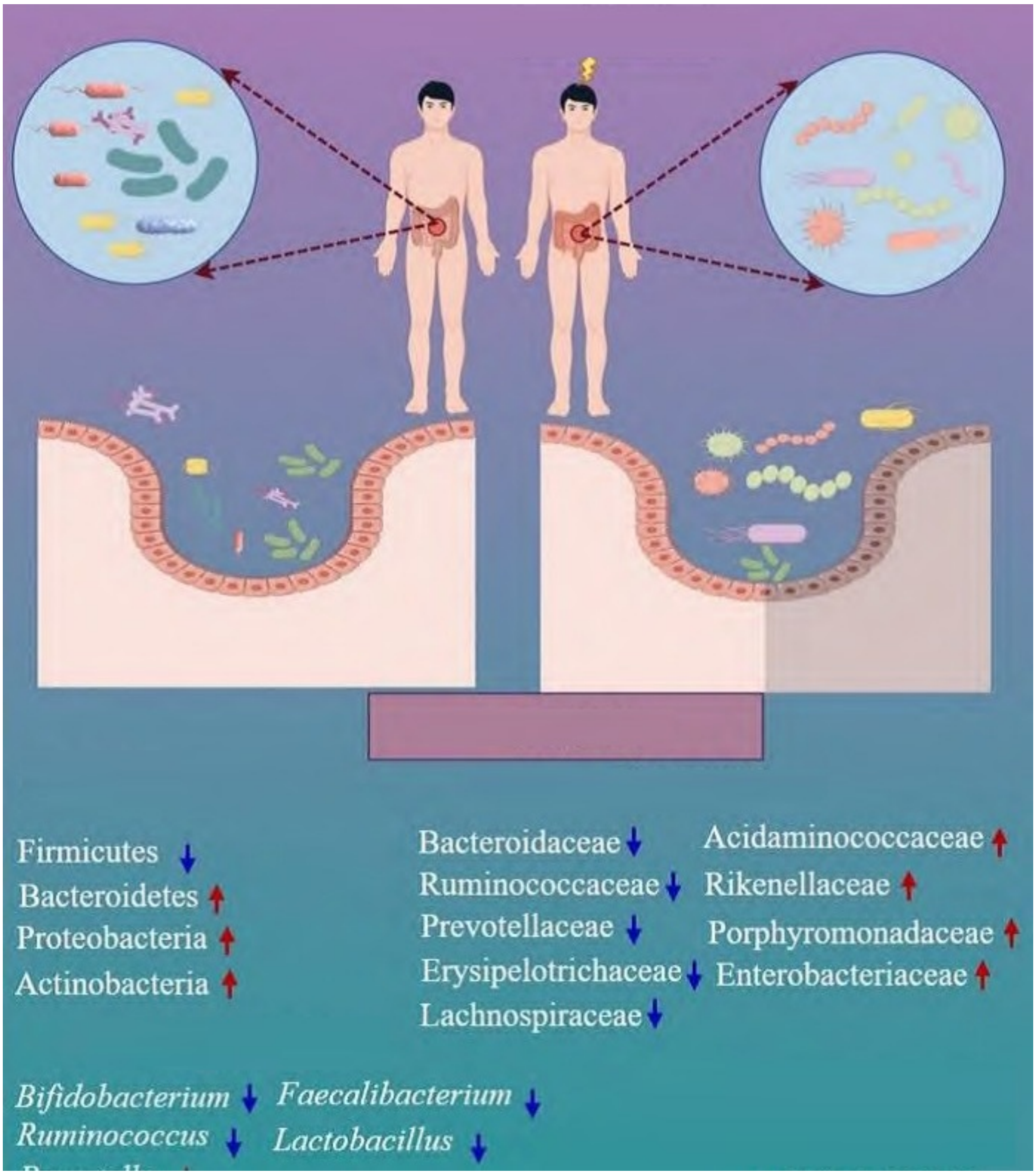


Figure 2 Changes in gut microbiota between healthy individuals and patients with depression

2.2 Role of the MGBA in the Pathogenesis of Depression

The gastrointestinal tract, by virtue of its central role in nutrient metabolism, immune regulation, and neuroendocrine signaling, is hailed as the second brain [16]. The bidirectional communication mechanism between the gut and the central nervous system (CNS) is formally referred to as the gut-brain axis [17]. This multidimensional network facilitates two-way signaling between the gastrointestinal tract and the brain via neural, immune, and metabolic pathways [8]. As a key channel for parasympathetic nerve signal transmission, the vagus nerve not only mediates basic physiological processes from mood regulation to immune homeostasis but also receives regulatory signals from gut microbiota metabolites [19]. Recent evidence indicates that gut microbes influence CNS activity through direct neuroendocrine stimulation and indirect autonomic nervous system regulation, with microbial metabolites, endocrine factors, and immunomodulatory molecules being the primary mediators [20].

Depression tracks closely with microbial metabolic drift—chiefly dwindling short-chain fatty acids (SCFAs) and a derailed tryptophan pathway. These SCFAs, fermentation gifts from fiber-loving anaerobes, make up >90 % of colonic fatty-acid mass [22]. Butyrate exerts neuroprotective effects by inhibiting histone deacetylases, enhancing hippocampal BDNF expression and synaptic plasticity; propionate, on the other hand, maintains blood-brain barrier integrity through a mechanism mediated by free fatty acid receptor 2 [23]. Notably, 95% of 5-HT synthesis occurs in enterochromaffin cells, and the bioavailability of its precursor, tryptophan, is highly dependent on microbial regulation. Dysbiosis-induced impairment of tryptophan-to-5-HT conversion disrupts monoaminergic neurotransmission, becoming a key pathway in the development of depressive symptoms.

Persistent brain inflammation sits at the core of depression. Once the gut barrier leaks, microbial fragments such as LPS slip into the bloodstream, latch onto pattern-recognition receptors and ignite a cytokine storm that reaches the CNS [24]. This inflammatory microenvironment disrupts blood-brain barrier integrity, promotes microglial activation and their conversion to a pro-inflammatory M1 phenotype. Activated microglia release reactive oxygen species and excitotoxins, which, through the combined effects of oxidative stress and glutamatergic dysfunction, induce neurodegeneration in the prefrontal cortex and hippocampus [25]. Concurrent HPA axis hyperactivity, manifested as elevated adrenocorticotropic hormone (ACTH)/corticosterone levels and suppressed BDNF expression, forms a vicious cycle of neuroendocrine dysfunction and impaired neuroplasticity (Fig. 3) [26].

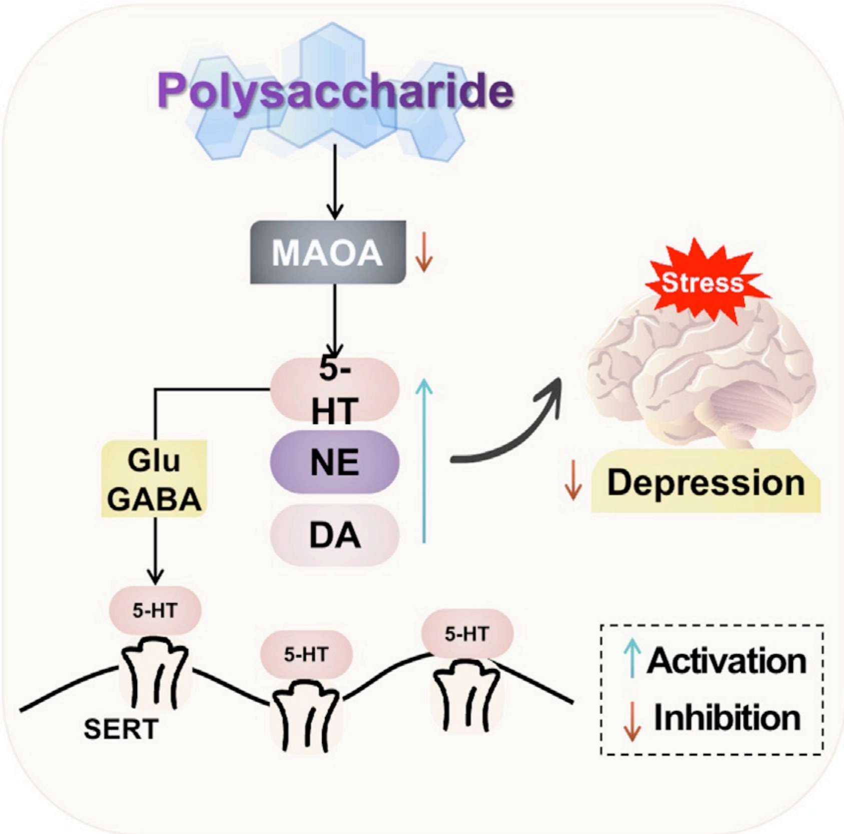


Figure 3 Pathogenic mechanisms of depression mediated by MGBA

3 Characteristics of Natural Polysaccharides and Their Regulatory Effects on Gut Microbiota

3.1 Maintaining Gut Microbiota Ecological Balance

Polysaccharides are difficult to degrade by enzymes encoded in the host genome, but degradation enzymes secreted by the gut microbiota can break down polysaccharides, facilitating their digestion and absorption by the host. The fermentation of indigestible polysaccharides by gut microbiota generates short-chain fatty acids (SCFAs). These SCFAs not only serve as an energy source for intestinal epithelial cells, stimulating their proliferation and supporting intestinal barrier integrity, but also contribute to maintaining intestinal homeostasis and bolstering immune tolerance [27]. Furthermore, in terms of microbiota composition, polysaccharides can stimulate the proliferation of probiotics while inhibiting the growth of harmful bacteria, thereby modulating the gut microbiota and promoting a more balanced microbial structure [28]. Studies have found that Astragalus polysaccharides can increase the abundance of Bacteroides in the intestines of mice with alcoholic liver injury, improving gut microbiota dysbiosis [29]. Licorice polysaccharides can upregulate the abundance of Lactobacillaceae, Verrucomicrobiaceae, Bifidobacteriaceae, S24-7, and Erysipelotrichaceae, while downregulating the abundance of Ruminococcaceae, Lachnospiraceae, Enterobacteriaceae, Erysipelotrichaceae, and Desulfovibrionaceae [30]. Polysaccharides from Polygonatum sibiricum leaves can elevate the relative abundance of Firmicutes while reducing that of Bacteroidetes in the mouse intestine. At the genus level, they increase the abundance of Lactobacillus while decreasing Lachnospiraceae and Bacteroides [31]. Dendrobium officinale polysaccharides can lower the Firmicutes/Bacteroidetes (F/B) ratio and raise the abundance of Lactobacillus in the intestines of aging model mice [32]. Pueraria lobata polysaccharides effectively alleviate colonic lesions and gut microbiota dysbiosis induced by antibiotic-associated diarrhea by promoting the growth of beneficial intestinal bacteria and suppressing pathogenic bacteria. Asparagus polysaccharides can modulate SCFA levels in the intestines of mice with colitis, increasing the total content of alanine, isovaleric acid, and other SCFAs. Rehmannia glutinosa polysaccharides can be fermented by gut microorganisms to produce SCFAs, raising the levels of acetate, propionate, and butyrate in the gut, thereby exerting beneficial effects on mouse colitis. Additionally, Astragalus polysaccharides can increase SCFA content, thus regulating the gut microbiota [33]. Bamboo shavings polysaccharides promote SCFA production by upregulating the abundance of Bacteroidetes and Prevotella while downregulating Clostridium and Bilophila, demonstrating bioactive effects in modulating gut microbiota balance. Hericium erinaceus polysaccharides can increase the abundance of SCFA-producing bacteria, normalize SCFA levels in the body, and thus alleviate cyclophosphamide-induced immunosuppression in mice. Fucoidan can increase the proportions of Bacteroides, Akkermansia muciniphila, Blautia, and Prevotella, improving metabolic syndrome and intestinal malnutrition in mice. Therefore, natural polysaccharides can optimize the composition and ratio of beneficial intestinal bacteria, promote the growth of healthy microbiota and reduce the abundance of pathogenic bacteria, thereby helping the host maintain a healthy microecological balance system (Fig. 4).

3.2 Enhancing Effects on Intestinal Barrier Function

The intestine, as the organ with the largest contact area with the external environment in animals, is not only a crucial site for digestion and absorption but also a defensive barrier against exogenous pathogens and toxins [34]. Studies demonstrate that polysaccharides can strengthen the mechanical integrity of the intestinal barrier by modulating the expression and spatial organization of tight junction (TJ) proteins. The dynamic equilibrium of TJ proteins forms the structural foundation for maintaining intestinal selective permeability, and their function is regulated by signaling pathways such as myosin light-chain kinase, protein kinase C, and mitogen-activated protein kinase (MAPK). Polysaccharides derived from Plantago ovata, coix seed, and Spirulina can elevate the transepithelial electrical resistance of human colorectal adenocarcinoma Caco-2 cells, decrease the paracellular transport of fluorescently labeled dextran, and concurrently upregulate the expression of claudin-1, claudin-3, ZO-1, and other TJ proteins. Spatholobus suberectus polysaccharides enhance the gene expression of ZO-1 and claudin-1 in the jejunal mucosa of cyclophosphamide-induced immunosuppressed chickens, thereby improving intestinal barrier function. The regulatory effect of polysaccharides on TJ proteins can be reflected by serum markers: the combination of Astragalus polysaccharides and xylose can reduce the levels of diamine oxidase and D-lactic acid in broiler plasma, while upregulating the gene expression of jejunal claudin-1, claudin-3, and occludin, improving growth performance. Polysaccharides can also protect intestinal epithelial cells from reactive oxygen species-mediated damage by inhibiting oxidative stress. Studies found that red algae polysaccharides can reduce malondialdehyde content in colon tissues of a 2,4,6-trinitrobenzenesulfonic acid-induced rat model, inhibit the overproduction of inducible nitric oxide synthase and peroxynitrite, thereby alleviating intestinal barrier damage. Oat β-glucan can boost the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and glutathione reductase, while lowering oxidative stress marker levels in the spleen of a rat model of lipopolysaccharide-induced enteritis; its mechanism may be related to its molecule's ability to scavenge exogenous hydrogen free radicals [35]. In shrimp, broilers, and weaned piglets, polysaccharides effectively restore the oxidant-antioxidant system imbalance and maintain intestinal homeostasis by increasing the activities of SOD, GSH-Px, and catalase in serum [36]. These findings indicate that polysaccharides can resist ROS damage to the intestinal barrier through synergistic regulation of enzymatic and non-enzymatic antioxidant systems. Furthermore, the combined administration of Astragalus polysaccharides and American ginseng polysaccharides suppresses the aberrant activation of the TLR4/myeloid differentiation factor 88 (MyD88)/NF-κB signaling pathway in the intestines of lipopolysaccharide-treated weaned piglets, thereby lowering serum levels of IL-1β and TNF-α and consequently preserving intestinal epithelial barrier integrity [37]. Ziziphus jujuba var. spinosa polysaccharides, by downregulating TLR4/NF-κB signaling, reduce the expression of IL-6, IL-1β, and TNF-α in the intestines of a sepsis model mouse, reversing cecal ligation and puncture-induced intestinal barrier dysfunction. Notably, the anti-inflammatory effects of polysaccharides are not limited to inhibiting pro-inflammatory factors but also involve immunomodulation by inducing the secretion of the anti-inflammatory cytokine IL-10. Arabinogalactan can inhibit NF-κB activity in Caco-2 cells and stimulate IL-10 production, thereby reducing distal colon permeability and maintaining barrier integrity. Composite fiber can increase the differentiation of regulatory T cells in the intestinal mucosa of IL-10 knockout mice, reduce CD4+ T cell infiltration, inhibit TNF-α/TNF receptor-mediated increase in TJ protein permeability, and ultimately alleviate chronic colitis [38]. In summary, polysaccharides synergistically maintain intestinal functional stability through multiple pathways, including antioxidation, anti-inflammation, regulation of TJ proteins, and promotion of SCFA production (Fig. 4).

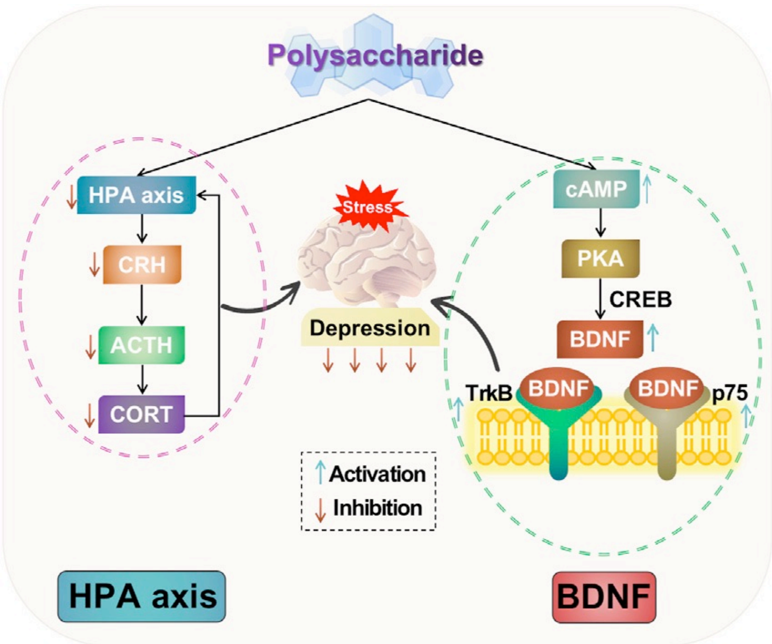


Figure 4 Mechanism by which polysaccharides improve intestinal health through modulation of gut microbiota and barrier function

4 Multidimensional Mechanisms by Which Natural Polysaccharides Regulate Depression via the Gut-Brain Axis

4.1 Changes in Gut Microbiota Structure and Homeostatic Regulation

Natural polysaccharides serve as significant prebiotics capable of effectively modulating gut microbiota structural imbalances and restoring intestinal microecological homeostasis. This microbial reset marks their first foothold for engaging the microbiota–gut–brain axis against depression. Okra polysaccharides, for instance, rebalance CUMS-exposed mice by trimming Bacteroidetes and Actinobacteria while expanding Firmicutes and *Lactobacillus* ranks [39]. Eucommia ulmoides polysaccharides, on the other hand, increase the abundance of Lactobacillaceae and simultaneously inhibit groups associated with inflammation or metabolic disorders such as Proteobacteria, Clostridia, and Prevotellaceae, exerting antidepressant effects by remodeling the microbiota structure [40]. Cistanche deserticola polysaccharides can increase the abundance of Bacteroidetes, Parabacteroides, and Blautia, changes that help regulate immune balance and increase SCFA levels [41]. Furthermore, Ginkgo biloba polysaccharides have been confirmed to effectively enhance the abundance of intestinal Lactobacillus, while peony polysaccharides, Schisandra chinensis polysaccharides, and Corydalis yanhusuo polysaccharides have also been reported to exert antidepressant effects by regulating imbalanced gut microbiota structure. These studies collectively indicate that natural polysaccharides can effectively reverse depression-related microbial ecological dysbiosis by targeting and modulating the abundance of specific phyla (Firmicutes, Bacteroidetes, Proteobacteria), classes, families (Lactobacillaceae), and genera (Lactobacillus, Russellella, Eubacterium).

4.2 Metabolites and Epigenetic Regulation

4.2.1 Regulation of Tryptophan Metabolism

Tryptophan, as an essential amino acid for the human body, is the sole precursor for 5-HT synthesis and plays a key role in the pathogenesis of depression. Tryptophan is metabolized mainly through three pathways: after intestinal absorption, about 95% enters the kynurenine metabolic pathway, while a small remaining amount is catalyzed by tryptophan hydroxylase to generate 5-HT, which is ultimately metabolized by monoamine oxidase to 5-hydroxyindoleacetic acid [42]. Studies show that acute tryptophan depletion reduces 5-HT synthesis and induces depressive symptoms, while elevated kynurenine levels exacerbate neural damage by activating immune and inflammatory responses. Polysaccharides can regulate the tryptophan metabolic pathway by modulating key enzyme activities, promoting 5-HT synthesis and inhibiting the production of the neurotoxic metabolite 3-hydroxykynurenine.

Studies show that *Cistanche deserticola* polysaccharides dampen the kynurenine pathway via microbiota crosstalk, reset both the HPA and HPG axes, and concurrently elevate hippocampal 5-HT and BDNF, lifting depressive-like behavior and neuroendocrine imbalance.

4.2.2 Epigenetic Regulatory Mechanisms of SCFAs

SCFAs are 1- to 6-carbon saturated acids churned out when gut microbes ferment plant-derived polysaccharides. As histone deacetylase (HDAC) inhibitors, SCFAs alter chromatin conformation by inhibiting HDAC activity. Among them, butyrate is the strongest natural HDAC inhibitor, specifically inhibiting HDAC2/3 activity and inducing a hyperacetylated state of histones H3 and H4, thereby activating the transcription of neuroprotective genes such as BDNF and glial cell line-derived neurotrophic factor. In the pathological mechanism of depression, SCFAs exert protective effects through the following pathways: (1) SCFAs calm the neuro-immune milieu: they block NF-κB to curb IL-6 and TNF-α output, lift IL-10 and TGF-β, and thus dial down hippocampal microglial overdrive [42]. (2) Maintaining blood-brain barrier integrity: SCFAs reduce intestinal permeability by upregulating the expression of ZO-1 and occludin, blocking the entry of pro-inflammatory components such as lipopolysaccharides into the CNS [43]. (3) Modulating the neurotransmitter system: SCFAs promote the synthesis of the 5-HT precursor tryptophan by activating enterochromaffin cells, while inhibiting indoleamine 2,3-dioxygenase activity and reducing kynurenine pathway activation, thereby increasing brain levels of 5-HT and dopamine [44]. Fecal SCFA measurements in depressed cohorts run consistently low, and the deficit tracks in reverse with Hamilton depression severity [45]. It is noteworthy that different SCFAs have distinct effects. Butyrate has the most significant effect on epigenetic regulation, while propionate and acetate act more indirectly through metabolic pathways. SCFA-mediated neuroprotection hinges on microbial richness: Xiong et al. showed Xiaoyaosan polysaccharides expand butyrate-producers, raise colonic butyrate and, in turn, blunt CUMS-evoked depressive behavior. Yan's team documented that okra polysaccharides reinstated colonic pools of butyrate, acetate and propionate in CUMS mice, supplying proof-of-concept that restoring SCFA balance could anchor next-generation antidepressant regimens.

4.3 Inflammatory Immunity and Neuroplasticity Regulation

4.3.1 TLR4/NF-κB Pathway and Neuroinflammation

Neuroinflammation is the chain reaction set off inside brain tissue when neurons, microglia and astrocytes react to injurious triggers; damage-associated motifs released after antigenic or mechanical insults ignite glia and erode blood–brain barrier tightness. The resulting breakdown ushers circulating immune cells into the parenchyma and unleashes a cytokine storm, locking the brain into a self-feeding inflammatory loop [46]. NF-κB sits at the hub of this circuitry, integrating signals that govern immunity, inflammation, stress resistance and cell fate. TLR4 uses MyD88 as a docking platform to summon inflammatory cells and dispatch NF-κB, TNF-α and IL-1β. Stress ramps up hippocampal TLR4 and NF-κB, whereas deleting TLR4 gene abolishes these stress-driven changes. Patient data reveal NF-κB ignition in depressed subjects exposed to physical or psychosocial stressors, and CUMS rodents mirror this biology—NF-κB drive fosters depressive behavior while stalling neurogenesis. Astragalus polysaccharides cool brain inflammation via gut–brain axis crosstalk, curb LPS-triggered MAPK/NF-κB signaling, trim phosphorylated JNK, ERK and p65, and consequently dial down IL-1β and TNF-α output. *Schisandra chinensis* polysaccharides raise microglial LRP-1, block NF-κB from entering the nucleus, cut TNF-α, IL-6 and IL-1β release, and push M2 markers IL-10 and arginase-1 upward. *Ganoderma lucidum* polysaccharides tamp down caspase-1, IL-1β and IL-18 by halting NLRP3 inflammasome assembly and stalling NF-κB signaling [47]. An acidic heteropolysaccharide isolated from *Acorus tatarinowii* blocks both TLR4-MyD88/NF-κB and PI3K-Akt axes in BV-2 microglia, curbs LPS-elicited TNF-α, IL-6, iNOS and COX-2, and averts ROS overflow plus mitochondrial injury. *Eucommia ulmoides* polysaccharides silence the TLR4/NF-κB/MAPK cascade in microglia, curb LPS release, reshape neurogenic programs and translate these changes into mood-elevating outcomes. Collectively, the data spotlight TLR4/NF-κB as a neuro-inflammatory hub and frame structurally varied plant polysaccharides as a versatile, multi-pronged arsenal against depression.

4.3.2 Regulatory Role of MAPK/PI3K/Akt Signaling Pathway on Neuroplasticity

By reshaping gut microbes and their metabolites, natural polysaccharides can remotely switch on the MAPK/PI3K/Akt axis in the brain, dialing synaptic plasticity up or down. In depression, various molecular alterations collectively affect the Akt and MAPK signaling pathways. Akt sits at the metabolic crossroads, steering glucose use, cell survival, division and movement via crosstalk with MAPK and mTOR networks [47]. The characteristic neurological dysfunction in depression is impaired neuroplasticity. Akt has become a key regulatory factor in psychiatric disorders, and its functional deficiency is closely related to depressive behaviors [48]. This kinase also integrates dopamine and 5-HT neurotransmission and is involved in the pathogenesis of major depressive disorder [49]. The MAPK cascade converts extracellular stimuli into diverse responses, regulating stress responses, inflammation, and cell survival through nuclear translocation mechanisms, while also affecting synaptic plasticity and higher cognitive functions [50]. Research indicates that MAPK is involved in the pathogenesis and treatment response of depression [34]. This pathway phosphorylates transcription factors such as Ets-like protein-1 and cAMP-response element binding protein (CREB) via ERK, transmitting signals from environmental factors to genomic responses. Brain tissue from depressed humans and rodents alike displays dampened ERK signaling, and antidepressants regain efficacy precisely by restoring this pathway's activity [34]. In depression, Akt—operating downstream of PI3K—phosphorylates GSK-3β, halting tau hyper-phosphorylation, safeguarding synapses and fostering new dendritic spines; its dysfunction leads to reduced hippocampal BDNF expression and impaired synaptic plasticity. Lycium barbarum polysaccharides drive synaptic remodeling: they switch on IRS-1/PI3K/Akt, brake GSK-3β, curb tau phosphorylation and lift synaptic scaffold proteins [35]. Okra polysaccharides improve tau pathology and restore synaptic function by activating the PI3K/Akt pathway [36].

Schisandra chinensis polysaccharides repair hippocampal neuronal morphology by reducing p38/ERK/JNK phosphorylation levels [37].

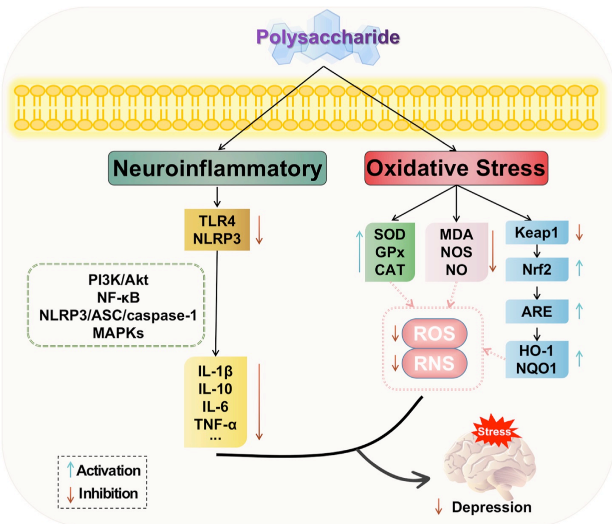
4.4 Neuro-endocrine and Neurotransmitter System Remodeling

4.4.1 HPA Axis Regulation

Depression locks the hypothalamic–pituitary–adrenal (HPA) axis in overdrive—the body's main stress circuit. Chronic pressure breaks the CRH-ACTH feedback loop, corticosterone stays high, and the axis slips into persistent dysregulation [38]. This process can damage hippocampal neurons, thereby inducing or exacerbating depression. Therefore, reducing corticosterone, CRH, and ACTH levels and restoring the HPA axis negative feedback mechanism have become important strategies for antidepressant treatment. Studies have found that Polygonatum sibiricum polysaccharides can inhibit corticosterone levels in lipopolysaccharide and CUMS models [39]; Lycium barbarum polysaccharides tighten HPA-axis feedback in PTSD rats by trimming NR2B and CaMKII signals and lowering serum corticosterone, translating into mood recovery [40]；A lily–Astragalus polysaccharide blend lessens CA1 neuronal injury and outperforms either alone at cutting corticosterone and ACTH [41]; Dendrobium officinale polysaccharides likewise dial down CRH, ACTH and corticosterone in depressed mice, normalizing the HPA axis [42]. These results indicate that polysaccharides can exert antidepressant effects by inhibiting HPA axis overactivation and promoting negative feedback regulation.

4.4.2 BDNF/Tyrosine Kinase Receptor B (TrkB)/CREB Pathway

BDNF is widely expressed in the CNS and exerts neuroprotective effects by binding to its specific receptor TrkB, which then phosphorylates Akt and activates the transcription factor CREB [43]. Through the activation of presynaptic and postsynaptic TrkB receptors, BDNF regulates neuronal survival and synaptic plasticity [44]. The neurotrophic model posits that sustained stress erases hippocampal BDNF, a loss mirrored in depressive symptoms. Once BDNF docks with TrkB, the duo sparks synaptic rewiring through the NMDAR/CaMKII relay. Phosphorylated TrkB enhances NMDAR function to promote glutamatergic transmission while preventing excitotoxicity [45]. Schisandra chinensis polysaccharides can modulate TrkB receptor phosphorylation to enhance BDNF expression and CREB phosphorylation, inhibit hippocampal neuronal apoptosis, and restore 5-HT system function [47]. Porphyra polysaccharides switch on the hippocampal BDNF/TrkB/ERK/CREB cascade, lifting BDNF output and driving TrkB, ERK and CREB phosphorylation [48]. This cascade reaction can reduce neuronal apoptosis, stimulate neurogenesis and increased dendritic spine density, and antagonize chronic stress-induced depressive behaviors. Polygonum multiflorum polysaccharides can shift the polarization of microglia from the lipopolysaccharide-induced M1 phenotype toward the M2 phenotype and promote neuronal survival and synaptic plasticity by activating the BDNF/TrkB/CREB pathway [49]. Zanthoxylum polysaccharides ignite the CREB–BDNF axis, fortify synaptic performance and thereby generate mood-lifting outcomes [50]. The mechanism of natural polysaccharides improving depression through the MGBA is shown in Fig. 5.



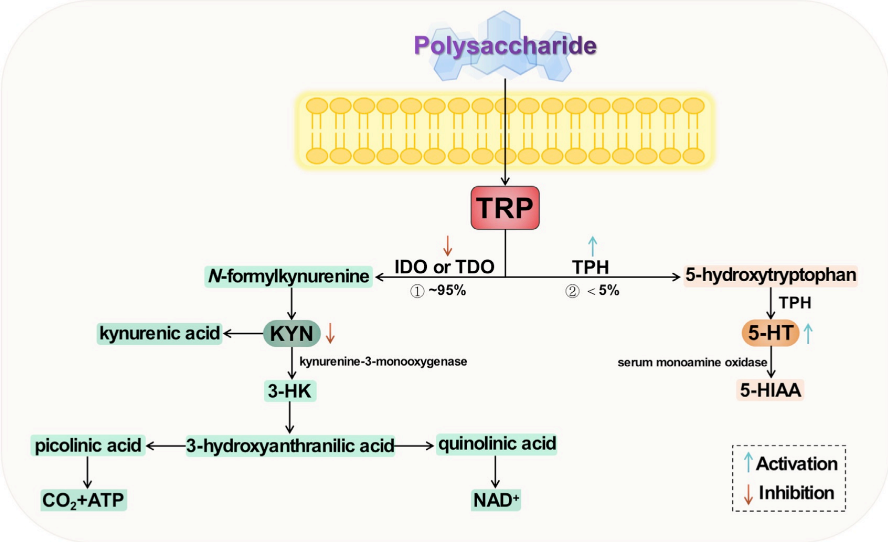


Figure 5 Mechanism of natural polysaccharides improving depression through MGB axis

5 Current Status of Clinical Research

Fresh rodent data reveal that polymeric carbohydrates lighten despair-type conduct by re-shaping the gut flora, sealing the intestinal wall and re-tuning brain neurotransmitter ratios. However, such research is currently limited to model animals and in vitro mechanism exploration, and the clinical translation of polysaccharides as antidepressants is still in its early stages. In a six-week, randomized, double-blind study, adolescents with subthreshold depression receiving 300 mg Lycium barbarum polysaccharide daily experienced a significantly steeper drop on the 24-item Hamilton scale than placebo users, driven by sharper gains in cognition, psychomotor speed and sense of hope. One in three participants in the polysaccharide arm achieved remission—more than four times the 7 % seen with placebo [11]. Mechanistic studies suggest that Lycium barbarum polysaccharides may act through anti-inflammatory pathways, manifested by selectively reducing IL-17A levels and modulating cytokine network connectivity [32]. Among depressed patients who also carry coronary artery disease, only the tandem of inulin plus live bacteria lowered Beck scores and TNF-α, while expanding microbial diversity and raising IL-10 [33]. Although these results are positive, multicenter, large-sample trials are still needed to determine the optimal dosing regimen, long-term efficacy, and precise mechanisms of action.

6 Conclusion

Natural polysaccharides provide a new multi-target intervention strategy for depression treatment through synergistic regulation of gut microbiota, metabolic pathways, and neuroprotective mechanisms. They show clear potential in enhancing the intestinal barrier, inhibiting TLR4/NF-κB neuroinflammation, and activating the BDNF/TrkB/CREB pathway, and closely link microbial metabolism with neuroplasticity via SCFA-mediated epigenetic regulatory mechanisms. However, research in this field still has important limitations: current evidence mostly remains at the correlational level (association between behavioral improvement and 16S sequencing-based microbiota changes) or provides potential mechanistic clues (changes in key signaling molecule expression), but experimental verification capable of establishing causality is still insufficient, especially studies using germ-free animals, fecal microbiota transplantation, or specific metabolite supplementation strategies to empirically demonstrate the necessity of the microbiota and their metabolites in the antidepressant effects of polysaccharides are relatively scarce. Furthermore, the structure-activity relationship of polysaccharides needs systematic elucidation, including the effects of relative molecular mass, glycosidic bond types, and branching structures on their prebiotic effects and neuroregulatory functions. Although animal models like CUMS and lipopolysaccharide-induced models have shown positive efficacy, differences in microbiota composition and the blood-brain barrier between species still hinder clinical translation. Existing clinical studies are also limited by sample size and insufficient standardization of polysaccharide preparations. There is a need to promote large-scale Phase III trials combined with microbiome analysis to identify responsive populations and optimize dosing strategies. Future efforts should focus on strengthening research designs at the causal level and integrating multidisciplinary technologies such as spatial transcriptomics, in vivo real-time sensing, and artificial intelligence to deeply analyze the "polysaccharide-microbiota-brain" interaction network, ultimately promoting the advancement of depression treatment towards personalized, microecology-targeted intervention models.

References

[1] Breda, C., Sathyasaikumar, K. V., Sograte Idrissi, S., Notarangelo, F. M., Estranero, J. G., Moore, G. G. L., et al. (2016). Tryptophan-2,3-dioxygenase (TDO) inhibition ameliorates neurodegeneration by modulation o f kynurenine pathway metabolites. Proc. Natl. Acad. Sci. 113, 5435–5440. doi:10.1073/pnas.1604453113

[2] Averina, O. V., Zorkina, Y. A., Yunes, R. A., Kovtun, A. S., Ushakova, V. M., Morozova, A. Y., et al. (2020). Ba cterial metabolites of human gut microbiota correlating with depression. Int. J. Mol. Sci. 21, 9234. doi:10. 3390/ijms21239234

[3] Barbuti, M., Menculini, G., Verdolini, N., Pacchiarotti, I., Kotzalidis, G. D., Tortorella, A., et al. (2023). A sys tematic review of manic/hypomanic and depressive switches in patients with bipolar disorder in naturalis tic settings: the role of antidepressant and antipsychotic drugs. Eur. Neuropsychopharmacol. 73, 1–15. do i:10.1016/j.euroneuro.2023.04.013

[4] Joo, M.-K., Ma, X., Yoo, J.-W., Shin, Y.-J., Kim, H.-J., and Kim, D.-H. (2023). Patient-derived Enterococcus m undtii and its capsular polysaccharides cause depression through the downregulation of NF-κB-involved s erotonin and BDNF expression. Microbes Infect. 25, 105116. doi:10.1016/j.micinf.2023.105116

[5] Jovanovic, P., Wang, Y., Vit, J.-P., Novinbakht, E., Morones, N., Hogg, E., et al. (2022). Sustained chemogen etic activation of locus coeruleus norepinephrine neurons promotes dopaminergic neuron survival in synu cleinopathy. PLOS ONE 17, e0263074. doi:10.1371/journal.pone.0263074

[6] Carniel, B. P., and da Rocha, N. S. (2021). Brain-derived neurotrophic factor (BDNF) and inflammatory mar kers: perspectives for the management of depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 108, 110151. doi:10.1016/j.pnpbp.2020.110151

[7] Benedetti, F., Aggio, V., Pratesi, M. L., Greco, G., and Furlan, R. (2020). Neuroinflammation in bipolar depr ession. Front. Psychiatry 11, 71. doi:10.3389/fpsyt.2020.00071

[8] Bhatt, S., Nagappa, A. N., and Patil, C. R. (2020). Role of oxidative stress in depression. Drug Discov. Today 25, 1270–1276. doi:10.1016/j.drudis.2020.05.001

[9] Chen, G., Zhou, S., Chen, Q., Liu, M., Dong, M., Hou, J., et al. (2022). Tryptophan-5-HT pathway disorder w as uncovered in the olfactory bulb of a depression mice model by metabolomic analysis. Front. Mol. Neur osci. 15, 965697. doi:10.3389/fnmol.2022.965697

[10] Chen, H., Kan, Q., Zhao, L., Ye, G., He, X., Tang, H., et al. (2023). Prophylactic effect of Tongxieyaofang poly saccharide on depressive behavior in adolescent male mice with chronic unpredictable stress through the microbiome-gut-brain axis. Biomed. Pharmacother. 161, 114525. doi:10.1016/j.biopha.2023.114525

[11] Chen, K., Chen, S., Ren, J., Lin, S., Xiao, M., Cheng, L., et al. (2021). Antidepressant effect of acidic polysacc harides from Poria and their regulation of neurotransmitters and NLRP3 pathway. China J. Chin. Mat. Med ica 46, 5088–5095. doi:10.19540/j.cnki.cjcmm.20210610.705

[12] Chen, P., Hei, M., Kong, L., Liu, Y., Yang, Y., Mu, H., et al. (2019). One water-soluble polysaccharide from G inkgo biloba leaves with antidepressant activities via modulation of the gut microbiome. Food Funct. 10, 8 161–8171. doi:10.1039/C9FO01178A

[13] Han, W., Wang, N., Han, M., Ban, M., Sun, T., and Xu, J. (2022). Reviewing the role of gut microbiota in the pathogenesis of depression and exploring new therapeutic options. Front. Neurosci. 16, 1029495. doi:10. 3389/fnins.2022.1029495

[14] Höglund, E., Øverli, Ø., and Winberg, S. (2019). Tryptophan metabolic pathways and brain serotonergic ac tivity: a comparative review. Front. Endocrinol. 10, 158. doi:10.3389/fendo.2019.00158

[15] Brancato, S. K., Thomay, A. A., Daley, J. M., Crane, M. J., Reichner, J. S., Sabo, E., et al. (2013). Toll-like rec eptor 4 signaling regulates the acute local inflammatory response to injury and the fibrosis/neovasculariz ation of sterile wounds. Wound Repair Regen. 21, 624–633. doi:10.1111/wrr.12061

[16] Kim, Y.-K., Na, K.-S., Myint, A.-M., and Leonard, B. E. (2016). The role of pro-inflammatory cytokines in ne uroinflammation, neurogenesis and the neuroendocrine system in major depression. Prog. Neuropsychop harmacol. Biol. Psychiatry 64, 277–284. doi:10.1016/j.pnpbp.2015.06.008

[17] Belujon, P., and Grace, A. A. (2017). Dopamine system dysregulation in major depressive disorders. Int. J. Neuropsychopharmacol. 20, 1036–1046. doi:10.1093/ijnp/pyx056

[18] Fu, Y., Peng, Y., Huang, X., Yang, Y., Huang, L., Xi, Y., et al. (2021). Lycium barbarum polysaccharide-glycoprotein preventative treatment ameliorates aversive. Neural Regen. Res. 16, 543–549. doi:10.4103/1673-5374.293156

[19] Gao, F., Yang, S., Wang, J., and Zhu, G. (2022). cAMP-PKA cascade: an outdated topic for depression? Biomed. Pharmacother. 150, 113030. doi:10.1016/j.biopha.2022.113030

[20] Chu, S. (2019). Protective effects of Lycium barbarum polysaccharide on depression rats with post-traumatic stress disorder. Mod. Prev. Med. 46, 2622–2637.

[21] Gong, X., Chang, R., Zou, J., Tan, S., and Huang, Z. (2023). The role and mechanism of tryptophan–kynurenine metabolic pathway in depression. Rev. Neurosci. 34, 313–324. doi:10.1515/revneuro-2022-0047

[22] Grinchii, D., and Dremencov, E. (2020). Mechanism of action of atypical antipsychotic drugs in mood disorders. Int. J. Mol. Sci. 21, 9532. doi:10.3390/ijms21249532

[23] Guo, X., Rao, Y., Mao, R., Cui, L., and Fang, Y. (2020). Common cellular and molecular mechanisms and interactions between microglial activation and aberrant neuroplasticity in depression. Neuropharmacology 181, 108336. doi:10.1016/j.neuropharm.2020.108336

[24] Guo, Y., Chen, X., Gong, P., Li, Z., Wu, Y., Zhang, J., et al. (2023). Advances in the mechanisms of polysaccharides in alleviating depression and its complications. Phytomedicine 109, 154566. doi:10.1016/j.phymed.2022.154566

[25] Hou, C., Yin, M., Lan, P., Wang, H., Nie, H., and Ji, X. (2021). Recent progress in the research of Angelica sinensis (Oliv.) Diels polysaccharides: extraction, purification, structure and bioactivities. Chem. Biol. Technol. Agric. 8, 13. doi:10.1186/s40538-021-00214-x

[26] Ji, X., Guo, J., Cao, T., Zhang, T., Liu, Y., and Yan, Y. (2023). Review on mechanisms and structure-activity relationship of hypoglycemic effects of polysaccharides from natural resources. Food Sci. Hum. Wellness 12, 1969–1980. doi:10.1016/j.fshw.2023.03.017

[27] Agus, A., Planchais, J., and Sokol, H. (2018). Gut microbiota regulation of tryptophan metabolism in health and disease. Cell Host Microbe 23, 716–724. doi:10.1016/j.chom.2018.05.003

[28] Attwells, S., Setiawan, E., Wilson, A. A., Rusjan, P. M., Miler, L., Xu, C., et al. (2020). Replicating predictive serum correlates of greater translocator protein distribution volume in brain. Neuropsychopharmacology 45, 925–931. doi:10.1038/s41386-019-0561-y

[29] Cai, Q., Li, Y., and Pei, G. (2017). Polysaccharides from Ganoderma lucidum attenuate microglia-mediated neuroinflammation and modulate microglial phagocytosis and behavioural response. J. Neuroinflammation 14, 63. doi:10.1186/s12974-017-0839-0

[30] Cheng, D., Chang, H., Ma, S., Guo, J., She, G., Zhang, F., et al. (2018). Tiansi Liquid modulates gut microbiota composition and tryptophan–kynurenine metabolism in rats with hydrocortisone-induced depression. Molecules 23, 2832. doi:10.3390/molecules23112832

[31] Chai, Y., Li, Q., Wang, Y., Tao, E., and Asakawa, T. (2022). The value of HPA axis hormones as biomarkers for screening and early diagnosis of postpartum depression: updated information about methodology. Front. Endocrinol. 13, 916611. doi:10.3389/fendo.2022.916611

[32] Kim, Y.-S., O'Sullivan, D. M., and Shin, S.-K. (2019). Can 24 weeks strength training reduce feelings of depression and increase neurotransmitter in elderly females? Exp. Gerontol. 115, 62–68. doi:10.1016/j.exger.2018.11.009

[33] Comai, S., Bertazzo, A., Brughera, M., and Crotti, S. (2020). Tryptophan in health and disease. Adv. Clin. Chem. 95, 165–218. doi:10.1016/bs.acc.2019.08.005

[34] Deng, Z., Yuan, C., Yang, J., Peng, Y., Wang, W., Wang, Y., et al. (2019). Behavioral defects induced by chronic social defeat stress are protected by Momordica charantia polysaccharides via attenuation of JNK3/PI3K/AKT neuroinflammatory pathway. Ann. Transl. Med. 7, 6. doi:10.21037/atm.2018.12.08

[35] Castrén, E., Võikar, V., and Rantamäki, T. (2007). Role of neurotrophic factors in depression. Curr. Opin. Pharmacol. 7, 18–21. doi:10.1016/j.coph.2006.08.009

[36] Ding, C., Xu, Y., and Ge, Y. (2021). Research on the mechanism and the effects of Angelica polysaccharide on the behavior of chronic stress depression mice. West. J. Tradit. Chin. Med. 34, 21–27. doi:10.12174/j.issn.2096-9600.2021.06.06

[37] Ding, J., Jiang, C., Yang, L., and Wang, X. (2022). Ameliorative effect of Acanathopanax senticosus polysaccharides on depressive behavior in rats by regulating PI3K/Akt/mTOR pathway. Sci. Technol. Food Ind. 43, 369–375. doi:10.13386/j.issn1002-0306.2021090141

[38] Abdoulaye, I. A., Wu, S., Chibaatar, E., Yu, D., Le, K., Cao, X., et al. (2021). Ketamine induces lasting antide pressant effects by modulating the NMDAR/CaMKII-mediated synaptic plasticity of the hippocampal dent ate gyrus in depressive stroke model. Neural Plast. 2021, e6635084. doi:10.1155/2021/6635084

[39] Bian, H., Yan, F., Li, W., Tu, W., and Ji, X. (2022). Tert-butylhydroquinone prevents neuroinflammation and relieves depression via regulation of NLRP3 signaling in mice. Int. Immunopharmacol. 107, 108723. doi:1 0.1016/j.intimp.2022.108723

[40] Khosravifarsani, M., Tolouian, R., Yadollahifarsani, S., Soleimani, P., Sarazen, M., Mostafizi, P., et al. (202 2). Medical plants for lung cancer: an overview of current knowledge. Immunopathol. Persa 9, e38455. do i:10.34172/ipp.2022.38455

[41] Bouvier, E., Brouillard, F., Molet, J., Claverie, D., Cabungcal, J.-H., Cresto, N., et al. (2017). Nrf2-dependent persistent oxidative stress results in stress-induced vulnerability to depression. Mol. Psychiatry 22, 1701–1713. doi:10.1038/mp.2016.144

[42] Cheema, H. S., and Singh, M. P. (2021). The use of medicinal plants in digestive system related disorders: a systematic review. J. Ayurvedic Herb. Med. 7, 182–187. doi:10.31254/jahm.2021.7303

[43] Duman, R. S., Sanacora, G., and Krystal, J. H. (2019). Altered connectivity in depression: GABA and glutam ate neurotransmitter deficits and reversal by novel treatments. Neuron 102, 75–90. doi:10.1016/j.neuron. 2019.03.013

[44] Dwivedi, Y. (2009). Brain-derived neurotrophic factor: role in depression and suicide. Neuropsychiatr. Dis. Treat. 5, 433–449. doi:10.2147/ndt.s5700

[45] Eicher, T. P., and Mohajeri, M. H. (2022). Overlapping mechanisms of action of brain-active bacteria and b acterial metabolites in the pathogenesis of common brain diseases. Nutrients 14, 2661. doi:10.3390/nu14 132661

[46] Fan, L., Peng, Y., Wang, J., Ma, P., Zhao, L., and Li, X. (2021). Total glycosides from stems of Cistanche tubu losa alleviate depression-like behaviors: bidirectional interaction of the phytochemicals and gut microbiot a. Phytomedicine 83, 153471. doi:10.1016/j.phymed.2021.153471

[47] Farahani, M. S., Bahramsoltani, R., Farzaei, M. H., Abdollahi, M., and Roja, R. (2015). Plant-derived natural medicines for the management of depression: an overview of mechanisms of action. Rev. Neurosci. 26, 3 05–321. doi:10.1515/revneuro-2014-0058

[48] Appleton, J. (2018). The gut-brain axis: influence of microbiota on mood and mental health. Integr. Med. Clin. J. 17, 28–32.

[49] Feng, X., Fan, Y., and Chung, C. Y. (2020). Mefenamic acid can attenuate depressive symptoms by suppres sing microglia activation induced upon chronic stress. Brain Res. 1740, 146846. doi:10.1016/j.brainres.20 20.146846

[50] Fond, G., Loundou, A., Rabu, C., Macgregor, A., Lançon, C., Brittner, M., et al. (2014). Ketamine administra tion in depressive disorders: a systematic review and meta-analysis. Psychopharmacol. (Berl.) 231, 3663–3676. doi:10.1007/s00213-014-3664-5