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Targeting the Spleen-Gut-Brain Axis in Depression: Immune-Microbiota Drivers of Neuroinflammation

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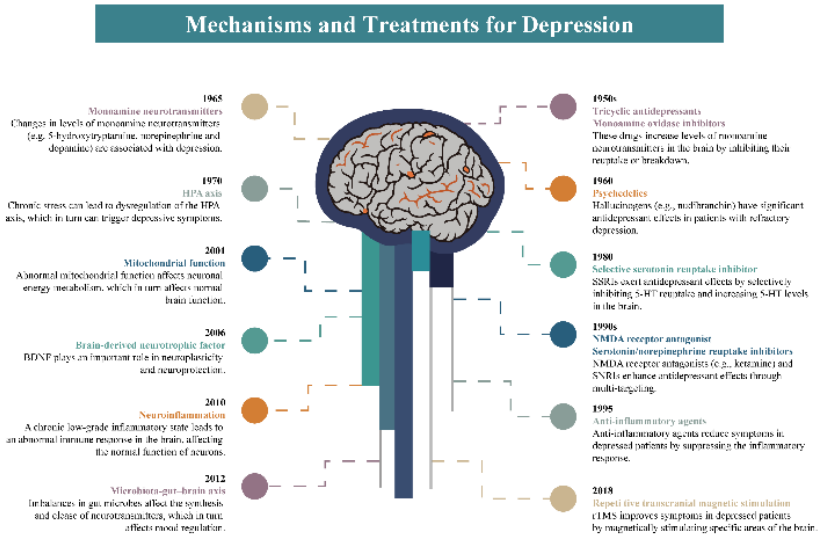
Abstract: Emerging evidence highlights the spleen-gut-brain axis as a pivotal therapeutic frontier in depression, orchestrating crosstalk among peripheral immunity, gut microbiota, and neuroinflammatory cascades. Chronic stress triggers splenic hypersecretion of pro-inflammatory cytokines (e.g., IL-1β, TNF-α) and gut barrier dysfunction, which synergistically activate hippocampal microglial NLRP3 inflammasome via α7 nicotinic acetylcholine receptor (α7nAChR)-mediated vagal signaling. This neuroimmune cascade exacerbates synaptic loss and depressive-like behaviors by amplifying oxidative stress and suppressing BDNF/TrkB-dependent neuroplasticity. Natural compounds (e.g., astragaloside IV and baicalin) exhibit multi-target efficacy through dual modulation of HMGB1/TLR4/NF-κB-driven neuroinflammation and restoration of gut microbiota homeostasis. This review highlights novel therapeutic strategies involving natural compounds with dual immunomodulatory and microbiota-restoring properties, which not only circumvent the limitations of monoamine-centric drugs but also offer safer adjunctive therapies. Focusing on systemic inflammation as a root cause—rather than merely symptom management—these strategies hold promise for patients unresponsive to conventional antidepressants, potentially reducing relapse rates through sustained immunomodulation. By bridging immunology, microbiology, and neuropharmacology, this work proposes a paradigm shift of precision psychiatry—one where depression is treated not as a chemical imbalance, but as a systemic network modulation.

Keywords: Depression; Spleen-Gut-Brain Axis; Neuroinflammation; Immunomodulation; Gut Microbiota.

1. Introduction

Major depressive disorder (MDD) imposes a staggering global burden, with rising incidence among adolescents and young adults[1, 2]. Despite advances in neurobiological research, first-line antidepressants (e.g., SSRIs/SNRIs) fail in 40-60% of patients, with 30% relapsing after initial treatment[3]. This therapeutic crisis stems from a fundamental oversight: depression is not merely a brain disorder, but a systemic disease where peripheral immunity orchestrates neuroinflammation[4, 5]. While classical hypotheses (HPA axis dysregulation, monoamine deficiency) explain specific symptoms[6], they neglect the spleen's pivotal role as an immunometabolic hub connecting gut dysbiosis to CNS pathology. The limitations of current therapies underscore this gap. Novel interventions (ketamine, psychedelics, VNS) show transient efficacy but often ignore peripheral inflammatory drivers (Figure 1).



Depression is the result of the interaction of multiple complex mechanisms. The figure summarizes key advances in biological mechanisms and treatments for depression.

Figure 1. Key advances in biological mechanisms and treatments for depression

Emerging evidence redefines MDD as a disorder of the spleen-gut-brain axis. While the gut-brain axis has dominated depression research, the spleen—a peripheral immune hub—has emerged as a critical mediator bridging gut dysbiosis and

neuroinflammation[7-9]. Unlike the gut-centric view, the spleen-gut-brain axis emphasizes systemic immune priming: splenic macrophages release pro-inflammatory cytokines under stress, which impair gut barrier function and amplify neuroinflammatory cascades via vagus nerve signaling. This paradigm shift challenges the conventional monoamine hypothesis and offers novel targets for multi-compound natural drugs.

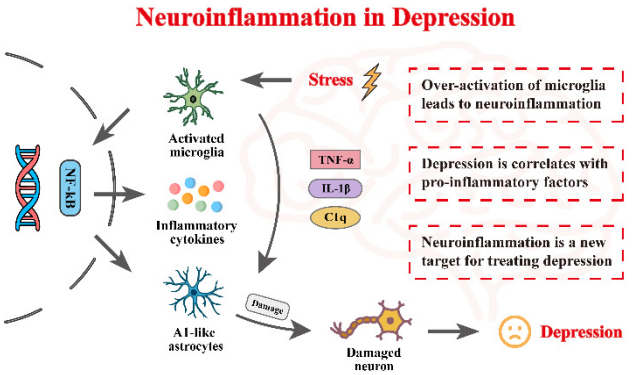
We comprehensively summarise the mechanisms and analyze the multifaceted role and systemic effects of the spleen-gut-brain axis in depression and innovatively explore the potential of natural medicines targeting the spleen-gut-brain axis for the treatment of depression. This work establishes the theoretical foundation for the development of novel therapeutic strategies for depression, highlighting its significant scientific relevance and promising prospects for clinical application.

2. Neuroinflammation in Depression

(1) Microglia-Mediated Neuroinflammation

Neuroinflammation manifests as a dynamic interplay between immune activation and neuronal dysfunction. Microglia, resident macrophages of the central nervous system (CNS), orchestrate neuroinflammatory responses[10-12]. Under chronic stress, microglia polarize toward a pro-inflammatory phenotype, releasing cytokines (IL-1β, TNF-α) and ROS, while activated microglia induce astrocytes to shift to a neurotoxic A1 phenotype [13-16]. The NLRP3 inflammasome, activated by stress-induced DAMPs via TLR4/NF-κB signaling, drives neuroinflammation[17, 18].

(2) Neuroinflammation As a Therapeutic Target in Depression



During the pathology of depression, stress leads to the over-activation of microglia, which releases pro-inflammatory cytokines such as TNF-α, IL-1β, and C1q. These inflammatory mediators further contribute to the inflammatory response by activating the NF-κB signaling pathway. Meanwhile, activation of microglia also induces astrocytes to shift to the cytotoxic A1 type, exacerbating neuroinflammation. The inflammatory response leads to neuronal damage, which in turn triggers depressive symptoms. Furthermore, depression is strongly associated with elevated levels of several pro-inflammatory factors, suggesting that neuroinflammation may be a novel target for depression treatment.

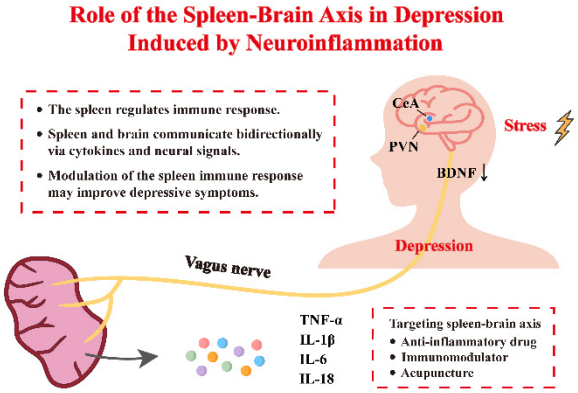
Figure 2. Mechanisms of neuroinflammation in depression.

Meta-analyses have reported significant changes in the concentrations of pro-inflammatory cytokines TNF-α and IL-6 in patients with depression compared to healthy controls[19, 20]. In recent years, the antidepressant effects shown by some anti-inflammatory drugs also imply that neuroinflammation may be one of the key factors in the development of depression[21]. For instance, a randomized controlled trial showed adjunctive minocycline (a microglial inhibitor) significantly reduced depressive symptoms in patients[22]. Interventions targeting specific immune signaling pathways, such as inflammasomes or Toll-like receptors (TLRs) in microglia and the HMGB1/NF-kB signaling pathway, may contribute to alleviating neuroinflammation and associated depressive symptoms [17, 23, 24]. Recent single-cell transcriptomic studies identified pro-inflammatory microglial subpopulations (e.g., C1q+ Trem2+) in the prefrontal cortex of depressed patients, offering precision targets for immunomodulation[25] (Figure 2).

3. Role of the Spleen-Brain Axis in Depression Induced by Neuroinflammation

(1) Mechanisms of the Spleen-Brain Axis

The spleen is the largest peripheral immune organ in the human body and coordinates systemic immunity by removing aged or abnormal blood cells, extramedullary hematopoiesis, and producing cytokines[26, 27]. The spleen and the brain establish a bidirectional neuro-immune regulatory network, which involves humoral and neural routes. The spleen not only communicates indirectly with the CNS through the blood and lymphatic systems but also directly with the brain through the central nucleus of the amygdala (CeA) and the paraventricular nucleus (PVN), thus identifying a specific splenic-brain neural connection. Additionally, the vagus nerve (VN) signaling also suppresses splenic NF-κB activation via α7nAChR signaling, attenuating cytokine release[28-30]. It also indirectly influences splenic function by inhibiting inflammatory responses through the activation of the HPA axis[31].



The spleen communicates bidirectionally with the brain through neural connections such as CeA, PVN, and VN, allowing brain signals to modulate spleen function. At the same time, the spleen, as a major peripheral immune organ, produces cytokines that can also influence brain function and behavior. These cytokines, such as TNF-α, IL-1β, IL-6, and IL-18, affect the CNS through blood circulation, leading to decreased levels of BDNF, which in turn triggers neuroinflammation and neuronal dysfunction, and is closely associated with the development of depression. Modulating the immune response in the spleen, such as with anti-inflammatory drugs, immunomodulators, or acupuncture, may help improve depressive symptoms.

Figure 3. Role of the spleen-brain axis in depression induced by neuroinflammation.

(2) Therapeutic Implications of the Spleen-Brain Axis

There is growing evidence for the role of the spleen in depression associated with inflammation[32, 33]. Splenic hypersecretion of TNF-α, IL-1β, IL-6, and IL-18 acts on the

brain via the blood circulation, leading to a reduction in brain-derived neurotrophic factor (BDNF), exacerbating neuroinflammation and neuronal dysfunction—key pathways in depression pathogenesis[34]. Thus, targeting the spleen-brain axis provides new perspectives on the potential treatments for depression.

Anti-inflammatory drugs or immunomodulators may help restore normal spleen-brain communication, thereby reducing depressive symptoms. The novel antidepressant arketamine plays an important role in antidepressant-like effects via the spleen-brain axis mediated by VN through the oxidative phosphorylation pathways, transforming growth factor (TGF)-β1 and heme biosynthesis II pathways in the prefrontal cortex (PFC)[35, 36]. Acupuncture has shown promise in ameliorating depressive symptoms by regulating inflammation through the spleen-brain axis [37] (Figure 3).

4. Gut-Brain Axis in Depression: Microbial Dysbiosis to Neuroinflammation

(1) Gut Microbiota and Mental Health

Depression is linked to changes in the gut microbiota (GM) composition. A large population-based cohort study explored the correlation between the GM and quality of life, as well as depression[9]. It was found that Butyrate-producing Faecalibacterium and Coprococcus were associated with higher quality-of-life indicators, whereas Coprococcus and Dialister were reduced in depressed patients. In addition, the ability of the GM to synthesize dopamine metabolites was positively correlated with psychological quality of life, which may link the neuroactive metabolic capacity of the GM with mental health[38].

(2) Signaling Pathways in Gut-Brain Crosstalk

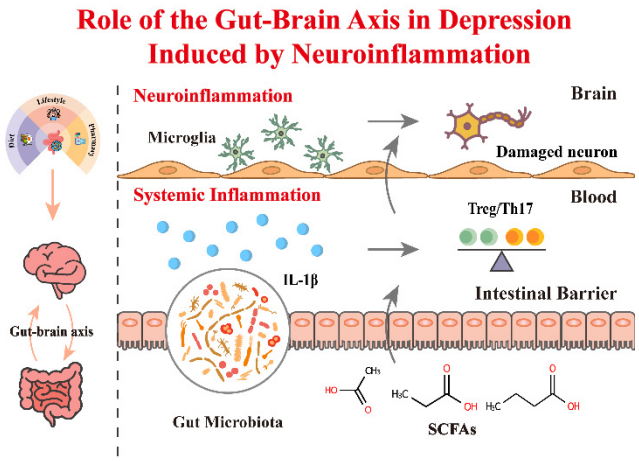
The gut-brain axis is a bidirectional communication system between the GM and the CNS, involving a variety of signaling molecules and metabolites. The GM communicates with the host by secreting metabolites such as short-chain fatty acids (SCFAs)[39], which can influence intestinal barrier function and the maturation and function of immune cells, ultimately impacting the CNS[40]. Conversely, the CNS can also affect the composition and function of the GM through the neuroendocrine and autonomic nervous systems, forming a complex regulatory network.

In addition, microglia activation appears to be key in triggering the signaling cascade and changes in gene expression. Recent studies have pointed out that stress can dysregulate GM, and these changes in GM can lead to systemic inflammation. Increased circulating markers of inflammation can cross the blood-brain barrier to stimulate immune and related brain mechanisms, in particular microglia activation, which impairs the function of both the gut and the cerebral vascular barrier, increasing the risk of neurodegenerative diseases[41-43].

(3) Influence of the gut-brain axis in the pathogenesis of depression

Currently, many studies have found that patients with depression and anxiety disorders often exhibit significant changes in the diversity and abundance of GM. The link between the cell ratio of Treg/Th17 in the gut and the production of hippocampal chemokine and PFC IL-1β has also been associated with stress-induced behavioral deficits[44, 45]. GM may play an important role in the treatment and prevention of anxiety and depression through stress-related neuroendocrine, autonomic, and immune pathways[46]. Modulating the gut-brain axis by restoring dysregulated GM has become an emerging therapeutic strategy to ameliorate these conditions[47, 48].

Increasing the production of GM-derived SCFAs may enhance intestinal barrier function and modulate neuroinflammation, increase BDNF expression in the brain, and activate the synthesis of gut hormones and neurotransmitters, leading to potential therapeutic effects on depression[49, 50]. Dietary interventions, lifestyle changes, and pharmacological treatments have also been considered as potential means of ameliorating depression through the gut-brain axis[51-53]. Moreover, inflammatory bowel disease (IBD), especially colitis, is highly correlated with the prevalence of anxiety and depression[54-56], and probiotics are effective therapeutic agents for preventing this disease[57]. Probiotic supplementation may help to restore GM homeostasis, improve intestinal barrier function, and reduce inflammatory responses, thereby benefiting patients with depression[58-60]. Additionally, co-decoction of Lilii bulbus and Radix Rehmannia Recens and its key bioactive ingredient verbascoside[61], fermented red ginseng and red ginseng[62], and polyphenolic compounds in edible herbs[63] have also been shown to reduce inflammatory responses, improve intestinal barrier function impairment, and alleviate depressive-like behaviors, which provides new mechanisms and strategies for treating depression with traditional Chinese medicinal herbs (Figure 4).



GM plays a key role in the pathogenesis of depression by influencing bidirectional communication with the CNS through the secretion of metabolites such as SCFAs. Depression is closely related to GM composition and changes, and GM dysregulation may lead to systemic inflammation and activation of microglia, which in turn impairs gut and cerebral vascular barrier function and increases the risk of depression. Modulating the gut-brain axis through dietary interventions, lifestyle changes, and pharmacological treatments may help improve depressive symptoms.

Figure 4. Role of the gut-brain axis in depression induced by neuroinflammation

5. Immune-Neural-Microbiota Crosstalk in Depression: Spleen-Gut-Brain Axis

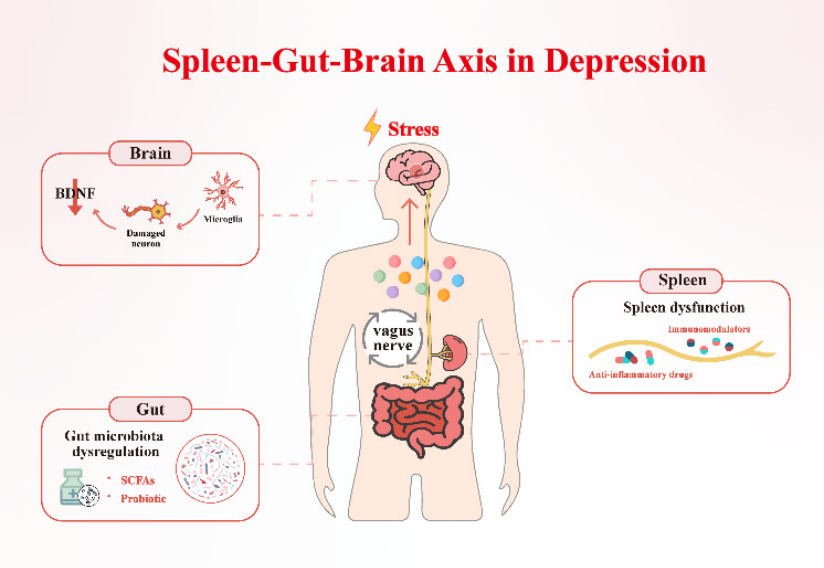
(1) Interaction Mechanisms

A study by Carsetti et al. found that the depletion of IgM memory B-cells in splenectomized patients was associated with defects in intestinal secretory IgA, suggesting the existence of a splenic-gut axis[64]. This was followed by

Douglas Buchmann Godinho et al. They explored how the pathophysiology of traumatic brain injury could be improved by influencing the immune crosstalk between the spleen, gut, and brain[65], and the VN appeared to play an important role in the neuroimmune connectivity of the spleen-gut-brain axis. The immune response in the spleen can influence GM homeostasis and modulate intestinal inflammation through the VN, establishing a direct connection to intestinal immunomodulation. The GM influences intestinal immune cell function and spleen function through the production of metabolites and immunomodulatory factors and communicates with the brain via the VN, which subsequently influences the neuroimmune environment of the brain, emotional states, and cognitive processes.

Increasing evidence shows that dysregulation of the GM related to the immune system can affect brain function. Thus, the spleen-gut-microbiota axis may play a crucial role in the prevention and treatment of related diseases by regulating immune homeostasis and GM composition. For example, Bourhy et al. explored the potential roles of the gut-brain and spleen-brain axis in stroke and sepsis. They noted that changes in GM and activation of splenic immune cells through neuro-immune interactions may have a significant impact on neuroinflammation and the recovery of brain function after stroke[66]. These findings indicate that the GM may influence neuroinflammatory and neurodegenerative processes by affecting immune cells in the gut and CNS, including macrophages, microglia, and astrocytes[67].

(2) Therapeutic Potential of the Spleen-Gut-Brain Axis in Depression



A complex network of interactions among the spleen, gut, and brain shows systemic effects on depression. Factors such as stress can lead to splenic dysfunction and GM dysregulation. Released inflammatory mediators, such as TNF-α, IL-1β, and IL-6, promote systemic inflammatory responses and activate microglia through the blood circulation and blood-brain barrier, leading to decreased BDNF levels and the onset of chronic neuroinflammation. The persistent inflammatory state further activates microglia and impacts the functions of both the spleen and gut, forming a vicious circle that ultimately leads to neuronal dysfunction and depressive symptoms. The VN plays an important role in the immune connections of the spleen-gut-brain axis.

Figure 5. Interactions among the spleen, gut, and brain in depression

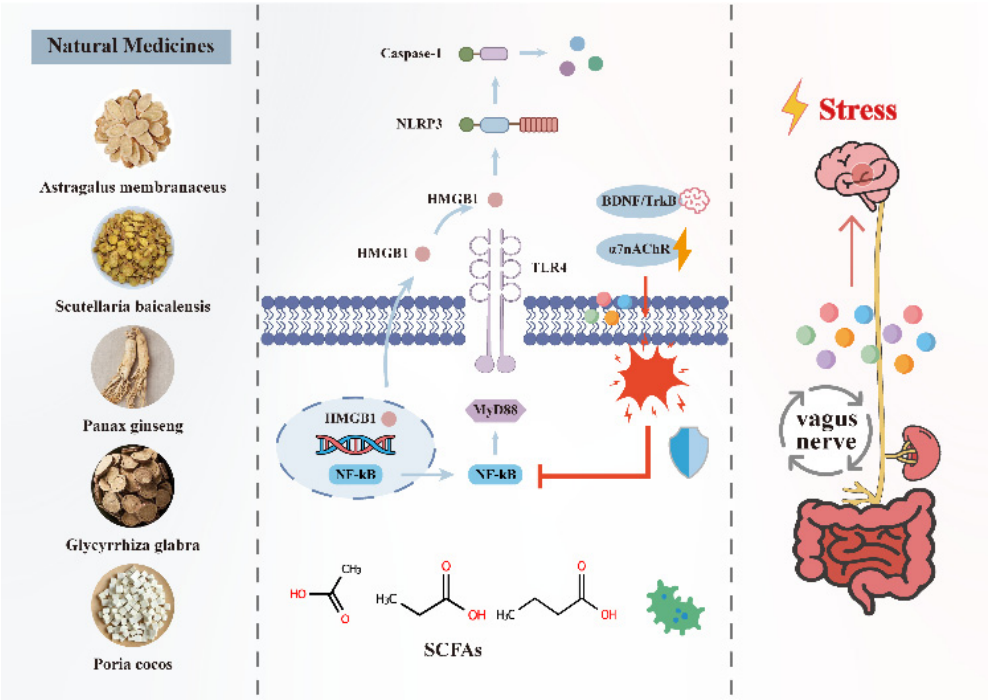
Based on these analyses, the spleen, gut, and brain may collaboratively contribute to the development of depression. The spleen-gut-brain axis has shown significant therapeutic potential in the research of depression. Two recent studies investigated the effects of splenic nerve denervation (SND) on depression-like behaviors, brain inflammatory responses, and gut microbial composition in Chrna7 knockout and lipopolysaccharide (LPS)-treated mice, revealing the role of the splenic nerve in inflammation-related depression through the spleen-gut-brain axis[68, 69]. The VN can synergize with splenic nerves to modulate the immune response in the spleen and gut, exerting an anti-inflammatory effect via the HPA axis, which in turn influences the depressive state. Vagus nerve stimulation (VNS) is also approved as a treatment for depression and is being increasingly studied. Additionally, it has also been shown that the VN is involved in mediating the spleen-gut communication mechanism that plays a key role in the reduction of systemic inflammation and enhancing the antidepressant effects of esketamine. In recent studies, arketamine, which has stronger efficacy and longer-lasting antidepressant effects compared to esketamine, has also been found to exert its antidepressant effects possibly through modulation of both the spleen-brain axis and the microbiota-gut-brain axis (Figure 5).

(3) Natural Medicines for Depression that Target the Spleen and Gut

Herbal medicines, with multi-component and multi-target characteristics, show promise in addressing monoamine-based drug resistance and neuroinflammation[70]. Emerging evidence demonstrates that botanical agents facilitate immune-neural-microbiota crosstalk through the spleen-gut-brain axis. This section summarizes key natural compounds targeting the spleen and gut for antidepressant effects[71, 72]. (Figure 6, Table 1).

In addition, traditional Chinese medicine prescriptions are also a main form of Traditional Chinese Medicine (TCM) for depression. In TCM, depression is defined as a symptom of liver depression and spleen deficiency. The Xingpijieyu formula improved the immune response, neuroinflammation, and astrocyte activation related to depression by influencing the GM[73]. The ZiBuPiYin recipe also positively impacted the immune function of the spleen and diabetes-related depressive-like behavior by regulating GM homeostasis[74]. Liu et al. revealed potential crosstalk genes and related

pathways between the treatment of depression and gastrointestinal disorders through their study of Guipi Tang. The active ingredients in Guipi Tang may be related to the immunomodulatory function of the spleen and treat both disorders by modulating targets related to inflammatory response and oxidative stress, such as EGF, PPARG, IL10, and CRP [75].



Key natural compounds exert antidepressant effects by targeting critical pathways, including NLRP3 inflammasome suppression, BDNF/TrkB signaling activation, and TLR4/NF-κB inhibition. These actions collectively improve splenic immunomodulation, gut barrier integrity, and neuroplasticity, ultimately alleviating depressive symptoms. Arrows indicate activation (→) or inhibition (⊣). Abbreviations: SCFAs, short-chain fatty acids; α7nAChR, alpha7 nicotinic acetylcholine receptor.

Figure 6. Multi-target mechanisms of natural medicines in modulating the spleen-gut-brain axis.

Table 1. Key natural compounds that target the spleen-gut-brain axis for antidepressant effects

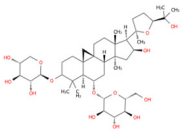
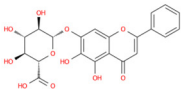
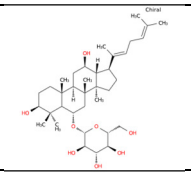
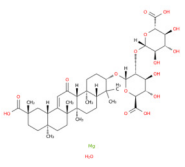
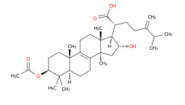
Natural products	Bioactive compound	Chemical structure	Model establishment	Mechanism	Ref.
Astragalus membranaceus	Astragaloside IV		SD rats; CUMS model; SPT, FST, OFT	Improve dysfunctions of microbiota, imbalance of T immune, and the abnormality of fecal metabolome	[71, 76, 77]
Scutellaria	Baicalin		ICR mice; CUMS model; SPT, OFT, TST, FST	inhibit HMGB1/TLR4/NF-κB pathways	[78-80]
Panax Ginseng	Ginsenoside Rh4		C57BL/6J mice; CUMS model; OFT, TST, FST	inhibit NLRP3/caspase-1/IL-1β signaling pathway to alleviate neuroinflammation	[81-83]
Glycyrrhiza glabra	Magnesium Isoglycyrrhizinate		ICR mice; LPS model; TST, FST, OFT	mediated by JAK/STAT/NF-κB signaling pathway	[84-86]
Poria cocos(Schw.)Wolf(PCW)	PCW Polysaccharides		Kunming mice; CUMS model; TST, FST	neuroprotective and immunomodulation	[72, 87, 88]

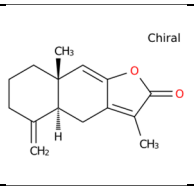
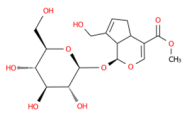
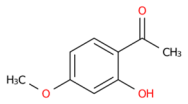
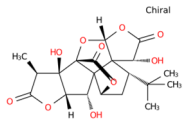
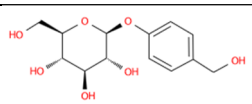
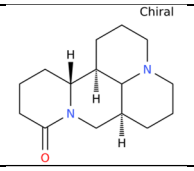
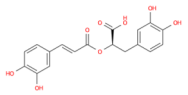
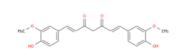
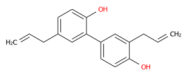
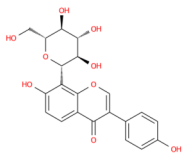
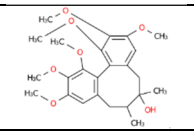
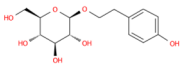
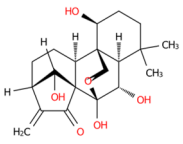
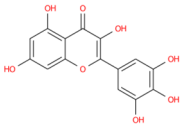
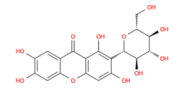
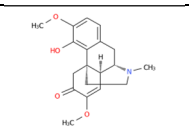
Table 1 (continued)					
Rhizoma Atractylodis	Atractylenolide I		C57BL/6J mice; CUMS model; EPM, OFT, FST, TST	Suppress the NLRP3-mediated A1 differentiation of astrocytes.	[89-91]
Gardenia jasminoides Ellis	Geniposide		SD rats; CUMS model; SPT, OFT, FST	Regulate the HPA axis, which is partly due to the recovery of the impaired GRα negative feedback function in hypothalamus	[92-94]
Paeonia suffruticosa Andrews	Paeonol		ICR mice; LPS model; OFT, FST, TST	through the BDNF/TrkB/NF-κB pathway	[95-97]
Ginkgo biloba	Ginkgolide B		C57BL/6J mice; myocardial infarction model; OFT, SPT,	increase IL-1β via STAT3 pathway.	[98-100]
Gastrodia elata Bl.	Gastrodin		C57BL/6J mice; LPS model; SPT, OFT, EPM, FST	promote an Arg-1^{+} microglial phenotype, which buffers the harmful effects of LPS-induced neuroinflammation via Nrf2.	[101-103]
Sophora Flavescens	Matrine		ICR mice; CUMS model; SPT, FST, OFT, NSFT	modulating the microbiota–gut–brain axis.	[104-106]
Rosmarinus officinalis	Rosmarinic acid		C57BL/6J mice; chronic corticosterone injection depression model; ST, TST, FST, SPT, NSFT	BDNF/TrkB/PI3K signaling axis regulate GR nuclear translocation	[107-109]
curcuma longa	Prophylactic		Wistar rats; LPS model; SPT, FST, OPT	miR-146a-5p/ERK signaling pathway within the hippocampal CA1 region.	[110-112]
Magnolia	Honokiol		SD rats; CUMS model; OFT, SPT	activation of the HIF-1α-VEGF signaling pathway, VEGFR-2-mediated PI3K/AKT/mTOR signaling pathway, and increased expression of the synaptic plasticity-related proteins, SYN 1 and PSD 95	[113-115]
Pueraria lobata	Puerarin		SD rats; CUMS model; OFT, SPT, FST	regulating intestinal flora imbalance, inhibiting inflammatory responses in the hippocampus, serum, and colon, and down-regulating TLR4/NF-κB pathway.	[116-118]
Schisandra chinensis	Schisandrin		C57BL/6 mice; LPS model; OFT, TST, FST	recover the gut microbial disorder of depressive mice through suppressing the expression of TLR4/NF-κB signaling pathway.	[119, 120]

Table 1 (continued)					
Rhodiola rosea	Salidroside		C57BL/6 mice; CUMS model; SPT, FST, OFT, MWM, SLAT	interfering microglia-mediated neuroinflammation	[121, 122]
Rabdosia Rubescens	Oridonin		SD rats; CUMS model; SPT, FST	inhibit neuroinflammation and autophagy impairment by blocking the interaction between NLRP3 and NEK7	[123, 124]
Myricaceae	Myricetin		C57BL/6 mice; CUMS model; FST, TST, OFT,	mediate BDNF levels and anti-oxidative stress in the hippocampus.	[125-127]
Mangifera indica L	Mangiferin		BALA/c mice; hormone-simulated pregnancy combined with ovariectomy model; NSFT, FST, TST	inhibit microglial activation and neuroinflammation.	[128-130]
Sinomenium acutum.	Sinomenine		mice; CSDS model; FST, TST	promote the hippocampal BDNF signaling pathway.	[131-133]

((LPS, lipopolysaccharide; CUMS, chronic unpredictable mild stress; CSDS, chronic social defeat stress; SPT, Sucrose Preference Test; FST, Forced Swimming *Test; OFT, Open Field Test; TST, Tail Suspension Test; EPM, Elevated Plus Maze Test; T-maze, T-maze test; MWM, Morris Water Maze Test; SLAT, Spontaneous Locomotor Activity Test; NSFT, Novelty-suppressed feeding test))*

6. Conclusion

In summary, depression is closely linked to neuroinflammation and the immune connections within the spleen-gut-brain axis. The spleen and gut are involved in immune signaling transmission through cytokine secretion and chemical mediators, exchanging information with the brain through the VN, thereby playing a significant role in the pathological process of depression. This study enhances our understanding of depression and provides new perspectives and therapeutic approaches for the treatment of depression. This work paves the way for a new age of precision psychiatry by integrating immunology, microbiology, and neuropharmacology, proposing that depression should be viewed not merely as a chemical imbalance, but rather as a failure of the systemic network.

Future studies need to further explore the mechanisms of the spleen-gut-brain axis in depression, especially the complex interaction between the spleen and GM. More clinical trials are needed to evaluate the efficacy and safety of immunomodulatory drugs and natural products as treatments for depression, determining optimal therapeutic targets, dosages, and durations.

Particularly, the combination of natural medicines has shown great potential for treating depression by regulating systemic immunity through the spleen-gut-brain axis. Future research could explore synergistic effects using the polypharmacological approach to develop more effective combination therapies. Additionally, we need to investigate how to regulate the spleen-gut-brain axis through lifestyle changes, such as diet and exercise. Meanwhile, future studies should also focus on cross-integration of these directions, such as combining genomic technology to assess patients' genetic predisposition, ultimately achieving precise treatment of depression.

Finally, in-depth characterization of the gut-immune-brain axis also has the potential to serve as a target for treating other neurological comorbidities of IBD, such as PD. We look forward to revealing the mysteries of these areas through sustained scientific endeavors, thereby shedding new light on the treatment of related disorders and ultimately achieving a wider societal impact.

References

[1] MARX W, PENNINX B W J H, SOLMI M, et al. Major depressive disorder [J]. Nature Reviews Disease Primers, 2023, 9(1): 44.

[2] DISEASES G B D, INJURIES C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019 [J]. Lancet, 2020, 396(10258): 1204-22.

[3] KATO M, HORI H, INOUE T, et al. Discontinuation of antidepressants after remission with antidepressant medication in major depressive disorder: a systematic review and meta-analysis [J]. Molecular Psychiatry, 2021, 26(1): 118-33.

[4] CUI L, LI S, WANG S, et al. Major depressive disorder: hypothesis, mechanism, prevention and treatment [J]. Signal Transduction and Targeted Therapy, 2024, 9(1): 30.

[5] ZHANG J, CHANG L, PU Y, et al. Abnormal expression of colony stimulating factor 1 receptor (CSF1R) and transcription factor PU.1 (SPI1) in the spleen from patients with major

psychiatric disorders: A role of brain–spleen axis [J]. Journal of Affective Disorders, 2020, 272: 110-5.

[6] NJENGA C, RAMANUJ P P, DE MAGALHãES F J C, et al. New and emerging treatments for major depressive disorder [J]. BMJ, 2024, 386: e073823.

[7] ZHANG W, XIAO D, MAO Q, et al. Role of neuroinflammation in neurodegeneration development [J]. Signal Transduction and Targeted Therapy, 2023, 8(1): 267.

[8] MILLER A H, RAISON C L. The role of inflammation in depression: from evolutionary imperative to modern treatment target [J]. Nature Reviews Immunology, 2016, 16(1): 22-34.

[9] VALLES-COLOMER M, FALONY G, DARZI Y, et al. The neuroactive potential of the human gut microbiota in quality of life and depression [J]. Nature Microbiology, 2019, 4(4): 623-32.

[10] GINHOUX F, GAREL S. The mysterious origins of microglia [J]. Nature Neuroscience, 2018, 21(7): 897-9.

[11] COLONNA M, BUTOVSKY O. Microglia Function in the Central Nervous System During Health and Neurodegeneration [J]. Annual Review of Immunology, 2017, 35(Volume 35, 2017): 441-68.

[12] HICKMAN S, IZZY S, SEN P, et al. Microglia in neurodegeneration [J]. Nature Neuroscience, 2018, 21(10): 1359-69.

[13] VALENTE L A, BEGG L R, FILIANO A J. Updating Neuroimmune Targets in Central Nervous System Dysfunction [J]. Trends in Pharmacological Sciences, 2019, 40(7): 482-94.

[14] KWON H S, KOH S-H. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes [J]. Translational Neurodegeneration, 2020, 9(1): 42.

[15] LIDDELOW S A, GUTTENPLAN K A, CLARKE L E, et al. Neurotoxic reactive astrocytes are induced by activated microglia [J]. Nature, 2017, 541(7638): 481-7.

[16] ROTHHAMMER V, BORUCKI D M, TJON E C, et al. Microglial control of astrocytes in response to microbial metabolites [J]. Nature, 2018, 557(7707): 724-8.

[17] XIA C-Y, GUO Y-X, LIAN W-W, et al. The NLRP3 inflammasome in depression: Potential mechanisms and therapies [J]. Pharmacological Research, 2023, 187: 106625.

[18] SURNAR B, SHAH A S, PARK M, et al. Brain-Accumulating Nanoparticles for Assisting Astrocytes to Reduce Human Immunodeficiency Virus and Drug Abuse-Induced Neuroinflammation and Oxidative Stress [J]. ACS Nano, 2021, 15(10): 15741-53.

[19] DOWLATI Y, HERRMANN N, SWARDFAGER W, et al. A Meta-Analysis of Cytokines in Major Depression [J]. Biological Psychiatry, 2010, 67(5): 446-57.

[20] RéUS G Z, MANOSSO L M, QUEVEDO J, et al. Major depressive disorder as a neuro-immune disorder: Origin, mechanisms, and therapeutic opportunities [J]. Neuroscience & Biobehavioral Reviews, 2023, 155: 105425.

[21] BAI S, GUO W, FENG Y, et al. Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomised controlled trials [J]. Journal of Neurology, Neurosurgery & Psychiatry, 2020, 91(1): 21.

[22] HUSAIN M I, CULLEN C, UMER M, et al. Minocycline as adjunctive treatment for treatment-resistant depression: study protocol for a double blind, placebo-controlled, randomized trial (MINDEP2) [J]. BMC Psychiatry, 2020, 20(1): 173.

[23] XU K, WANG M, WANG H, et al. HMGB1/STAT3/p65 axis drives microglial activation and autophagy exert a crucial role in chronic Stress-Induced major depressive disorder [J]. Journal of Advanced Research, 2024, 59: 79-96.

[24] LENG L, ZHUANG K, LIU Z, et al. Menin Deficiency Leads to Depressive-like Behaviors in Mice by Modulating Astrocyte-Mediated Neuroinflammation [J]. Neuron, 2018, 100(3): 551-63.e7.

[25] NAGY C, MAITRA M, TANTI A, et al. Single-nucleus transcriptomics of the prefrontal cortex in major depressive disorder implicates oligodendrocyte precursor cells and excitatory neurons [J]. Nature Neuroscience, 2020, 23(6): 771-81.

[26] MEBIUS R E, KRAAL G. Structure and function of the spleen [J]. Nature Reviews Immunology, 2005, 5(8): 606-16.

[27] LEWIS S M, WILLIAMS A, EISENBARTH S C. Structure and function of the immune system in the spleen [J]. Science Immunology, 2019, 4(33): eaau6085.

[28] ANDERSSON U, TRACEY K J. Reflex Principles of Immunological Homeostasis [J]. Annual Review of Immunology, 2012, 30(Volume 30, 2012): 313-35.

[29] ZHANG X, LEI B, YUAN Y, et al. Brain control of humoral immune responses amenable to behavioural modulation [J]. Nature, 2020, 581(7807): 204-8.

[30] HUSTON J M, OCHANI M, ROSAS-BALLINA M, et al. Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis [J]. Journal of Experimental Medicine, 2006, 203(7): 1623-8.

[31] PELLISSIER S, DANTZER C, MONDILLON L, et al. Tu2104 Uncoupling Between the Vagal Tone and HPA Axis in Inflammatory Bowel Disease and Irritable Bowel Syndrome: Relation to Stress and Inflammation [J]. Gastroenterology, 2013, 144(5, Supplement 1): S-930.

[32] ZHAN H, HUANG F, YAN F, et al. Alterations in splenic function and gene expression in mice with depressive-like behavior induced by exposure to corticosterone [J]. Int J Mol Med, 2017, 39(2): 327-36.

[33] ZHANG J, MA L, CHANG L, et al. A key role of the subdiaphragmatic vagus nerve in the depression-like phenotype and abnormal composition of gut microbiota in mice after lipopolysaccharide administration [J]. Translational Psychiatry, 2020, 10(1): 186.

[34] FINNELL J E, LOMBARD C M, MELSON M N, et al. The protective effects of resveratrol on social stress-induced cytokine release and depressive-like behavior [J]. Brain, Behavior, and Immunity, 2017, 59: 147-57.

[35] CHANG L, WEI Y, QU Y, et al. Role of oxidative phosphorylation in the antidepressant effects of arketamine via the vagus nerve-dependent spleen-brain axis [J]. Neurobiology of Disease, 2024, 199: 106573.

[36] MA L, WANG L, QU Y, et al. A role of splenic heme biosynthesis pathway in the persistent prophylactic actions of arketamine in lipopolysaccharide-treated mice [J]. Translational Psychiatry, 2023, 13(1): 269.

[37] CHEN W, CHEN Y, CHENG W, et al. Acupuncture exerts preventive effects in rats of chronic unpredictable mild stress: The involvement of inflammation in amygdala and brain-spleen axis [J]. Biochemical and Biophysical Research Communications, 2023, 646: 86-95.

[38] DU TOIT A. The gut microbiome and mental health [J]. Nature Reviews Microbiology, 2019, 17(4): 196-.

[39] DALILE B, VAN OUDENHOVE L, VERVLIET B, et al. The role of short-chain fatty acids in microbiota–gut–brain communication [J]. Nature Reviews Gastroenterology & Hepatology, 2019, 16(8): 461-78.

[40] DOROSZKIEWICZ J, GROBLEWSKA M, MROCZKO B. The Role of Gut Microbiota and Gut–Brain Interplay in Selected Diseases of the Central Nervous System [J]. International Journal of Molecular Sciences, 2021, 22(18): 10028.

[41] CARLONI S, RESCIGNO M. The gut-brain vascular axis in neuroinflammation [J]. Seminars in Immunology, 2023, 69: 101802.

[42] ADEBISI B T. Gut Microorganisms, Neuroinflammation and Behavioral Changes [J]. European Psychiatry, 2024, 67(S1): S625-S6.

[43] EICHER T P, MOHAJERI M H. Overlapping Mechanisms of Action of Brain-Active Bacteria and Bacterial Metabolites in the Pathogenesis of Common Brain Diseases [J]. Nutrients, 2022, 14(13): 2661.

[44] WESTFALL S, CARACCI F, ESTILL M, et al. Chronic Stress-Induced Depression and Anxiety Priming Modulated by Gut-Brain-Axis Immunity [J]. Frontiers in Immunology, 2021, 12.

[45] CHANG L, WANG C, PENG J, et al. Rattan Pepper Polysaccharide Regulates DSS-Induced Intestinal Inflammation and Depressive Behavior through Microbiota–Gut–Brain Axis [J]. Journal of Agricultural and Food Chemistry, 2024, 72(1): 437-48.

[46] LIU R. The Microbiome as a Novel Paradigm in Studying Stress and Mental Health [J]. American Psychologist, 2017, 72.

[47] FRAGA A, ESTEVES-SOUSA D, FACUCHO-OLIVEIRA J, et al. Mechanisms linking gut microbiota to depression [J]. European Psychiatry, 2021, 64(S1): S741-S.

[48] RIEDER R, WISNIEWSKI P J, ALDERMAN B L, et al. Microbes and mental health: A review [J]. Brain, Behavior, and Immunity, 2017, 66: 9-17.

[49] JUNZHE C, HONGKUN H, YUMENG J, et al. Gut microbiota-derived short-chain fatty acids and depression: deep insight into biological mechanisms and potential applications [J]. General Psychiatry, 2024, 37(1): e101374.

[50] LIU P, LIU Z, WANG J, et al. Immunoregulatory role of the gut microbiota in inflammatory depression [J]. Nature Communications, 2024, 15(1): 3003.

[51] CROSS C, DAVIES M, BATEMAN E, et al. Fibre-rich diet attenuates chemotherapy-related neuroinflammation in mice [J]. Brain, Behavior, and Immunity, 2024, 115: 13-25.

[52] RöSSLER W. Nutrition, sleep, physical exercise: Impact on mental health [J]. European Psychiatry, 2016, 33: S12.

[53] BI C, GUO S, HU S, et al. The microbiota–gut–brain axis and its modulation in the therapy of depression: Comparison of efficacy of conventional drugs and traditional Chinese medicine approaches [J]. Pharmacological Research, 2022, 183: 106372.

[54] ZHONG D, JIN K, WANG R, et al. Microalgae-Based Hydrogel for Inflammatory Bowel Disease and Its Associated Anxiety and Depression [J]. Advanced Materials, 2024, 36(24): 2312275.

[55] ZHAO B, WU J, LI J, et al. Lycopene Alleviates DSS-Induced Colitis and Behavioral Disorders via Mediating Microbes-Gut–Brain Axis Balance [J]. Journal of Agricultural and Food Chemistry, 2020, 68(13): 3963-75.

[56] LEE K-I, KIM M-S, YUK H J, et al. Alleviating depressive-like behavior in DSS-induced colitis mice: Exploring naringin and poncirin from Poncirus trifoliata extracts [J]. Biomedicine & Pharmacotherapy, 2024, 175: 116770.

[57] ZHAO H, CHEN X, ZHANG L, et al. Ingestion of Lacticaseibacillus rhamnosus Fmb14 prevents depression-like behavior and brain neural activity via the microbiota–gut–brain axis in colitis mice [J]. Food & Function, 2023, 14(4): 1909-28.

[58] DE SANTA F, STRIMPAKOS G, MARCHETTI N, et al. Effect of a multi-strain probiotic mixture consumption on anxiety and depression symptoms induced in adult mice by postnatal maternal separation [J]. Microbiome, 2024, 12(1): 29.

[59] MA J, WANG R, CHEN Y, et al. 5-HT attenuates chronic stress-induced cognitive impairment in mice through intestinal flora disruption [J]. Journal of Neuroinflammation, 2023, 20(1): 23.

[60] HUANG Y-Y, WU Y-P, JIA X-Z, et al. Lactiplantibacillus plantarum DMDL 9010 alleviates dextran sodium sulfate (DSS)-induced colitis and behavioral disorders by facilitating microbiota-gut-brain axis balance [J]. Food & Function, 2022, 13(1): 411-24.

[61] MAO Q, ZHANG H, ZHANG Z, et al. Co-decoction of Lilii bulbus and Radix Rehmannia Recens and its key bioactive ingredient verbascoside inhibit neuroinflammation and intestinal permeability associated with chronic stress-induced depression via the gut microbiota-brain axis [J]. Phytomedicine, 2024, 129: 155510.

[62] SHIN Y-J, LEE D-Y, KIM J Y, et al. Effect of fermented red ginseng on gut microbiota dysbiosis- or immobilization stress-induced anxiety, depression, and colitis in mice [J]. Journal of Ginseng Research, 2023, 47(2): 255-64.

[63] HAO W, GAN H, WANG L, et al. Polyphenols in edible herbal medicine: targeting gut-brain interactions in depression-associated neuroinflammation [J]. Critical Reviews in Food Science and Nutrition, 2022, 63: 12207-23.

[64] CARSETTI R, DI SABATINO A, ROSADO M M, et al. Lack of Gut Secretory Immunoglobulin A in Memory B-Cell Dysfunction-Associated Disorders: A Possible Gut-Spleen Axis [J]. Frontiers in Immunology, 2020, 10.

[65] BUCHMANN GODINHO D, DA SILVA FIORIN F, SCHNEIDER OLIVEIRA M, et al. The immunological influence of physical exercise on TBI-induced pathophysiology: Crosstalk between the spleen, gut, and brain [J]. Neuroscience & Biobehavioral Reviews, 2021, 130: 15-30.

[66] BOURHY L, MAZERAUD A, BOZZA F A, et al. Neuro-Inflammatory Response and Brain-Peripheral Crosstalk in Sepsis and Stroke [J]. Frontiers in Immunology, 2022, 13.

[67] FUNG T C, OLSON C A, HSIAO E Y. Interactions between the microbiota, immune and nervous systems in health and disease [J]. Nature Neuroscience, 2017, 20(2): 145-55.

[68] YANG Y, EGUCHI A, MORI C, et al. Splenic nerve denervation attenuates depression-like behaviors in Chrna7 knock-out mice via the spleen–gut–brain axis [J]. Journal of Affective Disorders, 2024, 362: 114-25.

[69] MA L, ZHANG J, FUJITA Y, et al. Effects of spleen nerve denervation on depression–like phenotype, systemic inflammation, and abnormal composition of gut microbiota in mice after administration of lipopolysaccharide: A role of brain–spleen axis [J]. Journal of Affective Disorders, 2022, 317: 156-65.

[70] MOK S W-F, WONG V K-W, LO H-H, et al. Natural products-based polypharmacological modulation of the peripheral immune system for the treatment of neuropsychiatric disorders [J]. Pharmacology & Therapeutics, 2020, 208: 107480.

[71] LIU X, WANG S, WU X, et al. Astragaloside IV Alleviates Depression in Rats by Modulating Intestinal Microbiota, T-Immune Balance, and Metabolome [J]. Journal of Agricultural and Food Chemistry, 2024, 72(1): 259-73.

[72] DUAN Y, HUANG J, SUN M, et al. Poria cocos polysaccharide improves intestinal barrier function and

maintains intestinal homeostasis in mice [J]. International Journal of Biological Macromolecules, 2023, 249: 125953.

[73] LI Y, YANG L, LI J, et al. Antidepression of Xingpijieyu formula targets gut microbiota derived from depressive disorder [J]. CNS Neuroscience & Therapeutics, 2023, 29(2): 669-81.

[74] GU C, ZHOU W, WANG W, et al. ZiBuPiYin recipe improves cognitive decline by regulating gut microbiota in Zucker diabetic fatty rats [J]. Oncotarget, 2017, 8(17).

[75] LIU M, FAN G, LIU H. Integrated bioinformatics and network pharmacology identifying the mechanisms and molecular targets of Guipi Decoction for treatment of comorbidity with depression and gastrointestinal disorders [J]. Metabolic Brain Disease, 2024, 39(1): 183-97.

[76] LI J-J, LI Y-L, CHU W, et al. Astragaloside IV alleviates cytarabine-induced intestinal mucositis by remodeling macrophage polarization through AKT signaling [J]. Phytomedicine, 2023, 109: 154605.

[77] ZHANG X, ZHANG F, LI Y, et al. Blockade of PI3K/AKT signaling pathway by Astragaloside IV attenuates ulcerative colitis via improving the intestinal epithelial barrier [J]. Journal of Translational Medicine, 2024, 22(1): 406.

[78] WANG X, XIE L, LONG J, et al. Therapeutic effect of baicalin on inflammatory bowel disease: A review [J]. Journal of Ethnopharmacology, 2022, 283: 114749.

[79] ZHANG S, LV H, ZHONG R, et al. Baicalin promotes appetite by regulating gut microbiome and immunity? [J]. Journal of Functional Foods, 2023, 105: 105557.

[80] LIU L, DONG Y, SHAN X, et al. Anti-Depressive Effectiveness of Baicalin In Vitro and In Vivo [J]. Molecules, 2019, 24(2): 326.

[81] ZHAO L, ZHANG T, ZHANG K. Pharmacological effects of ginseng and ginsenosides on intestinal inflammation and the immune system [J]. Frontiers in Immunology, 2024, 15.

[82] NIU Z, LIU Y, SHEN R, et al. Ginsenosides from Panax ginseng as potential therapeutic candidates for the treatment of inflammatory bowel disease [J]. Phytomedicine, 2024, 127: 155474.

[83] SHAO J, MA X, QU L, et al. Ginsenoside Rh4 remodels the periphery microenvironment by targeting the brain-gut axis to alleviate depression-like behaviors [J]. Food Chemistry, 2023, 404: 134639.

[84] CUI J, LI Y, JIAO C, et al. Improvement of magnesium isoglycyrrhizinate on DSS-induced acute and chronic colitis [J]. International Immunopharmacology, 2021, 90: 107194.

[85] XIA Y, SHI H, QIAN C, et al. Modulation of Gut Microbiota by Magnesium Isoglycyrrhizinate Mediates Enhancement of Intestinal Barrier Function and Amelioration of Methotrexate-Induced Liver Injury [J]. Frontiers in Immunology, 2022, 13.

[86] JIANG W, CHEN Q, LI P, et al. Magnesium Isoglycyrrhizinate attenuates lipopolysaccharide-induced depressive-like behavior in mice [J]. Biomedicine & Pharmacotherapy, 2017, 86: 177-84.

[87] XU H, WANG S, JIANG Y, et al. Poria cocos Polysaccharide Ameliorated Antibiotic-Associated Diarrhea in Mice via Regulating the Homeostasis of the Gut Microbiota and Intestinal Mucosal Barrier [J]. International Journal of Molecular Sciences, 2023, 24(2): 1423.

[88] ZHANG W, CHEN L, LI P, et al. Antidepressant and immunosuppressive activities of two polysaccharides from Poria cocos (Schw.) Wolf [J]. International Journal of Biological Macromolecules, 2018, 120: 1696-704.

[89] SONG H-P, HOU X-Q, LI R-Y, et al. Atractylenolide I stimulates intestinal epithelial repair through polyamine-mediated Ca2+ signaling pathway [J]. Phytomedicine, 2017, 28: 27-35.

[90] XU H, VAN DER JEUGHT K, ZHOU Z, et al. Atractylenolide I enhances responsiveness to immune checkpoint blockade therapy by activating tumor antigen presentation [J]. The Journal of Clinical Investigation, 2021, 131(10).

[91] ZHAI L, SHENG Y, WANG J, et al. Atractylenolide I Suppresses A1 Astrocyte Activation to Improve Depression in Mice [J]. Molecular Neurobiology, 2024, 61(9): 7037-45.

[92] PU Z, LIU Y, LI C, et al. Using Network Pharmacology for Systematic Understanding of Geniposide in Ameliorating Inflammatory Responses in Colitis Through Suppression of NLRP3 Inflammasome in Macrophage by AMPK/Sirt1 Dependent Signaling [J]. The American Journal of Chinese Medicine, 2020, 48(07): 1693-713.

[93] YU Y, BIAN Y, SHI J-X, et al. Geniposide promotes splenic Treg differentiation to alleviate colonic inflammation and intestinal barrier injury in ulcerative colitis mice [J]. Bioengineered, 2022, 13(6): 14616-31.

[94] CAI L, LI R, TANG W-J, et al. Antidepressant-like effect of geniposide on chronic unpredictable mild stress-induced depressive rats by regulating the hypothalamus–pituitary–adrenal axis [J]. European Neuropsychopharmacology, 2015, 25(8): 1332-41.

[95] ZHAO M, XIE X, XU B, et al. Paeonol alleviates ulcerative colitis in mice by increasing short-chain fatty acids derived from Clostridium butyricum [J]. Phytomedicine, 2023, 120: 155056.

[96] CHEN B, NING M, YANG G. Effect of Paeonol on Antioxidant and Immune Regulatory Activity in Hepatocellular Carcinoma Rats [J]. Molecules, 2012, 17(4): 4672-83.

[97] TAO W, WANG H, SU Q, et al. Paeonol attenuates lipopolysaccharide-induced depressive-like behavior in mice [J]. Psychiatry Research, 2016, 238: 116-21.

[98] LV Z, SHAN X, TU Q, et al. Ginkgolide B treatment regulated intestinal flora to improve high-fat diet induced atherosclerosis in ApoE−/− mice [J]. Biomedicine & Pharmacotherapy, 2021, 134: 111100.

[99] LI C, LIU K, LIU S, et al. Role of Ginkgolides in the Inflammatory Immune Response of Neurological Diseases: A Review of Current Literatures [J]. Frontiers in Systems Neuroscience, 2020, 14.

[100] GE Y, XU W, ZHANG L, et al. Ginkgolide B attenuates myocardial infarction-induced depression-like behaviors via repressing IL-1β in central nervous system [J]. International Immunopharmacology, 2020, 85: 106652.

[101] LI J, JIA J, TENG Y, et al. Gastrodin Alleviates DSS-Induced Colitis in Mice through Strengthening Intestinal Barrier and Modulating Gut Microbiota [J]. Foods, 2024, 13(15): 2460.

[102] ZHOU L, HU Z, LIU F, et al. Electrospun Self-Pumping dressing with gastrodin for immunomodulation and rapid healing of diabetic wounds [J]. Chemical Engineering Journal, 2024, 495: 153424.

[103] ZHANG J, LI L, LIU Q, et al. Gastrodin programs an Arg-1+ microglial phenotype in hippocampus to ameliorate depression- and anxiety-like behaviors via the Nrf2 pathway in mice [J]. Phytomedicine, 2023, 113: 154725.

[104] NIU Y, DONG Q, LI R. Matrine regulates Th1/Th2 cytokine responses in rheumatoid arthritis by attenuating the NF-κB signaling [J]. Cell Biology International, 2017, 41(6): 611-21.

[105] NI L, JING S, ZHU L, et al. The Immune Change of the Lung and Bowel in an Ulcerative Colitis Rat Model and the

Protective Effect of Sodium Houttuyfonate Combined With Matrine [J]. Frontiers in Immunology, 2022, 13.

[106] ZHANG M, LI A, YANG Q, et al. Matrine alleviates depressive-like behaviors via modulating microbiota–gut–brain axis in CUMS-induced mice [J]. Journal of Translational Medicine, 2023, 21(1): 145.

[107] CHUNG C H, JUNG W, KEUM H, et al. Nanoparticles Derived from the Natural Antioxidant Rosmarinic Acid Ameliorate Acute Inflammatory Bowel Disease [J]. ACS Nano, 2020, 14(6): 6887-96.

[108] WANG Y-L, NI W. Rosmarinic acid improves cyclophosphamide-induced immunosuppression in mice by immunomodulatory and antioxidant effects [J]. Food Bioscience, 2023, 56: 103152.

[109] ZENG J, XIE Z, CHEN L, et al. Rosmarinic acid alleviate CORT-induced depressive-like behavior by promoting neurogenesis and regulating BDNF/TrkB/PI3K signaling axis [J]. Biomedicine & Pharmacotherapy, 2024, 170: 115994.

[110] DOU Y, LUO J, WU X, et al. Curcumin attenuates collagen-induced inflammatory response through the "gut-brain axis" [J]. Journal of Neuroinflammation, 2018, 15(1): 6.

[111] RASHID K, CHOWDHURY S, GHOSH S, et al. Curcumin attenuates oxidative stress induced NFκB mediated inflammation and endoplasmic reticulum dependent apoptosis of splenocytes in diabetes [J]. Biochemical Pharmacology, 2017, 143: 140-55.

[112] FAN C, LI Y, LAN T, et al. Prophylactic treatment of curcumin in a rat model of depression by attenuating hippocampal synaptic loss [J]. Food & Function, 2021, 12(22): 11202-13.

[113] MUNROE M E, ARBISER J L, BISHOP G A. Honokiol, a Natural Plant Product, Inhibits Inflammatory Signals and Alleviates Inflammatory Arthritis1 [J]. The Journal of Immunology, 2007, 179(2): 753-63.

[114] NIU L, WANG S, XU Y, et al. Honokiol targeting ankyrin repeat domain of TRPV4 ameliorates endothelial permeability in mice inflammatory bowel disease induced by DSS [J]. Journal of Ethnopharmacology, 2024, 325: 117825.

[115] FAN X-X, SUN W-Y, LI Y, et al. Honokiol improves depression-like behaviors in rats by HIF-1α- VEGF signaling pathway activation [J]. Frontiers in Pharmacology, 2022, 13.

[116] JEON Y-D, LEE J-H, LEE Y-M, et al. Puerarin inhibits inflammation and oxidative stress in dextran sulfate sodium-induced colitis mice model [J]. Biomedicine & Pharmacotherapy, 2020, 124: 109847.

[117] CHANG Y, GUO A, JING Y-Y, et al. Immunomodulatory activity of puerarin in RAW264.7 macrophages and cyclophosphamide-induced immunosuppression mice [J]. Immunopharmacology and Immunotoxicology, 2021, 43: 223-9.

[118] SONG X, WANG W, DING S, et al. Exploring the potential antidepressant mechanisms of puerarin: Anti-inflammatory response via the gut-brain axis [J]. Journal of Affective Disorders, 2022, 310: 459-71.

[119] CHEN Z, GUO M, SONG G, et al. Schisandrin B inhibits Th1/Th17 differentiation and promotes regulatory T cell expansion in mouse lymphocytes [J]. International Immunopharmacology, 2016, 35: 257-64.

[120] SUN Y, YAN T, GONG G, et al. Antidepressant-like effects of Schisandrin on lipopolysaccharide-induced mice : Gut microbiota, short chain fatty acid and TLR4/NF-κB signaling pathway [J]. International Immunopharmacology, 2020, 89: 107029.

[121] LIU X, ZHOU M, DAI Z, et al. Salidroside alleviates ulcerative colitis via inhibiting macrophage pyroptosis and repairing the dysbacteriosis-associated Th17/Treg imbalance [J]. Phytotherapy Research, 2023, 37(2): 367-82.

[122] FAN Y, BI Y, CHEN H. Salidroside Improves Chronic Stress Induced Depressive Symptoms Through Microglial Activation Suppression [J]. Frontiers in Pharmacology, 2021, 12.

[123] HU A P, DU J M, LI J Y, et al. Oridonin promotes CD4+/CD25+ Treg differentiation, modulates Th1/Th2 balance and induces HO-1 in rat splenic lymphocytes [J]. Inflammation Research, 2008, 57(4): 163-70.

[124] LIANG L, WANG H, HU Y, et al. Oridonin relieves depressive-like behaviors by inhibiting neuroinflammation and autophagy impairment in rats subjected to chronic unpredictable mild stress [J]. Phytotherapy Research, 2022, 36(8): 3335-51.

[125] SUN Y, LIAN M, LIN Y, et al. Role of p-MKK7 in myricetin-induced protection against intestinal ischemia/reperfusion injury [J]. Pharmacological Research, 2018, 129: 432-42.

[126] BERKöZ M, YALıN S, ÖZKAN-YıLMAZ F, et al. Protective effect of myricetin, apigenin, and hesperidin pretreatments on cyclophosphamide-induced immunosuppression [J]. Immunopharmacol Immunotoxicol, 2021, 43(3): 353-69.

[127] MA Z, WANG G, CUI L, et al. Myricetin Attenuates Depressant-Like Behavior in Mice Subjected to Repeated Restraint Stress [J]. International Journal of Molecular Sciences, 2015, 16(12): 28377-85.

[128] DOU W, ZHANG J, REN G, et al. Mangiferin attenuates the symptoms of dextran sulfate sodium-induced colitis in mice via NF-κB and MAPK signaling inactivation [J]. International Immunopharmacology, 2014, 23(1): 170-8.

[129] LIM S-M, JEONG J-J, CHOI H S, et al. Mangiferin corrects the imbalance of Th17/Treg cells in mice with TNBS-induced colitis [J]. International Immunopharmacology, 2016, 34: 220-8.

[130] YAN M, BO X, ZHANG X, et al. Mangiferin Alleviates Postpartum Depression–Like Behaviors by Inhibiting MAPK Signaling in Microglia [J]. Frontiers in Pharmacology, 2022, 13.

[131] NIU Z, LI X, YANG X, et al. Protective effects of sinomenine against dextran sulfate sodium-induced ulcerative colitis in rats via alteration of HO-1/Nrf2 and inflammatory pathway [J]. Inflammopharmacology, 2024, 32(3): 2007-22.

[132] JUN W, PEI-GEN X, SHI-YING L, et al. The inhibitory effect of Sinomenine on immunological function in mice [J]. Phytotherapy Research, 1992, 6(3): 117-20.

[133] LI X, LIU C, JIANG B, et al. The antidepressant-like effects of sinomenine in mice: a behavioral and neurobiological characterization [J]. Behavioural Pharmacology, 2018, 29(4): 306-15.