Review

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Research Progress on Mechanisms of Modulating Gut Microbiota to Improve Symptoms of Major Depressive Disorder

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Major depressive disorder (MDD) is a clinical condition that significantly impacts patients' physical and mental well-being, quality of life, and social functioning. The pathogenesis of MDD remains unclear, but accumulating evidence suggests a close relationship between gut microbiota and the occurrence and progression of MDD. Gut microbiota refers to the microbial community in the human intestine, which engages in bidirectional communication with the host via the "gut-brain axis" and plays a pivotal role in influencing the host's metabolism, immune system, endocrine system, and nervous system. Modulating gut microbiota entails restoring the balance and function of the intestinal flora through methods such as probiotic intake, fecal transplantation, and dietary intervention. Such modulation has been shown to effectively alleviate depressive symptoms in the host. This review synthesizes recent advancements in research on gut microbiota modulation for ameliorating depressive symptoms and can serve as a foundation for further exploration of the gut microbiota's role in MDD and its potential therapeutic benefits.

Keywords: gut microbiota; major depressive disorder

Overview of Major Depressive Disorder (MDD)

Major depressive disorder (MDD) is a clinical condition characterized by a range of symptoms including persistent low mood, diminished interest, lack of pleasure, and fatigue, all indicative of core emotional disturbances. In many cases, individuals may also experience feelings of self-blame and guilt and even exhibit suicidal tendencies [1]. According to the latest statistics from the World Health Organization (WHO), there are at least 320 million MDD patients globally [2]. Alarmingly, each year, MDD contributes to at least 700,000 deaths by suicide [3]. Furthermore, MDD stands as the leading cause of disability worldwide [2].

MDD significantly compromises mental health and diminishes the quality of life for affected patients. Globally, the annual incidence of MDD is approximately 3.1%, with rates ranging from 3% to 5% in China [4]. With shifts in work and lifestyle, there has been a steady increase in the occurrence of MDD [5], a trend that has been further exacerbated by the recent coronavirus disease 2019 (COVID-19) pandemic [6].

Despite the availability of various antidepressant medications with proven efficacy, managing MDD in the clinical settings remains challenging. Commonly used antidepressants often have a slow onset of action and can result in varying degrees of side-effects. Additionally, more than 50% of MDD patients do not respond well to the initial prescribed antidepressant [7]. Even after completing two or more adequate treatment courses with antidepressants, approximately 30% of patients may not experience symptom relief [8]. Moreover, the recurrence rate of MDD is as high as 80% [9]. The long-term treatment, high risk of relapse, and functional impairment associated with the illness impose a substantial physical, psychological, and economic burden on affected patients, their families, and the society at large. Currently, MDD ranks as the second highest contributor to the global burden of diseases, and it is anticipated to become the leading global burden by 2030 [2].

Overview of the Gut Microbiota

The human gastrointestinal tract hosts a vast microbial community comprising various bacteria, fungi, archaea, and viruses. Approximately 99% of these microbes are

bacteria residing in the intestine, coexisting with the human body for extended periods. Collectively known as the "gut microbiota", they amount to around 10^{13} to 10^{14} bacterial cells—more than ten times the number of cells in the human body [10]. Both the composition and functions of the gut microbiota are closely intertwined with the complex physiological regulation processes of the host body. These include the metabolism of polysaccharides, production of short-chain fatty acids and certain essential vitamins, development and modulation of the immune system, maintenance of tissue homeostasis, and prevention of pathogenic invasion [11].

The composition and function of the gut microbiota are typically maintained stably under normal conditions within the human body. However, individuals with MDD demonstrate significant differences in their gut microbiota composition compared to healthy counterparts. These alterations encompass reduced α-diversity index, diminished populations of beneficial bacteria, and an increased proportion of harmful bacteria [12]. Consequently, MDD may disrupt the equilibrium of the gut microbiota in affected individuals, leading to physiological dysregulation. The study has demonstrated that transplanting the imbalanced gut microbiota from MDD patients into germ-free animals can induce depression-like behavior [13], while modulation of the imbalanced gut microbiota has shown potential in alleviating depressive symptoms to some extent [14,15]. This close relationship between emotional and behavioral regulation and the gut microbiota suggests a novel therapeutic target for MDD.

Modulating Gut Microbiota to Improve Depression Symptoms

Currently, effective strategies to modulate the gut microbiota primarily involve the use of probiotics/prebiotics, fecal microbiota transplantation (FMT), and adopting a healthy diet.

Probiotics/Prebiotics Method

Probiotics are exogenous bacteria, predominantly lactic acid bacteria such as *Lactobacillus casei*, *Lactobacillus helveticus*,and *Bifidobacterium*, which have the ability to rebalance the host's gut microbiota and confer beneficial effects on the host's health [16]. Conversely, prebiotics are dietary supplements that are not digested or absorbed by the host but are selectively utilized by beneficial gut bacteria to enhance their proliferation and suppress harmful bacteria. Common prebiotics include fructo-oligosaccharides, galacto-oligosaccharides, and ω-3 fatty acids [16].

Animal experiments have demonstrated that probiotic supplementation markedly ameliorates depressive symptoms and may even produce effects comparable to those observed with conventional antidepressant treatments [17–19]. A random-effects meta-analysis of 34 controlled clinical trials revealed that probiotic supplementation significantly ameliorates depression symptoms. Moreover, combining multiple probiotics or probiotics with prebiotics has been shown to yield superior results compared to using a single probiotic [20]. Notably, approximately 66.7% of treatment-resistant patients with MDD experienced significant symptom improvement with the combination of probiotics and selective serotonin reuptake inhibitors [21].

However, the ability of probiotics and prebiotic supplementation to restore intestinal bacterial diversity is limited. In contrast, introducing a complete and stable gut microbiota via fecal microbiota transplantation (FMT) may offer greater benefits in addressing imbalances within the gut microbiota population. Consequently, FMT emerged as a promising approach.

FMT

FMT involves transferring the fecal microbiota of a healthy donor into the gut recipient through various methods such as oral ingestion, clysis, or colonoscopy. This process can rapidly and significantly adjust the recipient's microbiota, restore gut microbial balance, and improve symptoms [22]. FMT treatment of poisoning has been recorded in China from as early as the 4th century AD [23]. Since 2013, FMT has transitioned from a lesser-known remedy to a mainstream treatments for *Clostridium difficile* infection [24]. Clinical and preclinical studies have demonstrated promising results of FMT in alleviating depressive symptoms [25–27], underscoring its potential role in the management of MDD in the future. These findings affirm the scientific and rational basis of targeting the gut microbiota as a novel approach to MDD treatment.

However, due to the "elasticity" of the gut microbiota, neither probiotic/prebiotic supplementation nor FMT can sustain regulatory effects in the long run without concurrent changes in the patient's dietary structure.

Healthy Diet Method

The concept of the "homology of medicine and food" has roots in ancient Chinese culture. Recent evidence suggests that specific diets can impact the occurrence and progression of depressive behavior [28]. Western dietary patterns characterized by high fat, sugar, and protein intake and low fiber content can promote the growth of harmful bacteria while suppressing beneficial bacteria [29], potentially heightening the risk of MDD [30]. Conversely, healthy diets like the Mediterranean diet can promote the growth of beneficial bacteria, thereby enhancing the diversity and stability of the gut microbiota [31] and significantly lowering the risk of MDD [30].

The "Scientific Research Report on Dietary Guidelines for Chinese Residents (2021)" underscores a prevalent issue of an unreasonable dietary structure among the Chinese population. Specifically, high-fat diets are widespread, and the intake of key nutrients essential for

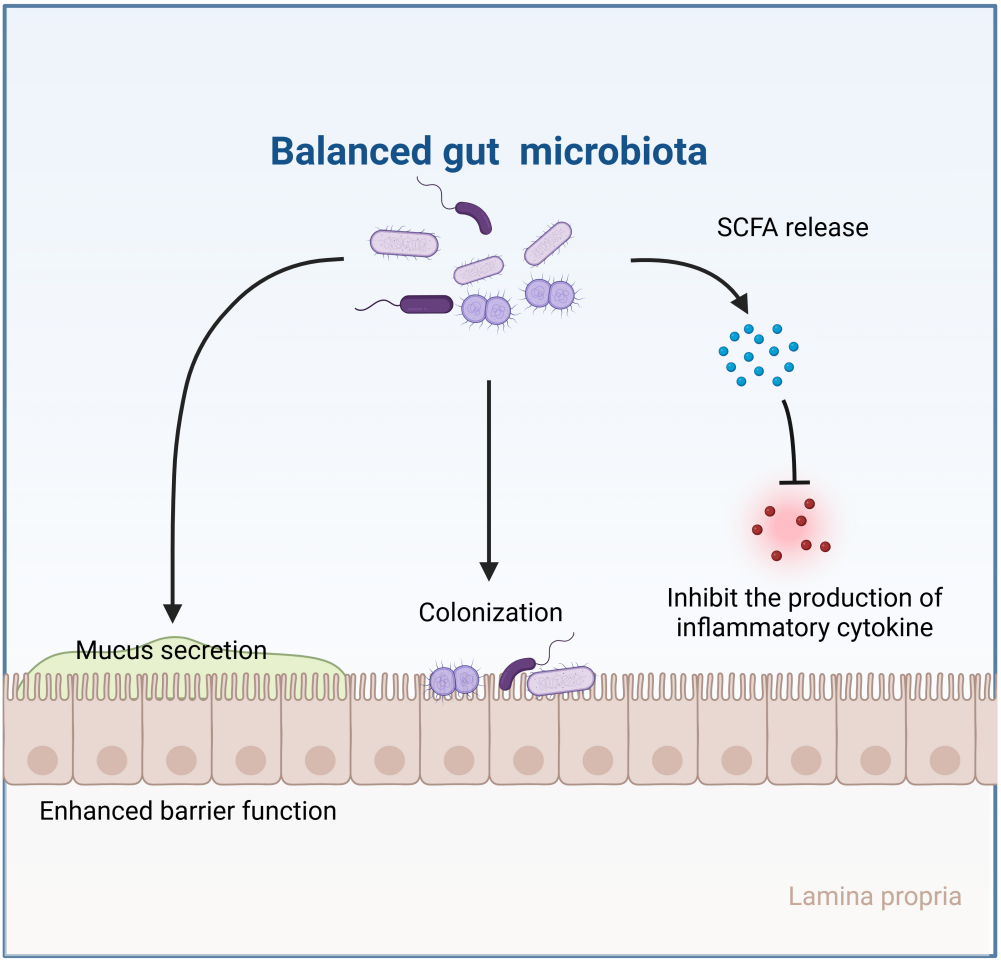

Fig. 1. Balanced intestinal microecology and healthy intestinal barrier (Created in BioRender.com). SCFA, short-chain fatty acid.

promoting beneficial gut bacteria, such as dietary fiber, is generally insufficient and declining over time [32]. Currently, the per capita daily dietary fiber intake among Chinese individuals is approximately 13.3 g, with less than 5% of the population meeting the recommended intake of 25 g [33]. Similar dietary irregularities have been reported globally [34].

Most individuals experience gut microbiota disorders due to an unreasonable and imbalanced dietary structure. Consequently, adjusting this dietary imbalance emerges as the most feasible, safe, reliable, and rapid strategy to regulate and maintain gut microbial balance.

Other Methods

In addition to the mainstream methods mentioned above, traditional Chinese treasures such as traditional Chinese medicinal formulations and acupuncture have demonstrated the ability to influence the composition and structure of the gut microbiota [35,36].

Medicinal herbs like Indian bread, desert-living cistanche, and Chinese magnolia vine fruit hold promise in alleviating depressive behavior by regulating the richness and diversity of the gut microbiota [37–39]. Similarly, traditional formulations such as Zhizichi decoction [40], Ganmai-dazao decoction, Guipi decoction, and Chaihu-Shugan powder have demonstrated efficacy in regulating imbalanced gut microbiota and ameliorating depressive symptoms [41–43].

Numerous clinical studies have confirmed the antidepressant effects of acupuncture, indicating its potential to regulate the gut microbiota [44–46]. A recent study demonstrated that acupuncture can not only augment the effectiveness of antidepressant treatment but also mitigate medication-related side effects [47], offering a novel perspective on the clinical diagnosis and treatment of MDD.

Possible Mechanisms for Improving MDD Symptoms via Modulation of the Gut Microbiota

The mechanism underlying the amelioration of MDD symptoms through gut microbiota modulation remains unclear. However, the pathogenesis of MDD is believed to involve dysregulation of immune function, neuroinflamma-

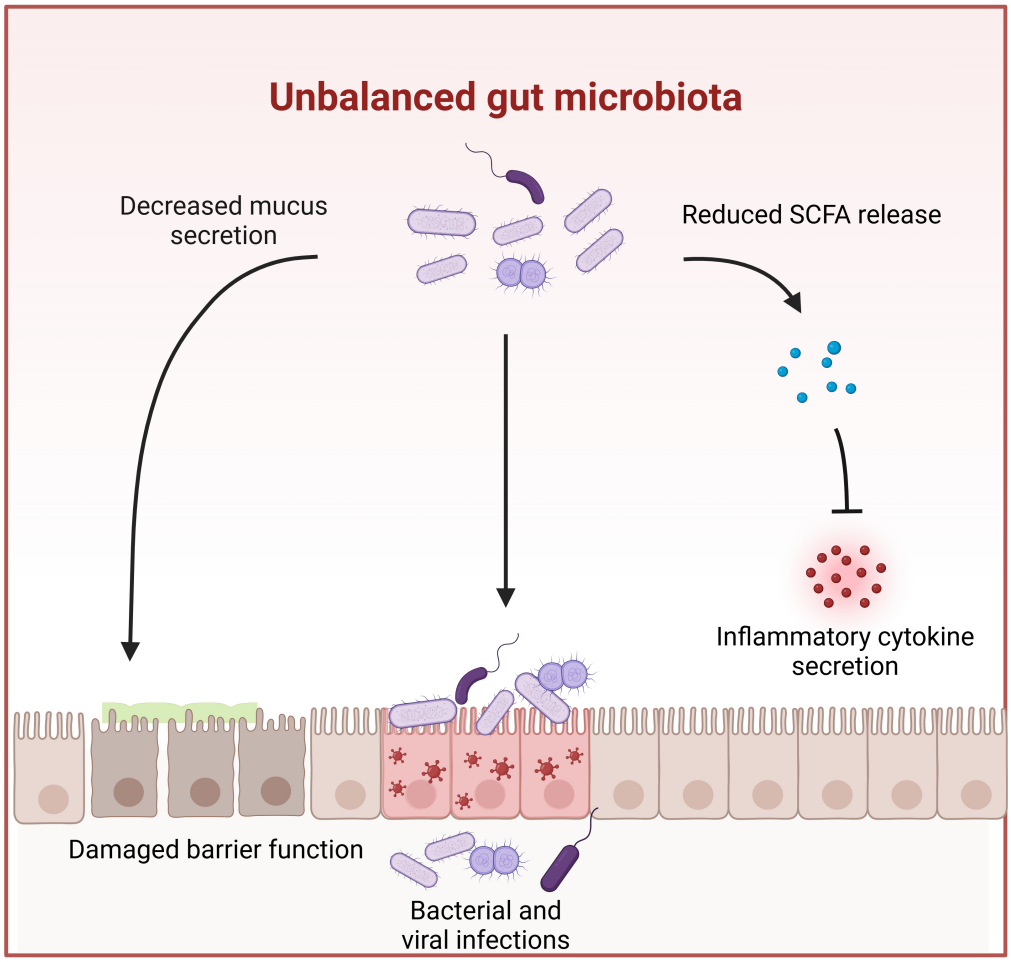

Fig. 2. Unbalanced intestinal microecology and damaged intestinal barrier (Created in BioRender.com).

tion, oxidative stress, and neurotransmitter imbalance [48–50], all of which may be interconnected with the imbalance in the gut microbiota composition [51]. In essence, the modulation of gut microbiota population may address the underlying cause of depressive symptoms.

Immunity and Inflammation

In the human gut, immune cells constitute 70%–80% of the body's total immune cells and play a critical role in immune regulation [52,53]. Individuals with MDD often display notable inflammatory responses, and the levels of inflammatory factors frequently correlate with the occurrence and progression of depressive symptoms [54,55]. Hence, it is conceivable to propose a bidirectional relationship between MDD and immune inflammation, with the gut microbiota serving as a pivotal link in this association [56,57].

Innate immunity refers to the host's inherent, nonspecific immune response to any antigen, which entails the removal of certain physical barriers and the activation of pattern recognition receptors and inflammatory mediators. Conversely, adaptive immunity involves a specific acquired immune response to a particular antigen, entailing the differentiation and activation of T cells and B cells. Broadly, the intestinal flora can influence the barrier function of intestinal epithelial cells, regulate the maturation and phenotype of dendritic cells, promote the differentiation and polarization of T cells and B cells, and generate various metabolites and molecular-mediated immunomodulation. Consequently, these actions establish a balance and tolerance between innate and adaptive immunity.

An imbalance in the gut microbiota composition can lead to a reduction in the protective mucosal layer surrounding intestinal epithelial cells. This reduction can damage the structure and functions of these cells through toxin secretion and degradation of tight junction proteins. These events can further exacerbate microbial imbalance and intestinal barrier damage by decreasing the production of antimicrobial peptides [58] (Figs. 1,2). Ultimately, this disruption compromises the integrity of the intestinal epithelial barrier, increases gut permeability, and permits the entry of bacteria and their secreted toxins into the lymphatic system and bloodstream [59]. Once in the bloodstream, components of bacterial cell walls such as lipopolysaccha-

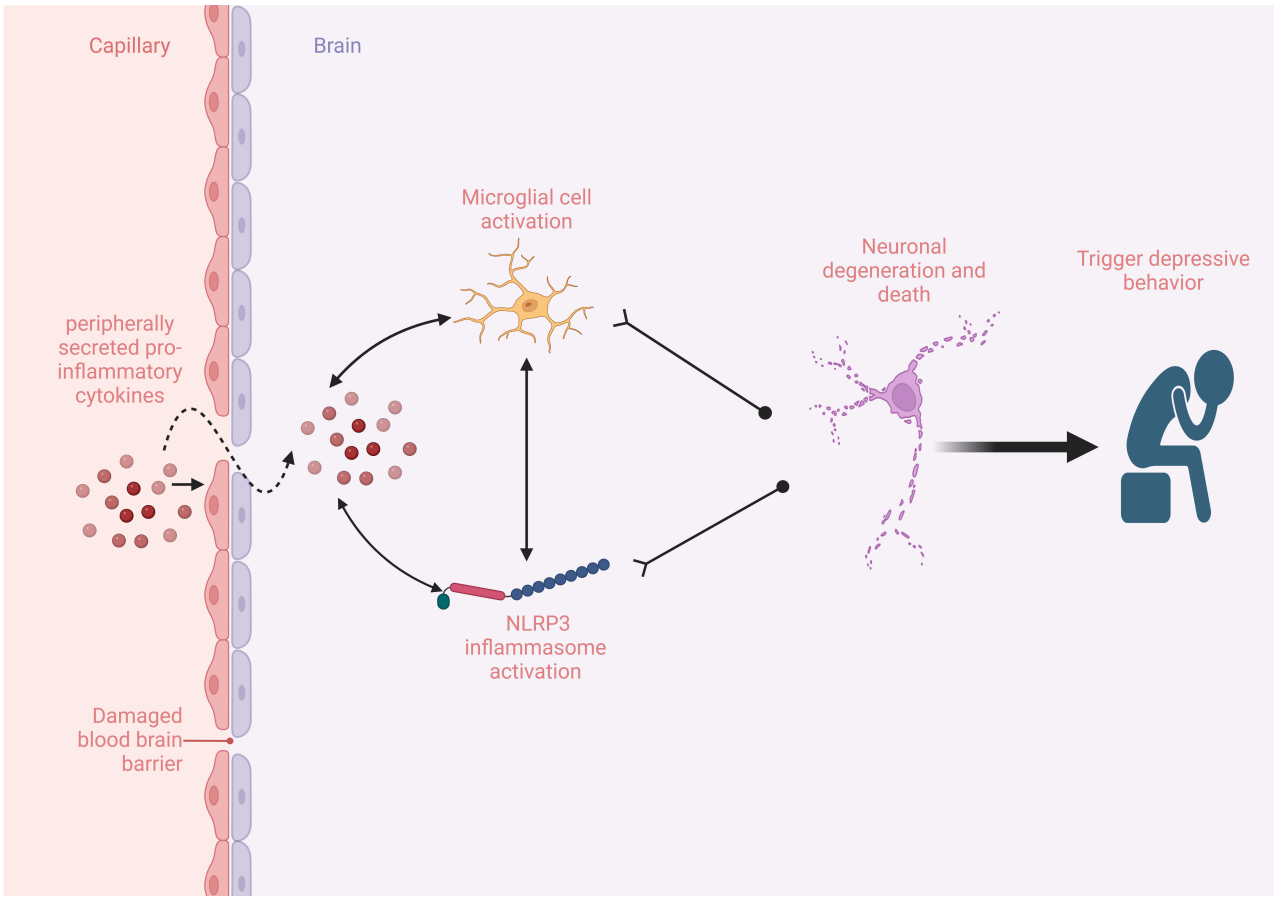

Fig. 3. Peripheral inflammatory factors cross the damaged blood-brain barrier, causing neurological degeneration and death and eventually leading to depression-like behavior (Created in BioRender.com). NLRP3, nucleotide oligomerization domain-like receptor protein 3.

rides and peptidoglycans can bind to Toll-like receptors 4 and 2 expressed on the host's intestinal epithelial or other immune cells, leading to the secretion of pro-inflammatory cytokines into the blood [60]. Additionally, gut bacteria can directly or indirectly interact with dendritic cells, affecting their maturation and activation. This interaction can influence the differentiation of effector T cells and ultimately promote organ-specific autoimmune responses and the release of inflammatory cytokines [61,62].

The peripherally secreted pro-inflammatory cytokines act on endothelial cells of the blood-brain barrier, altering its permeability and transport functions either directly or indirectly through the induction of chemokines and adhesion molecules [63,64]. Once inside the brain tissue, these cytokines bind to microglial receptors and activate downstream pathways, accelerating the release of additional cytokines [65]. They can also directly bind to nucleotide oligomerization domain-like receptor protein 3 (NLRP3) in the hippocampus, activating the NLRP3 inflammasome and promoting caspase-1 cleavage and subsequent cytokine release [66]. Microglia activation can trigger the NLRP3 inflammasome through various mechanisms such as lysosome injury, reactive oxygen species production, and adenosine triphosphate release [67]. Activated NLRP3 inflammasomes can further activate microglia, perpetuating a cycle of neuroinflammation [68], ultimately resulting in neuronal death and the onset of depressive behavior [66,69] (Fig. 3).

Modulating the imbalanced gut microbiota composition can help alleviate or reverse the aforementioned processes and ameliorate depressive symptoms. It is also believed to play a significant role in affecting the production of metabolic products. For example, microbiome restoration can facilitate the direct conversion of tryptophan to indoles and their derivatives, stimulating the production of aromatic hydrocarbon receptor (AhR) agonists, a crucial component of the gut and brain immune barriers [70]. Activation of AhR in the gut can mitigate tumor necrosis factor (TNF)-α-mediated activation of nuclear factor kappa B, reduce the expression of the pro-inflammatory cytokine interleukin (IL)-8, and enhance the expression of the anti-inflammatory cytokine IL-10 [71]. AhR activation can also exert anti-inflammatory effects by preserving the integrity of the intestinal barrier through IL-22 secretion, induction of IL-10R expression, and reinforcement of tight junction functions [72]. In the brain, AhR activation can further sup-

press astrocyte activity and neuroinflammation by promoting microglia-mediated secretion of transforming growth factor-α [73].

Simultaneously, modulation of the disordered microbiome may impact the generation of neuroactive short-chain fatty acids (SCFAs) [74,75]. These SCFAs have the ability to reverse microglial developmental and functional abnormalities in a free fatty acid receptor 2-dependent manner [76], as well as reduce intestinal barrier permeability and inhibit inflammatory factor production. SCFAs are also recognized for their role in promoting effector T cell differentiation by directly upregulating the expression of tight junction proteins and regulating the activity of intestinal epithelial cells [77]. Collectively, these mechanisms can alleviate inflammation and depressive symptoms.

Modulation of the intestinal microbiome is also recognized for enhancing bile salt hydrolase activity, which reduces primary bile acid accumulation and promotes secondary bile acid production [78]. Tauroursodeoxycholic acid, in particular, binds to G protein-coupled bile acid receptor 5, inhibiting neuroinflammation and reducing oxidative stress, consequently improving depressive symptoms [79].

Stress and Neuroendocrinology

A healthy gut microbiota plays a crucial role in balancing the hypothalamic-pituitary-adrenal (HPA) axis [80]. Any dysregulation in the gut microbiome can induce neuroinflammation, leading to the overactivation of the HPA axis, increased release of cortisol, and further disruption of the intestinal barrier, thus creating a vicious cycle [81]. Dysregulated gut microbiota can also induce the expression of tryptophan-2,3-dioxygenase and indoleamine-2,3-dioxygenase, shifting tryptophan metabolism toward the kynurenine pathway and reducing brain serotonin (5-HT) production [82]. This weakens the negative feedback inhibition of 5-HT on the HPA axis, increasing stress hormone production. Consequently, this phenomenon enhances the expression of indoleamine-2,3-dioxygenase, exacerbating the decrease in 5-HT production [80], leading to another vicious cycle. The consequences include insufficient production of 5-HT in the brain, decreased free 5-HT content, and overactivation of the HPA axis [36].

Additionally, the deficiency of SCFAs resulting from dysregulated gut microbiota can lead to the upregulation of key genes in the HPA axis, exacerbating HPA overactivation and depressive behaviors [83]. Modulating the gut microbiota can reverse these gene expression changes, suppress HPA axis overactivation [71,84], ameliorate stress-induced corticosterone increases [85], and consequently improve depressive symptoms.

The gut microbiota indeed has the capacity to produce neurotransmitters such as dopamine and norepinephrine, which can be transported into the brain. However, the relationship between neurotransmitter levels in the gut and brain remains unclear [86] and requires further research to elucidate.

Discussion

To summarize, it's evident that the intestinal flora can influence the occurrence and progression of depressive symptoms in hosts through neuroimmune and neuroendocrine regulation. Among these mechanisms, the interaction between intestinal flora and its metabolites with innate immunity is a key area of current research. By supplementing probiotics/prebiotics, conducting FMT, and adopting a healthy and balanced diet, we can counteract the changes caused by imbalances in the intestinal flora. Large-scale, multi-center, randomized controlled trials are necessary to evaluate the efficacy of probiotics/prebiotics in improving depressive symptoms [15,87–89]. While promising, treatments such as FMT may carry rare but serious adverse effects, including infection and death [90]. The lack of internationally recognized healthy donor standards hampers their widespread clinical application. Therefore, dietary regulation is currently considered the most feasible, safe, reliable, and sustainable approach to regulate and maintain gut microbiota balance. More comprehensive and long-term clinical studies focusing specifically on patients with MDD are needed to thoroughly assess the therapeutic potential of gut microbiota modulation in ameliorating depressive symptoms and to deepen our understanding of the causal relationship between pathogenic and beneficial bacteria in MDD.

Conclusion

In conclusion, the modulation of gut microbiota composition holds the potential to directly or indirectly ameliorate depressive symptoms by alleviating neuroinflammation, inhibiting the overactivation of the HPA axis, and regulating neurotransmitter levels, even in patients with refractory MDD.

Availability of Data and Materials

Not applicable.

Author Contributions

(I) Conception and design: JL, YC, EY; (II) Administrative support: EY; (III) Provision of study materials: JL, YC, TL, CZ, YQ; (IV) Collection and assembly of data: JL, YC, TL, CZ, YQ; (V) Data analysis and interpretation: JL, YC; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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