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Research progress on intestinal flora and depression

Zilei Zhang

School of Public Health, Wuhan University, Wuhan, Hubei, 430071, China

2023283050030@whu.edu.cn

Abstract. In recent years, the prevalence of depression and suicide rates have continued to increase, especially among adolescents, and existing treatment methods are still incomplete and have certain limitations. Although some progress has been made in studying the relationship between gut microbiota and depression, a clear explanation of the physiological mechanisms of the "Microbiota-Gut-Brain Axis" (MGBA) and a review of treatments for depression based on MGBA regulation are still lacking. This article examines the traits of the gut microbiota in patients with depression, highlighting that their richness and diversity are significantly lower compared to healthy controls. The neurological, endocrine and immune mechanisms of MGBA and its role in the pathogenesis of depression were further explored. This article also reviews MGBA-based treatments, such as Fecal Microbiota Transplantation (FMT) and probiotic therapy, noting their potential efficacy in alleviating depressive symptoms. This article unveils the pivotal role of gut microbiota in the development of depression, offering a new avenue for researching the pathological mechanisms of the disorder and laying a scientific foundation for creating novel antidepressant treatments. At present, there is no consistent conclusion about the changes in the composition of the intestinal flora in depression. Future studies can expand the sample size and conduct experiments on different groups to deeply reveal the changes in the intestinal flora of patients with depression.

Keywords: Intestinal flora, depression, MGBA.

1. Introduction

Depression is a common chronic mood disorder characterized by a high suicide rate [1]. Common symptoms include self-denial and suicidal tendencies. It is an important cause of global disability and disease burden. In recent years, the prevalence of depression and suicide rates have continued to increase. Nearly 40% of adolescents have recurring depressive symptoms, which may lead to suicidal thoughts and even behaviors. These trends highlight the limitations of existing treatments and are causing widespread concern [2].

The intestinal flora is the largest micro-ecosystem in the human body, with trillions of microorganisms colonizing the gastrointestinal tract2, affecting local and systemic metabolic processes, as well as brain development, thereby changing Central Nervous System (CNS) function and behavior [3]. Alterations in the structure and composition of gut microbiota due to disturbances may serve as a potential contributing factor to depression. Multiple studies have confirmed that transplanting intestinal flora from patients with depressive disorders into the intestines of germ-free mice can induce depressive-like behaviors in mice, and the changes in intestinal flora and metabolites are consistent with those in

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patients with depressive disorders. Recent studies have highlighted the significant impact of gut microbiota on the functioning of the CNS [3].

Therefore, some scholars have proposed that the MGBA serves as a bidirectional communication channel between the gut and the brain, involving the participation of intestinal flora. Gut microbiota can influence the host's CNS through neural, metabolic, and immune-mediated mechanisms [4], thereby impacting the host's cognitive functions. Numerous studies have proven that the complex interaction between the body's brain function and intestinal microbiota may mediate the pathophysiological changes of depressive disorders. Therefore, MGBA has become a potential target for new antidepressant treatments. Growing evidence supports the potential role of MGBA in influencing behaviors associated with anxiety and depression [2].

The richness and diversity of gut microorganisms in individuals with depression are considerably lower than those in healthy controls, with notable variations in both alpha and beta diversity. At the phylum, family, and genus levels, patients with depression experienced changes in the abundance of different bacterial species. Even though some studies may have different changes in bacterial flora due to differences in experimental conditions or experimental subjects, the general consensus is that patients with depression. The microbiota composition in patients with depression shows significant divergence from that of healthy individuals [5]. Although there is a clear disparity, more extensive research is required to convert these microbiome insights into novel clinical approaches, potentially improving treatment outcomes for those suffering from depression [6].

Currently, research in this area predominantly centers on several key aspects: the characteristics of gut microbiota in individuals with depression, the investigation of the relationship between gut microbiota and the onset of depression, the interaction between microorganisms and MGBA, and the subsequent effects on depressive conditions. Research has confirmed that intestinal flora plays a mechanistic role in severe mental illnesses such as autism and schizophrenia. Numerous prior studies have also demonstrated that significant differences exist in the gut microbiota of individuals with depressive disorders compared to healthy individuals [2]. However, there is a lack of reviews that briefly elucidate the interaction between depression and gut microbiota and various treatments for depression based on improving gut microbiota.

2. Depression and MBGA

The onset and progression of depression are influenced by multiple factors, including genetic predisposition, social and environmental influences, and the role of gut microbiota, which has recently become a significant focus of research. Intestinal flora can affect the host's CNS through various mechanisms such as nerves, metabolism, immunity, etc., thereby affecting cognitive function and emotional regulation. Disturbances of MGBA may be one of the important pathological mechanisms of depression1. Comprehending how gut microbiota influences the onset and progression of depression via the MGBA is not only important for revealing the pathological basis of depression, but also provides the possibility to develop new treatment methods, such as regulating intestinal flora to manage or prevent depression [4].

2.1. Function and role of intestinal flora

The gut microbiota is a complex community consisting of bacteria, viruses, fungi, and protozoa that inhabit the host's digestive tract, establishing a close symbiotic relationship with the host. Through its fermentation processes, the gut microbiota is integral to the synthesis of essential vitamins, such as vitamins K and B. Additionally, it produces short-chain fatty acids (SCFAs), including butyrate and acetate, which are vital for maintaining host health. These SCFAs are essential for maintaining gut immune balance and processing indigestible carbohydrates [7].

Gut flora communicate with the host brain through MBGA's complex communication methods, affecting the synthesis of neurotransmitters such as serotonin and dopamine. Research has demonstrated that there exists a bidirectional communication pathway between intestinal microorganisms and the CNS, exchanging information through metabolism-related molecular patterns such as double-stranded RNA

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and lipopolysaccharide, and these molecules are recognized through Toll-like receptors [8]. At the same time, intestinal microorganisms affect the synthesis of neurotransmitters, activation of immune cells, and the function of the Hypothalamic-Pituitary-Adrenal Axis (HPA) through their metabolites, which may directly or indirectly influence brain function and behavior, thereby impacting mental health, especially neuropsychiatric diseases such as depression [9].

Research findings indicate that the intestinal microbiota is not only the largest microecological system in the human body but also functions as a critical organ. It plays an indispensable role in nutrient absorption, immune system maturation, and maintaining nervous system health. Maintaining the stability of intestinal flora is of great significance in preventing mental illnesses such as depression.

2.2. Characteristics of intestinal flora in depression

Numerous studies have demonstrated that the diversity of gut microbiota in individuals with depression is significantly diminished compared to that of healthy individuals, and the abundance of the bacterial flora is also changed. For instance, one study revealed that individuals with depression exhibited significantly lower levels of Coprococcus. The reduction of Faecalibacterium in the intestine not only reduces the production of SCFAs, such as acetate and butyrate. However, these SCFAs are crucial factors in modulating the inflammatory response within the CNS [10].

One study highlighted that, at the phylum level, the intestines of patients with depression had lower abundances of Bacteroidetes, Synechococcus, Firmicutes, and Proteobacteria, while the abundances of Stemophora and Actinobacteria were higher. At the genus level, compared to healthy individuals, patients with depression showed relatively lower abundances of Bifidobacterium, Lactobacillus, Lauteria, Fischlenella, and Lachnospirillum. Conversely, the abundances of Luminococcus and the Dermanella genus within the Horaceae family were relatively higher [5].

In addition, one study found that compared with normal people, patients with depression had a decreased proportion of Firmicutes at the phylum level, an increased proportion of Bacteroidetes, Proteobacteria, and Actinobacteria, and an increased proportion of Lachnospiraceae and Ruminococcaceae at the family level. At the genus level, the abundance of Faecalibacterium, Ruminococcus, Lactobacillus and Bifidobacterium decreased.

Furthermore, animal model studies have also shown that transplanting feces from depressed mice into healthy mice will induce depressive symptoms in healthy mice, further proving the direct impact of changes in intestinal flora on emotional regulation and behavioral responses [9].

Gut flora and depression are inextricably linked. Due to factors such as sample size, individual differences in subjects, experimental equipment, and testing methods, although many studies have reached inconsistent conclusions on the changes in the specific flora of depressed and healthy people, the general consensus is that depression The composition of the patient's bacterial flora is significantly different from that of healthy patients, showing a direct link between intestinal flora imbalance and depression [9]. How to implement scientific and rigorous experiments to obtain more reliable results and more general conclusions is an issue that needs to be solved urgently.

3. Mechanism of MGBA

MGBA is a concept that describes the intricate bidirectional communication system between the gut and the brain, encompassing neurological, endocrine, and immune pathways. This system not only shows how physical health affects mental and emotional states, but also how psychological states affect gut function and microbial composition. Understanding the specific mechanisms of the MGBA will not only help uncover the fundamental biological processes underlying depression but also provide crucial biomarkers and therapeutic targets for developing new prevention and treatment strategies for the disorder.

3.1. Neural pathways

Neural pathways play an important role in MGBA, particularly influencing mood and cognitive function through direct connections between the Enteric Nervous System (ENS) and the vagus nerve. Gut

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microbiota can regulate neural signals by affecting the release of neurotransmitters in the ENS such as 5-HT and GABA or directly through its metabolites such as SCFAs. These signals are transmitted to the vagus nerve through the ENS and ultimately affect brain function2. The vagus nerve, the main neural pathway linking the gut to the brain, plays a crucial role in regulating stress responses and maintaining emotional balance. In addition, certain neuroactive compounds such as dopamine and norepinephrine can be synthesized by intestinal microorganisms and act directly on the brain through the blood system, further affecting mood and behavior [9].

3.2. Endocrine pathway

The endocrine pathway involves gut microbes influencing mood and stress responses by regulating hormone balance. Gut microbes can regulate the release of intestinal hormones such as Glucose-dependent Insulinotropic Polypeptide (GIP), Glucagon-like Peptide-1 (GLP-1), etc. These hormones can cross the blood-brain barrier and directly act on the hypothalamus region of the brain, thereby regulating emotional responses and eating behavior4. In addition, the HPA is the main neuroendocrine system in response to stress, and its activation is closely related to the status of intestinal flora. The release of hormones such as cortisol is regulated by metabolites produced by gut microbes such as SCFAs, which influence the body's response to stress as well as emotional stability [10].

3.3. Immune pathways

In the immune pathway, many studies have pointed out that intestinal flora affects mood and behavior by regulating the host's immune response. Specific changes in intestinal flora can promote the production of inflammatory factors such as IL-1β and TNF-α, which enter the brain through blood circulation and activate immune cells such as astrocytes and microglia in the CNS. This activation may lead to neuroinflammation, which in turn affects the function of neurotransmitter systems and induces depressive and anxious behaviors [11]. In addition, intestinal flora imbalance may also cause intestinal barrier dysfunction, further making it easier for inflammatory factors to enter the CNS, exacerbating the neuroinflammatory response, thereby affecting mood and cognitive functions [8].

4. Depression treatment application based on MGBA

Currently, conventional treatments for depression include medication, psychotherapy, etc. However, conventional therapies still have shortcomings such as poor medication compliance and high costs, so it is necessary to develop new and effective therapies. Currently, MGBA can be used as a target for intervention measures to treat depression.

4.1. Fecal microbiota transplantation

FMT is a technique that restores disrupted intestinal microecology by transferring the gut microbiota from a healthy donor into the recipient's intestine [8]. This emerging technique has been shown to be effective in treating certain gastrointestinal diseases, and is gradually being applied to the treatment of neurobehavioral disorders related to MGBA, such as depression [7].

Recent studies have shown that fecal microbiota transplantation has a significant therapeutic effect on Chronic Unpredictable Mild Stress (CUMS)-induced depression rat model. In a study conducted by Wang et al., CUMS mice were transplanted with the feces of normal rats to evaluate depression levels through the Forced Swim Test (FST). The results indicated that the immobility time of rats in the CUMS group was significantly longer compared to the control group. However, rats in the CUMS group that received FMT treatment exhibited a substantial reduction in immobility time, reflecting a notable decrease in depressive symptoms in these rats. Zheng et al., Huang et al., Liu et al. also reached consistent conclusions [12]. In addition, FMT also significantly increased the sucrose preference index, indicating its antidepressant effects [10].

Multiple studies have demonstrated that FMT can reduce anxiety and depression-like behaviors in rats. It helps to alleviate imbalances in intestinal flora, inhibit the activation of microglia and astrocytes, decrease the release of pro-inflammatory cytokines, and reduce NLRP3 inflammation in the brain. The

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activation of corpuscles exerts a neuroprotective effect [10]. Furthermore, FMT can rectify the imbalance of gut microbiota in CUMS rats by boosting the population of beneficial bacteria like Bifidobacterium and decreasing the prevalence of harmful bacteria. This correction helps to mitigate both intestinal and neuroinflammation, subsequently easing depressive symptoms [1].

Although fecal microbiota transplantation has shown significant therapeutic effects, its adverse effects such as diarrhea, constipation, etc. also need to be paid attention to. Future research needs to further evaluate the side effects of FMT and the safety of donors, and develop more standardized and convenient treatment methods, such as freeze-dried fecal bacteria capsules, to achieve safe, effective and convenient use [10].

In summary, FMT, as an emerging treatment for depression, has demonstrated its potential in improving depressive symptoms and reshaping the intestinal flora. Future research should further explore its mechanism and application prospects, and conduct pilot studies on humans after the research is mature to achieve wider and safer clinical application and promotion.

4.2. Probiotic therapy

Probiotics are active microorganisms that benefit the host's health and have shown potential in treating depression by modulating the gut microbiota and the MGBA [9].

A review written by Agata et al. mentioned that Lactobacillus plantarum DP189 (a type of probiotic) significantly improved 5-HT, NA and DA levels in the brain and reduced depressive-like behaviors in CUMS rats. Furthermore, Lactobacillus rhamnosus JB-1 can also improve stress-induced depressive-like behaviors by regulating brain metabolite levels. Other probiotics have also significantly reduced anxiety and depression-like behaviors in mice within the CUMS model, restoring the normal function of the MGBA [13].

Clinical research has indicated that probiotics have a substantial impact on alleviating symptoms in individuals with depression. Wallace and Milev's study on 10 patients diagnosed with major depressive disorder revealed that supplementation with Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 significantly reduced levels of anxiety, improved overall mood, and alleviated anhedonia. Moreover, in a double-blind randomized controlled trial, Rudzki et al. found that the combination of Lactobacillus plantarum 299v and selective serotonin reuptake inhibitors (SSRIs) led to significant improvements in cognitive function among patients with depression, highlighting the potential of probiotics as an adjunctive treatment [12].

Several studies have found that probiotics have multiple advantages as an antidepressant treatment. For example, probiotics are well tolerated and do not cause adverse effects even in patients with liver disease [5]. Secondly, probiotics change the intestinal flora in a self-sustaining manner, so long-term medication is not required, which is different from the use of conventional antidepressants, thereby improving patients' medication compliance [14]. In addition, probiotics can comprehensively improve depressive symptoms by regulating neurotransmitter systems, reducing inflammatory responses, and improving intestinal barrier function [1].

Although probiotics have considerable potential in antidepressant treatment, there are currently some limitations. For example, the mechanism of antidepressant effects has not been fully elucidated and requires further research to determine. Second, differences between different probiotic strains and treated individuals may affect efficacy14. In addition, the sample size of existing clinical studies is small, and there is a lack of research on patients with clinical depression. The efficacy of probiotics in patients with different depression needs to be further verified [15].

In summary, probiotics have good prospects in treating depression. Future clinical trials with larger sample sizes and more rigorous designs are necessary to validate the true efficacy of probiotics in treating depression. As research on the MGBA and gut microbiota advances, probiotics hold promise to emerge as a novel, safe, and effective treatment option for depression.

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5. Conclusion

This article briefly discusses the relationship between depression and intestinal flora, the mechanism of MGBA and its application in the treatment of depression. Numerous studies have highlighted that the diversity and abundance of gut microbiota in patients with depression are considerably lower than in healthy individuals, with a significantly different composition. The disorder of intestinal flora may be one of the important pathological mechanisms of depression. In addition, FMT and probiotic therapy have potential efficacy in alleviating depressive symptoms by modulating intestinal flora and affecting central nervous system function by regulating neural, metabolic and immune pathways, thereby improving patients' depressive symptoms.

This article uncovers the crucial role of gut microbiota in the development of depression and reviews emerging therapies that target the MGBA to treat depression. This offers a new avenue for exploring the pathological mechanisms of depression and establishes a scientific foundation for developing novel antidepressant therapies. The focus is on the potential applications of FMT and probiotic therapy.

This article offers a concise review of the relationship between depression and gut microbiota, but there are still some limitations. First of all, when this article reviews the specific mechanism of MGBA, it does not go into depth due to space reasons, so it is relatively brief. Secondly, in the discussion of MGBA-based treatments for depression, only FMT and probiotics were mentioned, and treatments such as prebiotics and functional foods have not been discussed due to space reasons.

Finally, future research should focus on clinical trials with larger sample sizes and more rigorous implementation to verify the actual effect and safety of FMT and probiotic therapy in patients with different types of depression. At the same time, in the future, the specific mechanism of action of intestinal flora should be studied in depth and other possible regulatory means should be explored, such as oral flora. Through multidisciplinary cooperation, it is expected to provide more effective and safer treatment strategies for patients with depression.

References

[1] Li Y Mo T & Yao Y 2023 Mechanism and application prospects of intestinal flora regulating inflammatory response and oxidative stress in depression Chin Sci Bull 33 4480-4490
[2] Dash S Clarke G Berk M & Jacka F N 2015 The gut microbiome and diet in psychiatry: Focus on depression Curr Opin Psychiatry 281 1-6
[3] Thapa S Sheu J C Venkatachalam A Runge J K Luna R A & Calarge C A 2021 Gut microbiome in adolescent depression J Affect Disord 292 500-507
[4] Scassellati C Marizzoni M Cattane N et al 2021 The complex molecular picture of gut and oral microbiota–brain-depression system: What we know and what we need to know Front Psychiatry 12 722335
[5] Ke C & Ye L 2021 Research progress on the characteristics of intestinal flora of adolescents and the effects of probiotics on their depression J PLA Med J 9 855-859
[6] Barandouzi Z A Starkweather A R Henderson W A Gyamfi A & Cong X S 2020 Altered composition of gut microbiota in depression: A systematic review Front Psychiatry 11 536093
[7] Merkouris E Mavroudi T Miliotas D et al 2024 Probiotics' effects in the treatment of anxiety and depression: A comprehensive review of 2014–2023 clinical trials Microorganisms 122 411
[8] Aslam H Green J Jacka F N et al 2020 Fermented foods the gut and mental health: A mechanistic overview with implications for depression and anxiety Nutr Neurosci 239 659-671
[9] Xu R Ma Y Wang D Zhang X Yang X Yu Y & Xu X 2023 Research progress on the involvement of intestinal flora in depression based on the "microbe-gut-brain" axis Food Sci 5 383-391
[10] Cai T Zheng S P Shi X et al 2022 Therapeutic effect of fecal microbiota transplantation on chronic unpredictable mild stress-induced depression Front Cell Infect Microbiol 12 900652
[11] Foster J A & Neufeld K A M 2013 Gut–brain axis: How the microbiome influences anxiety and depression Trends Neurosci 365 305-312

DOI: 10.54254/2753-8818/47/2024PJ0104

[12] Xie Y 2024 Research on the role and mechanism of intestinal flora in the occurrence and treatment of depression
[13] Chudzik A Orzyłowska A Rola R & Stanisz G J 2021 Probiotics prebiotics and postbiotics on mitigation of depression symptoms: Modulation of the brain–gut–microbiome axis Biomolecules 117 1000
[14] Wang P Xia C Zhang Y Liu R & Liao M 2019 Probiotic therapy: A blessing for patients with depression? Microbiol Bull 9 2404-2410
[15] Liu R T Walsh R F & Sheehan A E 2019 Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials Neurosci Biobehav Rev 102 13-23