



Narrative Review

The Second Brain: Understanding the Role of Gut Microbiome in Depression

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Abstract

The gut microbiome (enterobiome) has emerged as a key regulator of the gut–brain axis, influencing mental health through neural, immune, endocrine, and metabolic pathways^(3,4,5). Increasing evidence suggests that gut dysbiosis is closely associated with Major Depressive Disorder (MDD)^(1,3,11), contributing to chronic inflammation, altered neurotransmitter synthesis, impaired intestinal barrier function, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation^(2,20). Depression and gut microbiome alterations appear to share a bidirectional relationship, with each capable of exacerbating the other. Experimental and clinical studies support the role of microbial imbalance in depressive symptoms, highlighting the therapeutic potential of microbiota-targeted interventions, including dietary modification, probiotics, prebiotics, symbiotics, postbiotics, and faecal microbiota transplantation as adjunctive treatments^(25,26,30). We explore the relationship between the gut microbiome and mental health with special emphasis on the role in depression.

Keywords: Gut microbiome, enterobiome, mental health, depression.

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Introduction

The enterobiome, also known as gut microbiome, refers to large community of microorganisms that live naturally in the human gastrointestinal tract^(1,4). These microorganisms include bacteria, viruses, fungi and archaea, all of which play an important role in maintaining overall health⁽⁷⁾. Earlier the gut microbiome was mainly associated with digestion, but recent research has shown that

its function extends beyond the digestive system. It helps in nutrient metabolism, support the immune system, maintain the intestinal barrier, protect against microorganisms, and produce several important metabolites that influence different organs of the body, including the brain. In healthy individuals gut microbiota is mainly composed of bacteria belonging to Firmicutes and Bacteroidetes phyla⁽¹⁾.

The composition of gut microbiota is not fixed and can change throughout life. Factors such as age, diet, stress, antibiotic use, lifestyle and environment exposure continuously influence balance of gut microorganisms⁽¹⁾. When this balance is disturbed, a condition known as gut dysbiosis develops^(1,3). Dysbiosis is characterized by a decrease in beneficial bacteria, an increase in harmful microorganisms, and reduced microbial diversity^(1,3). These changes not only affect gut health but also alter immune responses, inflammatory pathways and the production of microbial metabolites. Because the gut communicates closely with the brain through the gut-brain axis, disturbances in gut microbiome have increasingly been linked to several chronic diseases, particularly neuropsychiatric disorders such as depression⁽⁵⁾. In this narrative review we aim to find the relationship between gut microbiota and depression.

Methodology

This article is a narrative review that summarizes the available scientific evidence on the relationship between the enterobiome (gut microbiome) and depression. A literature search was carried out using electronic databases including PubMed, Google Scholar, Frontiers and ScienceDirect. Search terms such as *gut microbiome*, *enterobiome*, *gut-brain axis*, *depression*, *major depressive disorder*, *gut dysbiosis*, *microbiota*, *probiotics*, and *psychobiotics* were used individually and in combination to identify relevant studies.

Peer-reviewed review articles, original research articles, experimental studies, and clinical studies published in English were considered for inclusion. Priority was given to recent publications while also including landmark studies that have significantly contributed to the understanding of the gut-brain axis and its role in depression. Duplicate articles, studies unrelated to the topic, and publications without sufficient scientific evidence were excluded.

The selected articles were carefully reviewed, and information related to gut dysbiosis, gut-brain

communication, neurotransmitter regulation, immune and inflammatory mechanisms, microbial metabolites, intestinal barrier function, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and microbiota-based therapeutic approaches was extracted, compared, and synthesized. The findings were then organized into different sections to provide a comprehensive overview of the current understanding of the role of the enterobiome in depression.

Depression

Major Depressive Disorder (MDD) is one of the most common mental health disorders worldwide and is a leading cause of disability⁽¹⁾. It affects millions of people and has a significant impact on individual's quality of life, daily functioning, and overall wellbeing. People with depression commonly present with sadness, loss of interest in activities they once enjoyed, fatigue, disturbed sleep, changes in appetite, poor concentration, feelings of worthlessness or hopelessness. In addition to affecting mental health, depression also influences physical health, increasing the burden on healthcare systems and society⁽¹⁾.

Depression is now understood to be a complex disorder caused by interaction of genetic, environmental, psychological and biological factors⁽²⁾. Earlier research mainly focused on an imbalance of neurotransmitters such as serotonin, dopamine and noradrenaline⁽¹⁶⁾. However, recent studies suggest that depression involves much more than neurotransmitter deficiency. It is also associated with chronic inflammation, immune system dysfunction, oxidative stress, impaired neuroplasticity, dysregulation of hypothalamic-pituitary-adrenal (HPA) axis, and alteration in gut microbiome^(2,3,20). Since depression affects several body systems, including sleep, appetite, metabolism and immunity, researchers now consider it a whole-body disorder rather than a condition affecting only the brain. Although antidepressant medications are effective for many patients, they do not provide complete relief in

everyone, making it necessary to explore newer biological mechanisms involved in depression.

Enterobiome and Mental Health

In recent years, relationship between gut microbiome and mental health has become an important area of research. The gut and the brain communicate continuously through a system called gut-brain axis, which allows both organs to influence each other⁽⁵⁾. This communication occurs through several pathways, including the vagus nerve, immune system, hormones and various microbial metabolites produced by gut bacteria^(14,15). Because of this close interaction, changes in gut microbiome can directly affect brain function, while changes in brain activity, particularly during stress, can also influence the gut microbiome.

Gut microorganisms play an important role in producing or regulating several neurotransmitters that are essential for normal brain function and emotional wellbeing^(17,16). These include serotonin, dopamine, gamma-aminobutyric acid (GABA), glutamate and noradrenaline⁽¹⁷⁾. Approximately 90-95 % of the body's serotonin is produced in the gastrointestinal tract, highlighting importance of gut health in mood regulation⁽¹⁷⁾. In addition to neurotransmitters, gut bacteria produce metabolites such as short-chain fatty acids (SCFAs), bile acids and tryptophan metabolites, which influence neuronal activity, immune response and brain function⁽²¹⁾. A healthy gut microbiome also helps to maintain the integrity of intestinal barrier and regulates inflammatory responses. However, when dysbiosis occurs, increased intestinal permeability allows bacterial products and inflammatory molecules to enter the blood stream, leading to systemic inflammation and neuroinflammation that may negatively affect mood and cognitive function^(22,24). Likewise chronic psychological stress activates HPA axis, increasing cortisol levels that further disturbs the gut microbiome. Therefore, mental health and gut health influence each other in a continuous two-way relationship⁽²⁾.

Enterobiome and Depression

Among all psychiatric disorders, depression has shown one of the strongest associations with changes in gut microbiome. Several clinical and experimental studies have reported that individuals with Major Depressive Disorder commonly exhibit gut dysbiosis, which is characterized by reduced microbial diversity, a decrease in beneficial bacteria, and an increase in harmful or pro-inflammatory microorganisms^(11,12,18). Studies have consistently reported reduced levels of beneficial bacteria such as *Faecalibacterium*, *Coprococcus*, *Bifidobacterium*, *Lactobacillus*, and *Sutterella* along with increased levels of bacteria including *Bacteroides* and *Eggerthella*^(3,29). These microbial changes may contribute to altered immune function, chronic inflammation, abnormal neurotransmitter production, and metabolic disturbances that are commonly seen in depression. Researches have proposed two possible explanations of this relationship. The first suggests that chronic stress and depression activate the HPA axis, leading to increased cortisol production, altered immune responses, and changes in gut microbial composition⁽²⁾. The second proposes that gut dysbiosis itself contributes to development of depression by altering neurotransmitter production, microbial metabolites, vagus nerve signaling, and inflammatory pathways. Experimental studies support both possibilities. In particular animal studies have shown that transferring gut microbiota from patients with depression into healthy animals can produce depression like behaviors suggesting that the gut microorganisms may directly influence mood. Therefore, current evidence indicates that the relationship between the gut microbiome and depression is bidirectional, meaning that depression can alter the gut microbiome, while gut dysbiosis can also worsen or contribute to depressive symptoms^(3,5). This understanding has encouraged researchers to explore microbiota therapies such as dietary modification, probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation as potential

complementary treatments for depression in future^(9,10,25,26,28,30).

Table 1. Mechanisms linking gut microbiome dysbiosis and depression

Mechanism	Role in Depression
Gut dysbiosis	Reduces beneficial bacteria and increases harmful microorganisms
Neurotransmitter changes	Alters serotonin, dopamine, GABA, glutamate, and noradrenaline
HPA axis activation	Increases cortisol levels and stress response
Immune activation	Increases inflammatory cytokines leading to neuroinflammation
Intestinal permeability	Allows bacterial products to enter circulation, promoting systemic inflammation
Microbial metabolites	Altered SCFAs and tryptophan metabolites affect brain function
Vagus nerve	Disturbs gut-brain communication and emotional regulation

Microbiota-Based Therapeutic Approaches

Growing evidence suggests that modulation of the gut microbiome may serve as a useful adjunctive approach in the management of depression. Although these therapies are not currently considered a replacement for conventional antidepressants, they have shown promising results in improving gut microbial balance, reducing inflammation, and influencing the gut–brain axis.

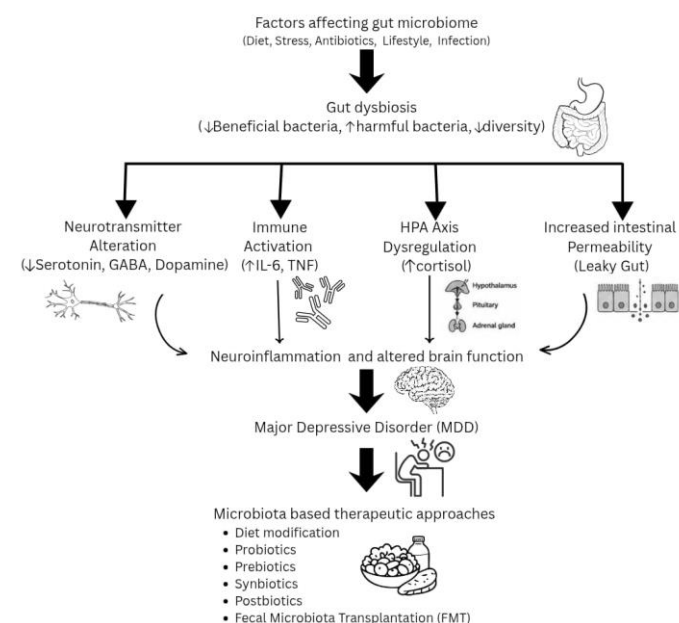
Probiotics are live microorganisms that provide health benefits when administered in adequate amounts. Several studies have reported that probiotic strains such as *Lactobacillus* and *Bifidobacterium* may improve depressive symptoms by restoring gut microbial balance, reducing inflammation, and regulating neurotransmitter production⁽²⁵⁾.

Prebiotics are non-digestible dietary components that promote the growth and activity of beneficial gut bacteria. They increase the production of short-chain fatty acids (SCFAs), improve intestinal barrier function, and may positively influence mood through the gut–brain axis⁽³⁾.

Synbiotics are a combination of probiotics and prebiotics that work together to enhance the survival and activity of beneficial microorganisms. Their combined effect may provide greater benefits than either therapy alone in maintaining gut health⁽²⁶⁾.

Postbiotics are bioactive compounds produced by beneficial microorganisms during fermentation. These microbial metabolites, including SCFAs, help regulate immune responses, reduce inflammation, and maintain intestinal barrier integrity, thereby supporting normal brain function^(3,20).

Fecal Microbiota Transplantation (FMT) involves the transfer of gut microbiota from a healthy donor to restore microbial diversity in individuals with gut dysbiosis. Although FMT has shown promising results in experimental studies, further large-scale clinical trials are required before it can be recommended as a routine treatment for depression⁽²⁸⁾.



Limitations

The current review is based on published literature and is limited by the availability and quality of existing studies. Most of the evidence demonstrates an association between gut microbiome alterations and depression, while a definite causal relationship has not yet been established. In addition, variations

in study populations, microbiome analysis techniques, dietary habits, and geographical differences may influence the findings. Therefore, further large-scale, well-designed clinical studies are required to better understand the role of the gut microbiome in depression and to validate microbiota-based therapeutic approaches.

Future Perspectives

Recent advances in microbiome research have opened new possibilities for understanding and managing depression. Future studies should focus on large-scale clinical trials to establish a clear causal relationship between gut dysbiosis and depression. The development of personalized microbiome-based therapies, including psychobiotics and targeted dietary interventions, may provide more effective treatment options. A better understanding of the gut–brain axis could also help identify novel biomarkers for early diagnosis and improve the overall management of depression^(3,27).

Conclusion

The gut microbiome has emerged as an important contributor to the pathogenesis of depression through its influence on the gut–brain axis. Although current evidence is promising, further large-scale clinical studies are needed to establish causality and optimize microbiota-based therapies. Targeting gut health may offer a valuable adjunctive approach to improving outcomes in patients with depression^(2,3).

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