Review Article

The Gut Microbiome and Mental Health: Mechanisms and Therapeutic Interventions

Silvana A. Sabrina Leddy

International School Nido de Aguilas, El Rodeo, Lo Barnechea, Región Metropolitana, 14200, Chile

ABSTRACT

The gut-brain axis comprises several components and mechanisms that affect mental health, including the vagus nerve, gut microbiome, neurotransmitters, and the stress response. The gut microbiome, a complex community of bacteria, plays a crucial role in regulating the brain's emotional state and behavior. Recent research emphasizes the profound influence of the gut-brain axis on mental health. Furthermore, therapeutic interventions, such as probiotics, prebiotics, and phage therapy, offer promising alternatives for influencing gut health, therefore influencing mental health. This literature review explores those pathways and the effects of probiotics, synbiotics, diet, and phage therapy, highlighting the role that gut-brain axis manipulation can have on mental health. Research has shown that the gut microbiome heavily influences the gut-brain axis and can influence anxiety, depression, and post-partum depression in mothers. Consuming prebiotics and probiotics could help reduce the effects and symptoms of anxiety and depression. While prebiotics and probiotics play a key role in supporting microbiomes, emerging alternatives, such as phage therapy and a balanced diet, offer promising opportunities for improving mental health. Future research will continue to explore additional strategies for developing more personalized treatments.

Keywords: Gut microbiome dysregulation; gut-brain axis; vagus nerve; probiotics; prebiotics; mental health; inflammation

INTRODUCTION

Depression and anxiety are among the most prevalent mental health disorders worldwide. Depression affected 21.4% of American adults, and 18.2% experienced anxiety symptoms in 2022 (1). Treatment-resistant depression response rates drop from 60-70% with initial treatments to 30-40% for resistant cases (2), with high relapse rates experienced within the first year of treatment discontinuation (3). These outcomes create an urgency for new targets and a deeper understanding of the underlying mechanisms contributing to treatment failure. While pharmacological options such as selective serotonin reuptake inhibitors (SSRIs) are effective for many patients, responses remain incomplete, and side effects are common. This has sparked interest in alternative treatment options or complementary strategies, including targeting the gut microbiome.

The gut-brain axis provides a framework for understanding how the gut microbiome influences psychological processes through a complex, bidirectional

Corresponding author: Silvana A. Sabrina Leddy, E-mail: sarosa2007@gmail.com.

Accepted September 23, 2025
https://doi.org/10.70251/HYJR2348.35454458

communication system (4), linking the enteric and central nervous system through neural, hormonal, and immunological responses. Recent research suggests that gut microbiome dysbiosis, characterized by a reduced microbial diversity and alteration of bacterial composition, contributes to neuroinflammation, disrupted neurotransmitter synthesis, and hypothalamic-pituitary axis (HPA) dysfunction (5). Key mechanistic pathways include vagal nerve signaling, short-chain fatty acids (SCFAs) production, and cytokine-mediated inflammation, which influence mood regulation and stress responses (6).

Figure 1 shows the essential components found in the gut-brain axis, which will be discussed in this section, such as the vagus nerve, gut microbiome, neurotransmitters, HPA axis, brain-derived neurotrophic factor (BDNF), and SCFAs.

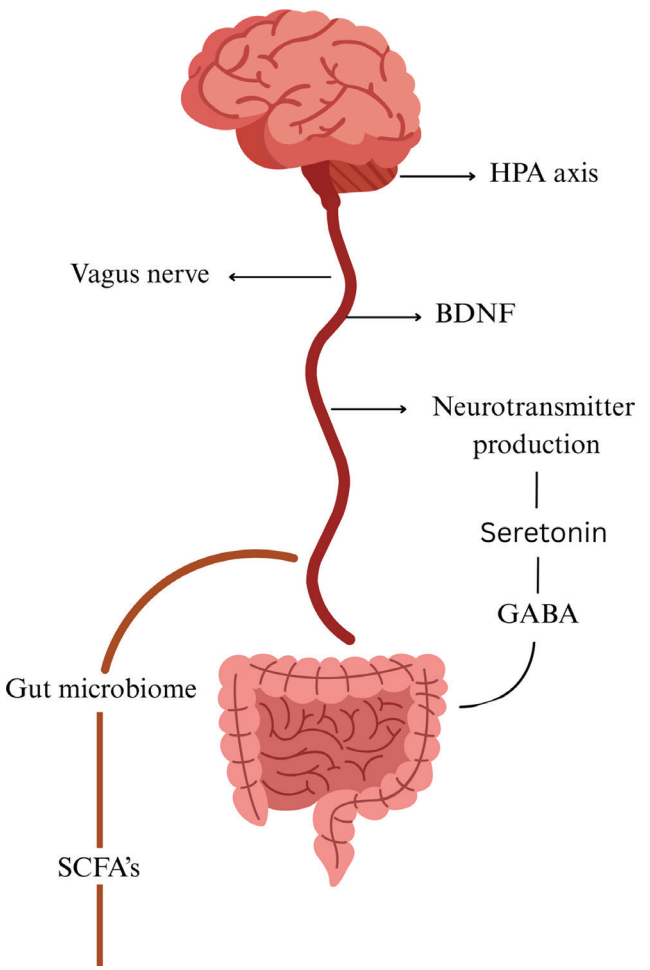

Figure 1. Modulating the gut microbiome: Factors that enhance or disrupt microbial balance.

THERAPEUTIC INTERVENTIONS: EVIDENCE SYNTHESIS AND CRITICAL ANALYSIS

Probiotics

Given the role of gut microbiota in regulating mood, researchers have explored probiotics and prebiotics as potential therapeutic interventions, as alternatives or supplementary options to traditional treatment routes such as SSRIs. Probiotics are microorganisms that, when ingested, improve gut microbial balance, while prebiotics are indigestible compounds that are metabolized by gut microorganisms, which regulate gut microbiome composition. Probiotics often consist of strains from the *lactobacillus* and *bifidobacterium* genera, which have been shown to reduce inflammation and modulate immune responses.

Probiotics can prevent the entry of the cytokine interleukin-8 (IL-8) into the human colon and help reduce intestinal permeability[1]. The entry of IL-8 into the colon can be problematic. IL-8 is a pro-inflammatory cytokine that attracts other immune cells and neutrophils to areas of infection in a process called chemotaxis. While IL-8 is essential for immune response, an excess in the colon can lead to chronic inflammation, tissue damage, and increased gut permeability (7).

Probiotics: Clinical Evidence and Limitations

Clinical Studies

Clinical studies investigating the effects on depression and anxiety have produced mixed, but in general positive results, although there are significant methodological concerns that limit the interpretation of the results. A key limitation that is seen across different studies is the use of antidepressants while being on clinical trials with probiotics, which confounds the assessment of probiotic efficiency alone.

For example, in a study consisting of 81 participants, those who received probiotics containing *Lactobacillus helveticus* and *Bifidobacterium longum* for eight weeks showed significant improvement in the Beck Depression compared to the placebo group; however, because all participants continued their antidepressant treatment, it is hard to isolate the effects of the probiotic. Similarly, their kynurenine-to-tryptophan ratio decreased. Kynurenine-to-tryptophan plays an important role in the nervous, endocrine, and immune systems, and inflammatory diseases (8). Increased kynurenine levels have been associated with neuroinflammation and serotonin deficiency. A significant change was seen in

the probiotic group, showing a decreased kynurenine to tryptophan ratio. This finding suggests that probiotics might improve depression by promoting tryptophan availability for serotonin production by reducing the number of enzymes that convert tryptophan into kynurenine (9).

Similarly, a pregnancy study consisting of 380 women receiving *Lactobacillus rhamnosus* demonstrated a significant decrease in depression. The study showed that women in the probiotic group had significantly lower depression scores (7.7) compared with the placebo group (9.0) in the Edinburgh Postnatal Depression scale. Similarly, the probiotic group also had a significantly lower anxiety score on the State-Trait Anxiety Inventory compared to the placebo group (10). This population represents an advantage since the participants were not under any type of antidepressant, providing clear evidence on probiotic effects. However, the findings are hard to generalize since the study was done on pregnant women, and pregnancy-related hormones could have changed the effects of the specific strain, which cannot be generalized to a larger population.

Synbiotic Interventions

There is limited evidence to suggest the effect of symbiotic supplementation (combination of probiotics and prebiotics) on depressive and anxiety-related symptoms. A 40-participant study with antibiotics in conjunction with fluoxetine, an antidepressant belonging to the group of medicines known as SSRIs, in patients with moderate depression was conducted. The study also included a placebo group with just fluoxetine. At the end of the study, the group on symbiotics experienced a significant decrease in the Hamilton Rating Scale for Depression score compared to the placebo group (19.25 in the treatment group and 17.75 in the placebo group). This study showed positive outcomes for symbiotics as an alternative therapy for patients with moderate depression[11]. However, the small size and brief intervention period limit the generality of the findings.

CRITICAL ASSESSMENTS OF ANIMAL STUDIES

Animal studies suggest that probiotics may mitigate depressive symptoms. For example, one study showed that introducing *Bifidobacterium infantis* to rats reverses experimentally induced stress and depression (12). Another study showed that administering *Lactobacillus* to rats for 28 days significantly decreased depressive symptoms (13).

Dietary Interventions

Over the last few decades, it has become clear that diet plays a key role in shaping an individual's gut microbiota, significantly affecting microbial diversity (14). It is evident that consuming a Western diet, which includes ultra-processed foods, sugar-rich foods, and low plant foods lacking their constituent fiber and polyphenols, can lead to a substantial loss in microbial diversity (15). It is widely recognized that having a healthy diet can positively modulate gut-brain axis communication and can be beneficial for both the prevention and treatment of common mental health disorders, such as anxiety and depression (16). There are emerging studies that focus on the incorporation of food items such as fruits and vegetables high in prebiotic fibers, showing promising results in modulating microbiome-host interactions (17).

Emerging Therapies: Phage Therapy

Another alternative for future research could be phage therapy, which relies on naturally occurring bacteriophages to infect and lyse harmful bacteria in the body at the site of infection, and has shown promising results in treating gastrointestinal diseases (18). Current research has shown that phages can be effective against multidrug-resistant infections and can be used as an alternative or supplement to antibiotic treatments (18). Phages found in the gut microbiome play a crucial role in regulating bacterial diversity. Given their immunomodulatory and bactericidal effects, phage therapy has been proposed as a clinical alternative to restore gut microbiota (19) and has been used to regulate gastrointestinal diseases such as cholera and diarrhea (20). While there is limited research to show its potential to improve symptoms of anxiety and depression, its properties could suggest a possible role in psychiatric treatments. Since the gut-brain axis is crucial in mental health, further research could demonstrate how phage therapy can influence the gut microbiome of individuals with anxiety and depression.

CONCLUSION

Summary and Interpretation of Findings

Research highlights how disruptions in the gut microbiota and vagal signaling can contribute to

psychiatric disorders, emphasizing the need for further exploration of the therapeutic interventions mentioned in the literature review. By understanding future therapeutic interventions like probiotics, prebiotics, and phage therapy, the treatment for anxiety and depression could be improved, and these alternatives, along with antidepressants, can improve symptoms of psychiatric disorders in patients. It is also important to understand how mechanisms, like neurotransmitters and SCFAs, act when disrupted, which can alter the gut microbiome, leading to an increased likelihood of psychiatric disorders. By deepening our understanding of this topic, we can create more targeted therapeutic interventions that will improve patients' mental health and overall well-being.

Limitations

The literary review examined the dysbiosis of the gut microbiome and the resulting problems related to mental health it can cause, enabling identification of alternative treatments to ensure mental health disorders such as depression and anxiety can be prevented. While most studies used common bacterial strains like *Lactobacillus* and *Bifidobacterium*, it is difficult to isolate the effect of individual strains on the patients due to the different combinations of strains. More studies could be conducted to determine particular strains' efficiency and impact on mood. The doses used changed across the various studies, making it hard to determine how different doses affected the patients. Additionally, other factors could affect the efficiency of the probiotics and prebiotics. For example, sleep variability is a factor that has a significant impact on anxiety and depression. The way that depression was measured also affects the results. The different studies used the BDI scale, the Hamilton Rating Scale for Anxiety or Depression, the Edinburgh Postnatal Depression Scale, and the State-Trait Anxiety Inventory. These scales use different methodologies to measure an individual's depression or anxiety, which could have also altered the findings of the studies. It would also be essential to understand if taking antidepressants while on probiotics or prebiotics affects a patient's response to probiotics and prebiotics, as well as knowing if these alone would also have the same results.

Future Research Priorities

Priority should be given to adequately randomized controlled trials comparing microbiome interventions to placebo participants with mild-to-moderate depression or anxiety. These studies should include standardized outcome measures and extend beyond 12 weeks to assess sustained effects (21).

As well, future research should include repeated microbiome assessments, using methods such as 16S rRNA sequencing and shotgun metagenomics, to clarify causation between microbial shifts and patient outcomes (22). In the present, most studies depend on scale scores instead of confirming parallel changes in the gut microbiome.

Research should also focus on developing personalized interventions based on the patients' microbiome profiles. This approach could give a more targeted treatment to each individual, without generalizing treatments amongst the population. Trials should also include biomarker assessments for (inflammatory cytokines, neurotransmitter metabolites, HPA axis function) to validate the proposed treatment for each patient, and the effectiveness it might have on the person. By implementing these methodological approaches, future research can move beyond the current limitations to establish gut-microbiome interventions as an alternative therapeutic pathway for mental health disorders.

FUNDING SOURCES

The author has no funding sources that supported the research and preparation of the article.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Statistics, National Center for Health. *National Health Statistics Reports, Number 213, November 4, 2024*. (Accessed on 2025-09-17).
2. Łysik Anna, *et al*. Innovative Approaches in the Treatment-Resistant Depression: Exploring Different Therapeutic Pathways. *GeroScience*. Aug. 2025; 47 (4): 5543–58. https://doi.org/10.1007/s11357-025-01615-8.
3. Yuhua Hu, *et al*. Association between Duration of Antidepressant Treatment for Major Depressive Disorder and Relapse Rate after Discontinuation: A Meta-Analysis. *Psychiatry Research*. July 2024; 337: 115926, https://doi.org/10.1016/j.psychres.2024.115926.
4. Yimin Han. Vagus Nerve and Underlying Impact

on the Gut Microbiota-Brain Axis in Behavior and Neurodegenerative Diseases. *Journal of Inflammation Research*. Nov. 2022; 15: 6213–30, https://doi.org/10.2147/JIR.S384949.

5. Marilia Carabotti. The Gut-Brain Axis: Interactions between Enteric Microbiota, Central and Enteric Nervous Systems." *Annals of Gastroenterology*. 2015; 28 (2): 203–09.
6. Kenneth J. O'Riordan, *et al*. The Gut Microbiota-Immune-Brain Axis: Therapeutic Implications. *Cell Reports. Medicine*. Mar. 2025; 6 (3): 101982. https://doi.org/10.1016/j.xcrm.2025.101982.
7. Jie Xu, and Yi Lu. The Microbiota-Gut-Brain Axis and Central Nervous System Diseases: From Mechanisms of Pathogenesis to Therapeutic Strategies. *Frontiers in Microbiology*. June 2025; 16. https://doi.org/10.3389/fmicb.2025.1583562.
8. Karlyle G. Bistas, and Jean Paul Tabet. The Benefits of Prebiotics and Probiotics on Mental Health. *Cureus*. Aug. 2023; 15 (8): e43217. https://doi.org/10.7759/cureus.43217.
9. Ruo-Gu Xiong. The Role of Gut Microbiota in Anxiety, Depression, and Other Mental Disorders as Well as the Protective Effects of Dietary Components. *Nutrients*. July 2023; 15 (14): 3258. https://doi.org/10.3390/nu15143258.
10. Caroline J. K. Wallace, and Roumen Milev. The Effects of Probiotics on Depressive Symptoms in Humans: A Systematic Review. *Annals of General Psychiatry*. Feb. 2017; 16: 14. https://doi.org/10.1186/s12991-017-0138-2.
11. Zeinab Ghorbani. The Effect of Synbiotic as an Adjuvant Therapy to Fluoxetine in Moderate Depression: A Randomized Multicenter Trial. *Archives of Neuroscience*. Apr. 2018; 5 (2). https://doi.org/10.5812/archneurosci.60507.
12. Matthew A. Odenwald, and Jerrold R. Turner. Intestinal Permeability Defects: Is It Time to Treat? *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association*. Sept. 2013; 11 (9): 1075–83. https://doi.org/10.1016/j.cgh.2013.07.001.
13. Fooks LJ, and Gibson GR. Probiotics as Modulators of the Gut Flora. *The British Journal of Nutrition*. Sept. 2002; 88 (Suppl 1): S39-49. https://doi.org/10.1079/BJN2002628.
14. Gary D. Wu. Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. *Science (New York, N.Y.)*. Oct. 2011; 334 (6052): 105–08. https://doi.org/10.1126/science.1208344.
15. Erica D. Sonnenburg, *et al*. Diet-Induced Extinctions in the Gut Microbiota Compound over Generations. *Nature*. Jan. 2016; 529 (7585): 212–15. https://doi.org/10.1038/nature16504.
16. Liu Lu, and Gang Zhu. Gut-Brain Axis and Mood Disorder. *Frontiers in Psychiatry*. May 2018; 9: 223. https://doi.org/10.3389/fpsyt.2018.00223.
17. David R. Jacobs, and Linda C. Tapsell. Food Synergy: The Key to a Healthy Diet. *The Proceedings of the Nutrition Society*. May 2013; 72 (2): 200–06. https://doi.org/10.1017/S0029665112003011.
18. Derek M. Lin. Phage Therapy: An Alternative to Antibiotics in the Age of Multi-Drug Resistance. *World Journal of Gastrointestinal Pharmacology and Therapeutics*. Aug. 2017; 8 (3): 162–73. https://doi.org/10.4292/wjgpt.v8.i3.162.
19. Qimao Yang. Regulations of Phage Therapy across the World. *Frontiers in Microbiology*. Oct. 2023; 14. https://doi.org/10.3389/fmicb.2023.1250848.
20. Beatriz Gutiérrez, and Pilar Domingo-Calap. Phage Therapy in Gastrointestinal Diseases. *Microorganisms*. Sept. 2020; 8 (9): 1420. https://doi.org/10.3390/microorganisms8091420.
21. Carl Heneghan, *et al*. Why Clinical Trial Outcomes Fail to Translate into Benefits for Patients. *Trials*. Mar. 2017; 18 (1): 1–7, https://doi.org/10.1186/s13063-017-1870-2.
22. David Bars-Cortina, *et al*. Comparison between 16S rRNA and Shotgun Sequencing in Colorectal Cancer, Advanced Colorectal Lesions, and Healthy Human Gut Microbiota. *BMC Genomics*. July 2024; 25 (1): 1–20. https://doi.org/10.1186/s12864-024-10621-7.