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Systematic Review Article

ROLE OF THE MICROBIOTA–GUT–BRAIN AXIS IN PSYCHIATRIC DISORDERS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Psychiatric disorders are influenced by multiple genetic, environmental, and neurobiological factors. Recent evidence highlights the microbiota–gut–brain axis as an important communication pathway between the gut and brain through neural, immune, endocrine, and metabolic mechanisms. Altered gut microbiota has been linked to disorders such as depression, schizophrenia, anxiety and autism. This systematic review evaluates the role of the microbiota–gut–brain axis in psychiatric disorders and its therapeutic potential. The objective is to evaluate the role of the microbiota–gut–brain axis in psychiatric disorders, examine the mechanisms linking gut microbiota with brain function and behavior, assess the association of gut microbial alterations with conditions such as depression, schizophrenia, anxiety and autism and review the therapeutic potential of probiotics, prebiotics, and microbiota-targeted interventions in psychiatric disorders.

Materials and Methods: A systematic review followed PRISMA guidelines and search of published literature was conducted to evaluate the role of the microbiota–gut–brain axis in psychiatric disorders. Relevant articles were identified through electronic databases including PubMed, Google Scholar, Web of Science and Scopus using keywords gut microbiota, microbiota–gut–brain axis, depression, schizophrenia, anxiety, probiotics and psychiatric disorders. Studies published from January 2000 onwards were included. Studies published in English involving human or animal models were included. Relevant data regarding mechanisms, microbial alterations and therapeutic interventions were extracted and analysed narratively.

Results: The reviewed studies highlight a significant link between the microbiota–gut–brain axis and psychiatric disorders such as depression, anxiety and schizophrenia. Gut microbial alterations were associated with changes in mood, cognition, neurotransmitter regulation, inflammation, and stress responses. Probiotics, prebiotics, and dietary interventions showed potential therapeutic benefits. However, most evidence comes from animal studies and small human samples, emphasizing the need for larger mechanistic and longitudinal studies to validate microbiota-based therapies in psychiatry.

Conclusion: Current evidence suggests that the microbiota–gut–brain axis plays an important role in psychiatric and neurological disorders through immune, neural, endocrine and metabolic pathways. Gut microbial alterations have been linked to conditions such as depression, anxiety, schizophrenia and cognitive dysfunction, while probiotics and prebiotics show potential therapeutic benefits. However, larger longitudinal and mechanistic studies are needed to clarify causal relationships and develop effective microbiota-based therapies.

Keywords: Gut microbiota, Microbiota–gut–brain axis, Depression, Schizophrenia, Anxiety, Probiotics, Psychiatric disorders.

INTRODUCTION

Major depressive disorder (MDD) is difficult to manage due to complex genetic and environmental factors, and current brain-targeted treatments often have limited success. Recent research highlights the microbiota–gut–brain axis as an important pathway influencing mental health through mechanisms involving the Hypothalamic–Pituitary–Adrenal (HPA) axis, immune system, vagus nerve, and enteric nervous system. Although evidence is still emerging, gut microbiota may represent a potential target for future therapies and personalized treatment in psychiatric disorders (Wang IC et al., 2024).[1]

Patients with major depressive disorder (MDD) had lower levels of Bifidobacterium and Lactobacillus compared with healthy controls, with reduced bacterial counts more common among patients and associated with irritable bowel syndrome. Fermented milk intake was linked to higher Bifidobacterium levels. These findings suggest that decreased beneficial gut bacteria may contribute to MDD, though results should be interpreted cautiously due to potential dietary and gender influences (Aizawa E et al., 2016).[2]

Increasing research suggests that individuals with psychiatric conditions often exhibit alterations in gut microbiota, and intestinal dysbiosis may contribute to systemic inflammation, which has been implicated in the development and progression of these disorders (Góralczyk-Bińkowska A et al., 2022).[3]

Preclinical and clinical studies suggest that prebiotics, probiotics, and fecal microbiota transplantation (FMT) may influence neuropsychiatric disorders, highlighting the role of gut microbiota in their pathophysiology. However, further research on microbial metabolites such as short-chain fatty acids (SCFAs) and tryptophan derivatives is needed for better understanding of microbiota–gut–brain interactions and to develop targeted therapies (Generoso JS et al., 2021).[4]

Individuals with conditions such as depression, anxiety, autism spectrum disorder, psychotic disorders, eating disorders, and stress-related conditions show distinct microbial profiles compared with healthy controls. In particular, many psychiatric disorders are characterized by a reduction in fermentative bacteria that produce short-chain fatty acids (SCFAs) and an increase in pro-inflammatory microbial taxa. These microbial imbalances may contribute to inflammation and potentially worsen the progression of these disorders (Grau-Del Valle C et al., 2023).[5]

Jenkins TA et al. (2016) highlighted that reduced serotonin, often due to lowered tryptophan levels, is associated with depressed mood and cognitive impairments, particularly in individuals with underlying biological vulnerability. Tryptophan depletion negatively affects memory, reasoning, and emotional processing, whereas supplementation can enhance attention and cognition. The study also emphasized the role of gut microbiota in regulating tryptophan and serotonin metabolism, thereby influencing behavior and higher brain functions. These findings suggest that alterations in the gut microbiome may contribute to psychiatric conditions such as depression, anxiety, and autism, offering potential avenues for novel therapeutic strategies.[6]

Hulsken S et al. (2013) reported that while conventional treatments for mood disorders, such as selective serotonin reuptake inhibitors and monoamine oxidase inhibitors, enhance brain serotonin levels, they are often associated with side effects. As serotonin synthesis depends on dietary tryptophan, intake of tryptophan-rich foods (e.g., poultry, soy, cereals, fish, nuts and bananas) may help support mood and cognition. The study highlights an inverted U-shaped relationship, where both low and excessively high tryptophan levels can impair cognition, while moderate levels are beneficial. This pattern is observed in both healthy and vulnerable individuals, suggesting that dietary modulation of serotonergic pathways may offer a supportive approach to mental well-being.[7]

Zhuang M et al. (2024) highlighted the gut microbiome as a key regulator of health through the microbiota–gut–brain axis, a bidirectional system influencing brain and barrier functions via neural, immune, and metabolic pathways. They also emphasize multi-barrier regulation and lymphatic involvement, suggesting new therapeutic potential for neurological and gastrointestinal disorders.[8]

Petra AI et al. (2015) described the microbiota–gut–brain axis as a bidirectional system involving neural, immune, and metabolic pathways. Signals from the gut—via vagal fibers, cytokines, neurotransmitters, and metabolites—inform the central nervous system, while brain pathways, including the HPA axis and neuropeptides, influence gut microbiota composition. These interactions are implicated in inflammatory conditions such as mood disorders, autism, Attention-Deficit/Hyperactivity Disorder (ADHD), multiple sclerosis, and obesity.[9]

Grenham S et al. (2011) highlighted the microbiome as a crucial component of the brain–gut axis, influencing behavior, mood, and various CNS disorders. Emerging evidence suggests that targeting the microbiome may offer new therapeutic or preventive strategies, including probiotics and microbiota-derived metabolites. However, limitations remain in defining a "healthy" microbiome, understanding its mechanisms and establishing clinical applications. Further research and rigorous trials are needed to determine whether microbiome-based interventions can complement or replace conventional treatments.[10]

Rutsch A et al. (2020) highlighted the critical role of the gut microbiota in both health and disease, noting that dysbiosis can influence central nervous system function through the microbiota–gut–brain axis.

This bidirectional communication involves neural, immune and metabolic pathways and may lead to blood–brain barrier disruption and neuroinflammation when dysregulated. The authors emphasize the role of immune mechanisms, particularly the inflammasome pathway, in linking microbial signals to neuroinflammatory and neuropsychiatric conditions such as depression, anxiety and neurodegenerative diseases, although the precise mechanisms remain to be fully understood.[11]

Given the growing evidence linking alterations in gut microbiota with various psychiatric disorders, a systematic review is necessary to comprehensively evaluate the current literature and clarify the strength of this association. Synthesizing findings from existing studies may help identify consistent microbial patterns and underlying mechanisms involved in the microbiota–gut–brain axis.

Objectives

This systematic review aims to investigate the role of the microbiota–gut–brain axis in psychiatric disorders, explore the mechanisms through which gut microbiota influence brain function and behavior, evaluate the relationship between gut microbial alterations and disorders such as depression, schizophrenia, anxiety, autism and assess the therapeutic potential of probiotics, prebiotics and other microbiota-targeted interventions in psychiatric care.

MATERIALS AND METHODS

A systematic review followed PRISMA guidelines and search of published literature was conducted to evaluate the role of the microbiota–gut–brain axis in psychiatric disorders. Relevant articles were identified through electronic databases including PubMed, Google Scholar, Web of Science and Scopus using keywords gut microbiota, microbiota–gut–brain axis, depression, schizophrenia, anxiety, probiotics, and psychiatric disorders. Studies published from January 2000 onwards were included. Studies published in English involving human or animal models were included. Eligible studies included observational studies, randomized controlled trials, case studies, review articles, and meta-analyses. Articles without extractable data, lacked clear outcome measures or evaluable results, conference abstracts were excluded.

Titles, abstracts, and full texts were independently screened by two reviewers, with disagreements resolved through discussion. Data extraction and quality assessment were performed independently using standardized tools appropriate to study design. Data were extracted using a standardized format, and the findings were synthesized narratively.

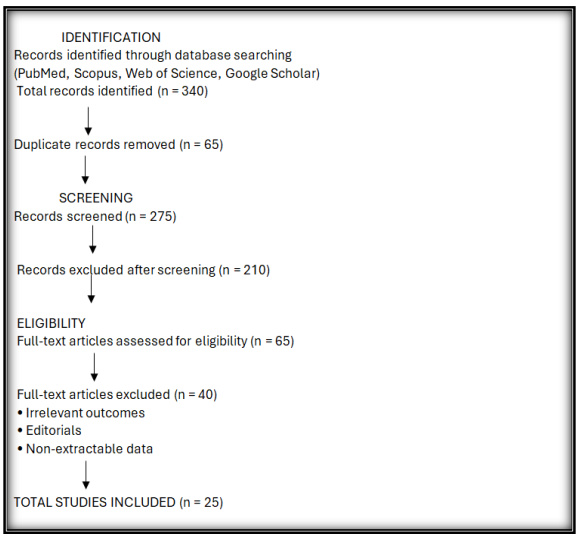

Figure 1: PRISMA flow diagram of study selection process

RESULTS

In a study by Jiang H et al., (2015) of 46 patients with major depressive disorder (29 active, 17 remitted) and 30 healthy controls, fecal analysis showed increased α-diversity in active MDD but not in remitted cases. Patients exhibited higher levels of Bacteroidetes, Proteobacteria, and Actinobacteria, with reduced Firmicutes. Notably, Enterobacteriaceae and Alistipes were elevated, while Faecalibacterium was decreased and inversely associated with symptom severity. These findings indicate a shift toward potentially harmful microbes and loss of beneficial bacteria in MDD, highlighting the microbiome's potential as a biomarker, though causal relationships require further investigation.[12]

Zhu J et al., (2021) reported that fecal microbiota profiles were broadly similar across participants, with Firmicutes, Bacteroidetes, and Proteobacteria predominating, and key genera including Faecalibacterium, Roseburia, and Prevotella. However, individuals with anxiety and depression showed a shift in dominant genera, with Prevotella replacing Faecalibacterium, along with reduced levels of Gemmiger, Ruminococcus, and Veillonella. Although alpha diversity was lower in affected individuals, the difference was not statistically significant, while beta diversity analysis demonstrated distinct microbial clustering. These findings indicate altered gut microbial patterns with potential clinical relevance, though further large-scale and mechanistic studies are needed.[13]

Kelly JR et al., (2016) studied 34 patients with major depression and 33 matched controls, assessing inflammatory markers, cortisol, tryptophan metabolism and gut microbiota composition. Depressed individuals showed reduced microbial richness and diversity. Notably, fecal microbiota transplantation from depressed patients into microbiota-deficient rats induced depression-like behaviors, including anhedonia and anxiety, along

with altered tryptophan metabolism. These findings support a potential causal role of the gut microbiota in depression and suggest it as a target for future therapies.[14]

Clarke G et al. (2013) demonstrated that gut microbiota play a crucial role in neurodevelopment and CNS signaling, particularly affecting the serotonergic system. Using germ-free animals, the study found increased hippocampal serotonin and its metabolite levels in males, along with elevated plasma tryptophan, suggesting a systemic pathway linking microbiota to brain function. These effects were sex-specific and persisted into adulthood even after later microbial colonization, indicating the importance of early-life microbiota. While behavioral changes like reduced anxiety were reversible, neurochemical alterations were not, highlighting a lasting impact of microbiota absence on brain function.[15]

Bosch JA et al. (2022) analyzed data from the HELIUS cohort (N = 3211) across six ethnic groups and found that gut microbiota diversity, both within and between individuals, is associated with depressive symptom severity after adjusting for demographic and clinical factors. These associations were consistent across ethnicities, although microbial variation partly explained differences in depression levels between groups. Key bacterial genera linked to depressive symptoms belonged to families such as Christensenellaceae, Lachnospiraceae, and Ruminococcaceae. Overall, the study supports a strong and generalizable link between gut microbiota and depression, with potential contributions to ethnic disparities in mental health.[16]

Ait-Belgnaoui A et al. (2014) demonstrated that in a water avoidance stress model, probiotic pretreatment reduced activation of the HPA axis and autonomic nervous system, decreased neuronal activity markers and prevented stress-induced impairment of hippocampal neurogenesis and synaptic plasticity. These effects were accompanied by improved gut barrier integrity, whereas Lactobacillus salivarius showed no benefit. The findings suggest that probiotics may counteract stress-related brain changes by modulating neurobiological pathways and gut function.[17]

Schaub AC et al. (2022) conducted a randomized controlled trial showing that short-term, high-dose probiotic supplementation as an add-on therapy led to a greater reduction in depression severity (Hamilton Depression Rating Scale) compared to placebo. The intervention maintained microbial diversity and increased Lactobacillus, which was associated with symptom improvement. Neuroimaging findings also demonstrated reduced putamen activation after probiotic treatment. These results support the role of the microbiota–gut–brain axis in depression and highlight probiotics as a potential therapeutic approach.[18]

Freijy TM et al. (2023) reported in a randomized controlled trial that a diet rich in prebiotic-containing whole plant foods improved mood, reduced anxiety and stress, and enhanced sleep in non-clinical adults. In contrast, the probiotic supplement showed limited benefit, and combining it with a high-prebiotic diet did not produce additional effects. These findings suggest dietary strategies may be more effective than specific probiotics for supporting mental well-being, although larger studies are needed.[19]

Table 1: Summary table of key findings of the included studies

Author (Year)	Key Findings
Jiang H et al. (2015)	Fecal analysis showed increased α-diversity in active MDD, with higher levels of Bacteroidetes, Proteobacteria, and Actinobacteria, reduced Firmicutes, elevated Enterobacteriaceae and Alistipes, and decreased Faecalibacterium inversely associated with symptom severity.
Zhu J et al. (2021)	Individuals with anxiety and depression showed altered gut microbial patterns, including Prevotella replacing Faecalibacterium and reduced Gemmiger, Ruminococcus, and Veillonella, with distinct microbial clustering on beta diversity analysis.
Kelly JR et al. (2016)	Depressed individuals showed reduced microbial richness and diversity, and fecal microbiota transplantation from depressed patients induced depression-like behaviors and altered tryptophan metabolism in microbiota-deficient rats.
Clarke G et al. (2013)	Gut microbiota influenced neurodevelopment and serotonergic signaling, with germ-free animals showing increased hippocampal serotonin and elevated plasma tryptophan, indicating lasting effects of early-life microbiota absence on brain function.
Bosch JA et al. (2022)	Gut microbiota diversity was associated with depressive symptom severity across multiple ethnic groups, with bacterial genera from Christensenellaceae, Lachnospiraceae, and Ruminococcaceae linked to depression.
Ait-Belgnaoui A et al. (2014)	Probiotic pretreatment reduced HPA axis activation, prevented stress-induced impairment of hippocampal neurogenesis and synaptic plasticity, and improved gut barrier integrity in a stress model.
Schaub AC et al. (2022)	High-dose probiotic supplementation reduced depression severity, maintained microbial diversity, increased Lactobacillus abundance, and reduced putamen activation on neuroimaging.
Freijy TM et al. (2023)	A diet rich in prebiotic-containing whole plant foods improved mood, reduced anxiety and stress, and enhanced sleep, while probiotic supplementation showed limited benefit.

CONCLUSION

The microbiota–gut–brain axis is a key regulator of brain function and homeostasis, influencing psychiatric and neurodegenerative disorders. Gut microbes communicate with the brain via immune, neural, and metabolic pathways, including tryptophan metabolism and microbial metabolites. Microbiota composition is shaped by early-life factors, stress and aging, and has been linked to conditions such as anxiety, autism and Alzheimer's disease. Emerging evidence highlights its role in neural processes and its potential as a target for novel therapies (Cryan JF et al., 2019).[20]

Yuan X et al. (2021) conducted a 24-week follow-up study in 107 first-episode, drug-naïve schizophrenia patients and 107 healthy controls. Patients showed reduced gut microbial diversity and distinct microbial composition at baseline. A microbiota-based model effectively differentiated patients from controls. Following risperidone treatment, microbial diversity increased toward normal levels. Specific genera, including Lachnoclostridium and Romboutsia, were associated with treatment response, suggesting that gut microbiota may serve as potential biomarkers for schizophrenia diagnosis and therapeutic outcomes.[21]

Reininghaus EZ et al. (2020) conducted a randomized placebo-controlled trial evaluating the multistrain probiotic Omnibiotic Stress Repair in individuals with depression over 28 days. Probiotic supplementation significantly altered gut microbial composition, increasing Ruminococcus gauvreauii and Coprococcus 3, bacteria associated with beneficial metabolic functions such as butyrate production. Although psychiatric symptoms improved in both probiotic and placebo groups, no significant difference in clinical outcomes or intestinal barrier marker levels was observed. Functional pathway analysis revealed enhanced inflammatory regulation and vitamin B metabolism, suggesting potential metabolic and anti-inflammatory effects of probiotics in depression.[22]

Eva E. Fröhlich et al. (2016) showed that antibiotic-induced gut dysbiosis impaired recognition memory in mice and altered microbial metabolites, brain signalling pathways and HPA axis activity. Since antibiotics were absent in the brain, the findings support a causal role of the microbiota–gut–brain axis in cognition and brain function.[23]

Kauê Felipe Lami et al. (2021) reported that the microbiota–gut–brain axis plays a significant role in neurological and psychiatric disorders through neural, endocrine, and immune pathways. However, larger human studies are needed to clarify the underlying mechanisms and multifactorial influences.[24]

Toader C et al. (2024) concluded that the gut microbiota plays an important role in psychiatric disorders, and microbiota-targeted therapies such as probiotics and prebiotics may support mental health treatment. However, further research is needed to clarify mechanisms and therapeutic effectiveness.[25]

Overall, current evidence strongly suggests that the microbiota–gut–brain axis plays an important role in the development and progression of psychiatric and neurological disorders through immune, neural, endocrine, and metabolic mechanisms. Alterations in gut microbiota composition have been associated with conditions such as schizophrenia, depression, anxiety, autism, and cognitive dysfunction, while microbiota-targeted interventions including probiotics and prebiotics show promising therapeutic potential. However, most existing studies are based on animal models or limited human populations. Therefore, further large-scale, longitudinal, and mechanistic studies are required to better understand causal pathways, identify reliable microbial biomarkers, and develop effective microbiota-based therapies for psychiatric disorders.

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