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THE ROLE OF GUT BRAIN AXIS IN PSYCHIATRIC DISORDERS NARRATIVE REVIEW

Narrative review

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ABSTRACT

Background: The gut–brain axis, a bidirectional communication system between the gastrointestinal tract and the central nervous system, has gained increasing attention for its potential role in the pathogenesis and management of psychiatric disorders such as depression and anxiety. Alterations in gut microbiota composition and function have been linked to neuroinflammation, hypothalamic–pituitary–adrenal axis dysregulation, and changes in neurotransmitter metabolism, making this a promising yet evolving area in mental health research.

Objective: This narrative review explores the emerging role of gut microbiota and the gut–brain axis in the development, progression, and management of depression and anxiety, with an emphasis on recent findings, clinical implications, and research gaps.

Main Discussion Points: Key themes include evidence of microbial dysbiosis in psychiatric populations, mechanistic pathways linking microbiota to brain function, psychobiotic and dietary interventions, and the heterogeneity of clinical outcomes. Limitations such as small sample sizes, short follow-up durations, methodological biases, and lack of standardized outcome measures are critically evaluated.

Conclusion: Current evidence suggests that microbiota–gut–brain interactions contribute to psychiatric pathophysiology and hold potential as adjunctive therapeutic targets. However, stronger, multicenter randomized controlled trials with standardized methodologies are required before clinical integration. Recognizing and addressing current research limitations will be essential for translating microbiome science into effective mental health interventions.

Keywords: Gut–brain axis, Depression, Anxiety, Gut microbiota, Psychobiotics, Narrative review.

INTRODUCTION

The gut–brain axis, a bidirectional communication system linking the gastrointestinal tract and the central nervous system via neural, endocrine, immune, and metabolic pathways, has emerged as a key determinant of mental health (1). This axis is modulated significantly by the gut microbiota, a diverse community of microorganisms residing in the human intestine, which exerts influence over brain function and behavior through mechanisms including immune signaling, vagal nerve activation, and the production of neuroactive metabolites (2). Psychiatric disorders, particularly depression and anxiety, represent a substantial global health burden, with the World Health Organization estimating that over 280 million people suffer from depression and over 300 million from anxiety disorders worldwide (3). These conditions collectively contribute to a significant proportion of disability-adjusted life years (DALYs), reduced quality of life, and increased healthcare costs (4). Despite decades of research and the availability of pharmacological and psychotherapeutic interventions, treatment efficacy remains limited, with many patients experiencing incomplete remission or relapse, highlighting the urgent need for novel etiological insights and therapeutic strategies (5).

Over the past decade, evidence from clinical and preclinical studies has increasingly pointed toward the gut microbiota as a potential modulator of psychiatric conditions. Systematic reviews have reported consistent, though heterogeneous, alterations in gut microbial composition in individuals with major depressive disorder (MDD), generalized anxiety disorder (GAD), bipolar disorder, and schizophrenia (6). For instance, a meta-analysis of 44 case–control studies, encompassing over 2,500 psychiatric cases and 2,400 controls, demonstrated characteristic dysbiosis patterns—often involving reduced microbial diversity and depletion of short-chain fatty acid (SCFA)-producing taxa, alongside enrichment of pro-inflammatory species (7). While the specific bacterial taxa implicated vary between studies, a recurring theme is the imbalance between anti-inflammatory and pro-inflammatory microbiota profiles in affected individuals (8).

Animal studies have provided critical mechanistic insights into how gut dysbiosis may influence brain function and behavior. Rodent models of stress-induced depressive-like behavior have revealed that alterations in microbial metabolites, such as tryptophan derivatives and SCFAs, are associated with neuroinflammation, altered neurotransmitter synthesis, and hypothalamic–pituitary–adrenal (HPA) axis hyperactivity (9). Experimental manipulation of the gut microbiota—through probiotics, antibiotics, or fecal microbiota transplantation—has been shown to modulate these behavioral and neurochemical changes, suggesting potential causal relationships (10). Importantly, germ-free mice colonized with microbiota from patients with depression or anxiety often exhibit increased anxiety-like or depressive-like behaviors, providing further support for a transmissible microbiome-related component to psychiatric vulnerability (11).

Human intervention studies targeting the gut microbiota—through probiotics (psychobiotics), prebiotics, dietary interventions, and, in rare cases, fecal microbiota transplantation—are an emerging area of research. While preliminary trials have reported modest improvements in mood and anxiety symptoms with certain probiotic strains, such as *Lactobacillus* and *Bifidobacterium*, the overall evidence remains inconclusive due to small sample sizes, short intervention durations, and methodological variability (12). Systematic reviews of psychobiotic interventions highlight the heterogeneity in outcomes and emphasize the need for larger, well-controlled randomized clinical trials to clarify efficacy and identify optimal microbial targets (13).

Despite this growing body of literature, significant research gaps remain. First, the majority of human studies are cross-sectional, limiting causal inference. Longitudinal cohort studies tracking microbiota changes preceding the onset of psychiatric symptoms are scarce (14). Second, the precise mechanistic pathways—whether immune, neuroendocrine, metabolic, or neural—by which microbial signals influence brain circuits remain incompletely understood (15). Third, potential confounding factors, such as diet, medication use, comorbidities, and lifestyle, are inconsistently controlled for, contributing to variability in reported microbial associations (16). Moreover, much of the microbiota–psychiatric disorder research has been conducted in high-income countries, raising questions about the generalizability of findings across diverse populations and dietary patterns (17).

The objective of this narrative review is to synthesize recent evidence on the role of the gut–brain axis and gut microbiota in the development and progression of psychiatric disorders, focusing particularly on depression and anxiety. This review will cover mechanistic findings from animal models, human observational studies, and early interventional research from the last five years. Controlled clinical trials, case–control studies, and mechanistic experiments are prioritized, with emphasis on studies elucidating microbial composition changes, functional metabolic outputs, and their links to psychiatric symptomatology.

By consolidating available evidence, this review seeks to bridge the gap between basic science discoveries and their clinical relevance. Understanding gut microbiota alterations in psychiatric disorders may open the door to biomarker development, enabling earlier diagnosis and targeted interventions. Furthermore, therapeutic strategies aimed at modulating the gut microbiota—whether via diet, probiotics, prebiotics, or other microbiome-based modalities—represent a promising adjunct to conventional psychiatric treatments.

Ultimately, this review underscores the growing recognition that the gut–brain axis represents not merely a peripheral curiosity, but a central player in the pathophysiology of mood and anxiety disorders. Addressing the research gaps through rigorously designed studies will be essential to translating microbiome science into actionable psychiatric interventions (18).

THEMATIC DISCUSSION:

1. Altered Microbial Diversity and Composition in Depression and Anxiety

Emerging evidence consistently reports reduced microbial richness and diversity in individuals with depression and generalized anxiety disorder (GAD), accompanied by enrichment of pro-inflammatory taxa and depletion of anti-inflammatory, short-chain fatty acid-producing bacteria (19, 20). Large multi-omics analyses confirm these associations, though variability exists across populations and sequencing platforms (20). These compositional shifts are thought to predispose to neuroinflammation and HPA-axis dysregulation.

2. Psychobiotic Interventions and Clinical Outcomes

Randomized clinical trials using *Bifidobacterium breve* CCFM1025 in patients with major depressive disorder showed significant reductions in depressive symptoms and normalization of tryptophan metabolism and HPA-axis markers (21). Another RCT incorporating a high-dose probiotic adjunct in MDD demonstrated improvements in mood alongside measurable changes in gut microbiota and brain functional markers (22). Collectively, these trials underscore the potential of psychobiotics as adjunctive treatments for depressive disorders.

3. Stress Reduction via Psychobiotic Diets

Dietary interventions styled as psychobiotic diets—rich in fiber, fermented foods, and probiotic sources—have been trialed in healthy adults. One study found that a 4-week intervention reduced perceived stress by 32% vs. 17% in controls, although biological stress markers remained unchanged (23). These diets also modulated fecal lipids and urinary tryptophan metabolites, and individuals with more stable microbial profiles experienced greater stress reduction. This highlights a link between diet, microbiota metabolic function, and stress resilience.

4. Heterogeneity in Probiotic Effects: Population and Lifestyle Factors

A placebo-controlled trial in healthy adults reported no significant effect of probiotics on anxiety or emotional regulation—but did find that lifestyle behaviors moderated any potential probiotic benefit (24). A broader human meta-study concluded that probiotics can ameliorate symptoms of anxiety, depression, and stress in clinical populations, though effects are inconsistent and often modest in otherwise healthy individuals (25). These findings highlight heterogeneity in response based on diagnosis, baseline microbiota, and lifestyle context.

5. Conceptual and Mechanistic Advances

Recent reviews and bibliometric analyses reinforce that research on microbiota–gut–brain axis in anxiety disorders remains emergent, with rising interest in mechanistic pathways such as vagal signaling and immune modulation (26). Modeling studies elucidate how microbial metabolites like SCFAs may signal via the vagus nerve to influence central neurotransmission and stress pathways—a novel mechanistic paradigm still under clinical investigation (27). Together, these conceptual advances are shaping precision-targeted microbiome interventions.

Gaps and Controversies

Despite consistent trends, the literature contains notable gaps. Most human trials remain small and short-term, limiting generalizability. Findings in healthy versus clinical populations diverge, reflecting variable baseline microbiota and lifestyle contexts. Causal inference remains weak without large, longitudinal cohort studies. Mechanistic pathways such as SCFA-vagal signaling remain theoretically plausible but insufficiently validated in humans. Further, the optimal probiotic strain, dose, and treatment duration remain unclear.

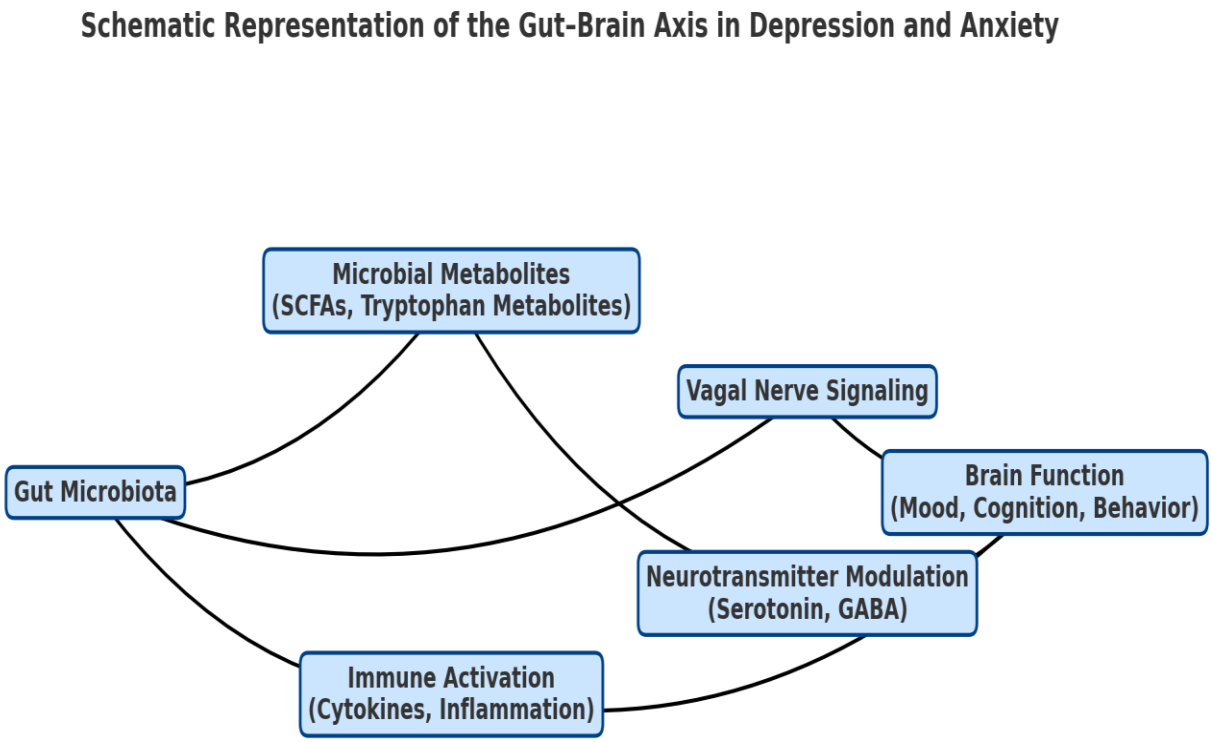

Table 1: Summary of Key Studies on Gut–Brain Axis in Psychiatric

Author & Year	Study Type	Population	Intervention/Focus	Key Findings
McGuinness et al., 2022	Systematic review	MDD, bipolar disorder, schizophrenia patients	Microbiota composition differences	Consistent dysbiosis patterns across disorders
Cao et al., 2025	Systematic review	Patients with depression and anxiety	Gut microbiota variation	Depression and anxiety associated with inflammatory taxa enrichment
Tzikos et al., 2025	Randomized controlled trial	MDD patients	Bifidobacterium breve CCFM1025 + antidepressants	Improved depressive symptoms and tryptophan metabolism
Schaub et al., 2022	Randomized controlled trial	MDD patients	Probiotic add-on therapy	Mood improvement and microbial/neural changes
Berding et al., 2023	Randomized controlled trial	Healthy adults	Psychobiotic diet	Reduced perceived stress vs. control
Morales-Torres et al., 2023	Randomized controlled trial	Healthy adults	Probiotic supplementation + lifestyle factors	Lifestyle moderated probiotic effect on anxiety
Johnson et al., 2025	Meta-analysis	Clinical and healthy populations	Probiotics and mental health outcomes	Probiotics modestly reduced symptoms in clinical groups
Butler et al., 2025	Narrative review	Patients with anxiety disorders	Gut microbiome–anxiety link mechanisms	Mechanistic pathways identified but require validation

Table 2: Mechanistic Pathways Linking Gut Microbiota to Psychiatric Disorders

Mechanism	Key Molecules / Pathways	Supporting Evidence	Clinical Relevance
Immune Activation	Cytokines (IL-6, TNF-α), microglial activation	Elevated inflammatory markers in MDD and anxiety; microbiota shifts promote inflammation	Targeting inflammation may improve psychiatric symptoms
Neuroendocrine Modulation	HPA-axis regulation, cortisol release	Gut dysbiosis linked to HPA-axis hyperactivity in stress-related disorders	Probiotics may normalize stress hormone levels
Metabolic Pathways	Short-chain fatty acids (butyrate, propionate)	SCFAs influence neurogenesis, neurotransmission	Dietary fiber and SCFA-producing bacteria may enhance mental health

Mechanism	Key Molecules / Pathways	Supporting Evidence	Clinical Relevance
Neurotransmitter Synthesis	Serotonin, GABA, dopamine	Gut bacteria synthesize or modulate neurotransmitters	Psychobiotics can alter brain neurotransmitter balance
Neural Signaling	Vagal nerve activation	Probiotic strains shown to activate vagal pathways in animal models	Potential non-pharmacological modulation of mood

CRITICAL ANALYSIS AND LIMITATIONS:

Existing literature on the gut–brain axis in psychiatric disorders shows several notable limitations that temper confidence in current findings. Many human studies suffer from small sample sizes, including randomized psychobiotic trials and observational cohorts with fewer than 50 participants. Such small cohorts limit statistical power and raise concerns about the reliability of reported effects (28). Furthermore, few randomized controlled trials (RCTs) exist, and those that do often have short follow-up durations—commonly four to eight weeks—making it difficult to assess long-term clinical outcomes (29). These design weaknesses undermine causal inference and restrict conclusions regarding therapeutic efficacy.

Methodological quality is also a concern. Several studies lack adequate blinding, leading to potential performance bias, while selection criteria often exclude patients with severe or comorbid psychiatric conditions, introducing selection bias and reducing representativeness (30). Additionally, studies rarely control for dietary habits, medication use, and lifestyle variables, all of which influence both gut microbiota and mental health, acting as substantial confounding factors (31). In some cases, interventions involve multiple components (e.g., diet, exercise, probiotics), yet their individual contributions are rarely disentangled.

Publication bias remains an under-explored issue. Positive trials demonstrating symptom improvement with probiotics or dietary interventions are more likely to be published, whereas null or negative results may remain unpublished. This selective reporting skews the literature toward overstating potential benefits (32). The lack of registered trials with full protocol transparency exacerbates concerns about unpublished negative data.

Another major limitation lies in variability of measurement outcomes. Studies differ widely in outcome metrics, ranging from self-report scales (e.g., Beck Depression Inventory) to biomarker panels or neuroimaging endpoints, making direct comparisons difficult. Differences in microbial sequencing platforms, taxonomic resolution, and bioinformatic pipelines further impede cross-study synthesis (33).

Finally, the generalizability of findings is often restricted. The majority of studies are conducted in high-income countries with specific dietary cultures, limiting applicability to populations with differing microbiota baselines or environmental exposures (34). Moreover, few studies include diverse age ranges, ethnicities, or socio-economic backgrounds, making it unclear whether observed associations hold across broader demographic groups.

Collectively, the limitations in study design—including small samples, short durations, and limited RCTs—compounded by methodological biases, publication bias, outcome variability, and narrow population scope, highlight the need for more rigorous, standardized, and inclusive research to definitively elucidate the gut–brain axis in psychiatric illness.

IMPLICATIONS AND FUTURE DIRECTIONS:

Emerging evidence linking gut microbiota and psychiatric disorders carries several implications for clinical practice. Treatment decisions may increasingly consider adjunctive strategies that target the gut–brain axis, such as incorporating specific psychobiotic formulations

(35). Clinicians might begin to assess dietary patterns, gastrointestinal symptoms, and stress-related gut disturbances as integral aspects of mental health evaluation.

At the policy level, the evidence—which remains emerging and heterogeneous—calls for the development of clinical guidelines that define appropriate use of microbiome-modulating interventions in psychiatry (36). Such guidelines would help standardize selection of probiotic strains, dosing regimens, and treatment durations, and clarify criteria for recommending microbiome-based adjuncts in routine care.

Several unanswered questions persist, and key research gaps should inform future investigations. It remains unclear which microbial taxa reliably correlate with depressive or anxiety symptomatology across diverse populations (37). The long-term safety and durability of psychobiotic therapies also warrant interrogation, especially in vulnerable groups such as adolescents, elderly individuals, or those with comorbid medical conditions. Furthermore, the relative contribution of diet, lifestyle, and medication confounders remains incompletely understood.

To address these gaps, future research should adopt rigorous methodological designs. Large-scale, multicenter randomized controlled trials with longer follow-up (six months to one year) are needed (38). Stratification by baseline microbiota profile or clinical subtype may help clarify who benefits most. Trials should integrate multimodal outcome assessments—combining clinical scales, microbiome sequencing, metabolomic profiling, and neuroimaging—to elucidate mechanistic pathways. Standardization of microbiome analysis methods and open-data sharing will enhance comparability across studies.

Policy-makers and funding agencies should incentivize registration of psychobiotic trials with pre-specified endpoints and full protocol transparency, to mitigate publication bias (39). Additionally, engagement with regulatory bodies could pave the way for approved psychobiotic products intended for mental health indications, subject to demonstration of safety, consistency, and efficacy.

Taken together, the review underscores that incorporation of gut–brain axis considerations into clinical decision-making could enhance personalized approaches to psychiatric care. Policy and guideline development are timely given expanding evidence, but must await stronger trials. Future research should be expansive, well-powered, and mechanistically informed in order to translate microbiome science into effective, safe, and scalable mental health interventions (40).

CONCLUSION:

The current synthesis highlights that the gut–brain axis plays a potentially significant role in the pathophysiology of depression and anxiety, with evidence pointing toward consistent microbial alterations, mechanistic links through immune, metabolic, and neuroendocrine pathways, and emerging benefits from microbiota-targeted interventions. While these findings are compelling, the strength of evidence remains moderate due to small, heterogeneous studies, limited randomized controlled trials, and variability in methodologies. For clinicians, awareness of the gut–brain connection can inform a more holistic approach to patient assessment and management, incorporating dietary counseling and consideration of emerging psychobiotic strategies as adjuncts. For researchers, the priority lies in conducting large, multicenter, mechanistically informed trials with standardized protocols to clarify causality, identify responsive patient subgroups, and establish safety and efficacy parameters. Moving forward, sustained interdisciplinary collaboration and methodological rigor will be essential to translate this promising field into reliable, evidence-based strategies for improving psychiatric care.

AUTHOR CONTRIBUTION

Author	Contribution
Rabbia Fatima*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Maryam Khan Sherwani	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Seema Habib Bhutto	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Kiran Naz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Iram Saddiqa Aamir	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Maria Rashid	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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