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THE GUT–BRAIN AXIS AND PSYCHOBIOTICS: IMPLICATIONS FOR MENTAL HEALTH – A NARRATIVE REVIEW

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ABSTRACT

Background: The gut–brain axis has emerged as a key regulatory network linking intestinal microbiota with central nervous system activity. Increasing evidence suggests that gut dysbiosis contributes to the pathophysiology of depression and anxiety disorders through mechanisms involving neuroinflammation, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, impaired intestinal barrier integrity, altered tryptophan metabolism, and abnormal microbial metabolite production.
Aim: This review aimed to summarize the current evidence regarding the role of the gut–brain axis and psychobiotics in mental health, with particular emphasis on mechanistic pathways and recent clinical studies.
Material and methods: A narrative review of the literature indexed in PubMed, Scopus, and Web of Science from 2019 to 2026 was conducted. Particular attention was given to randomized controlled trials, meta-analyses, mechanistic studies, and recent reviews on psychobiotics, gut microbiota, depression, anxiety, neuroinflammation, and precision psychiatry.
Results: Current evidence indicates that selected psychobiotic strains, particularly Lactobacillus and Bifidobacterium species, may improve depressive and anxiety symptoms by modulating inflammatory cytokines, microglial activation, vagus nerve signaling, short-chain fatty acid synthesis, and serotonin precursor metabolism. Clinical studies have suggested modest but clinically relevant improvements in mood, cognitive function, stress response, and sleep quality following psychobiotic supplementation. Synbiotic therapy and Mediterranean dietary interventions may further enhance therapeutic outcomes.
Conclusions: The gut–brain axis is a promising target in modern psychiatry. Although psychobiotics may constitute a valuable adjunctive strategy for treating depressive and anxiety disorders, further large-scale standardized clinical studies are necessary to establish strain-specific efficacy, optimal treatment duration, and clinically applicable biomarkers.

KEYWORDS

Psychobiotics, Gut–brain Axis, Depression, Anxiety, Microbiota, Neuroinflammation

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1. Introduction

Depressive and anxiety disorders remain among the leading causes of disability worldwide and constitute major global public health challenges [1]. According to the World Health Organization, depressive disorders affect more than 280 million individuals globally, whereas anxiety disorders are estimated to affect over 300 million people [2]. Despite the widespread use of pharmacotherapy and psychotherapy, a substantial proportion of patients fail to achieve remission or experience only partial improvement after standard treatments [3]. Delayed therapeutic onset, adverse effects, and treatment-resistant depression continue to pose significant clinical challenges.

In recent years, increasing scientific attention has been directed toward the gut–brain axis, a complex bidirectional communication system linking the gastrointestinal tract, intestinal microbiota, immune system, endocrine pathways, and central nervous system [4]. The intestinal microbiome participates in neurotransmitter synthesis, immune modulation, maintenance of intestinal barrier integrity, and metabolic signaling. Consequently, disturbances in gut microbiota composition may influence emotional regulation, stress responsiveness, cognition, and behavior [5].

The human gastrointestinal tract contains approximately 10^{14} microorganisms, including bacteria, viruses, fungi, and Archaea. The dominant bacterial phyla are Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria [6]. Several bacterial strains produce neuroactive compounds, such as γ-aminobutyric acid (GABA), serotonin precursors, dopamine metabolites, acetylcholine, and short-chain fatty acids (SCFAs), which may directly or indirectly influence brain function [7].

Experimental and clinical studies have increasingly suggested that gut dysbiosis contributes to the pathogenesis of depression and anxiety disorders [8]. Patients with depression often demonstrate reduced microbial diversity, increased intestinal permeability, elevated inflammatory cytokine levels, altered tryptophan metabolism, and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [9]. Furthermore,

chronic psychological stress may negatively alter the microbiota composition, creating a bidirectional pathological cycle [10].

The concept of psychobiotics was introduced by Dinan et al. as live microorganisms that confer mental health benefits through interactions with the gut–brain axis [11]. Currently, the term is frequently expanded to include pre-, syn-, and postbiotics and dietary interventions capable of modulating microbiota composition and function [12].

Recent studies have demonstrated that selected psychobiotic strains may reduce depressive symptoms, improve cognitive performance, modulate inflammatory pathways, decrease cortisol concentrations, and enhance brain-derived neurotrophic factor (BDNF) expression [13–15]. However, the available evidence remains heterogeneous, partly due to strain-specific effects, methodological variability, and differences in patient populations.

Research Objective. This review aimed to summarize the current evidence regarding the role of the gut–brain axis and psychobiotics in depression and anxiety disorders.

Research Problems. Can modulation of the gut microbiota influence psychiatric symptoms and inflammatory pathways associated with depression and anxiety disorders?

Research Hypotheses. Psychobiotics may improve depressive and anxiety symptoms by modulating neuroinflammation, intestinal permeability, microbial metabolite production, vagus nerve signaling, and HPA axis activity.

2. Research Materials and Methods

2.1. Participants

The review included randomized controlled trials, meta-analyses, observational studies, and mechanistic studies that investigated the relationship between the gut microbiota, psychobiotics, and mental health outcomes.

2.2. Procedure / Test Protocol / Skill Test Trial / Measure / Instruments

A literature search was conducted using the PubMed, Scopus, and Web of Science databases between January 2019 and February 2026. Keywords included: “gut–brain axis”, “psychobiotics”, “microbiota”, “depression”, “anxiety”, “SCFA”, “HPA-axis”, “neuroinflammation”, “vagus nerve”, and “tryptophan metabolism”. Only articles published in English were included.

Priority was given to:

- randomized controlled trials,
- systematic reviews and meta-analyses,
- mechanistic experimental studies,
- recent publications from 2024–2026.

2.3. Data Collection and Analysis / Statistical Analysis

2.3.1. Statistical Software

No independent statistical calculations were performed. A narrative qualitative synthesis of the current evidence was conducted.

2.3.2. AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. **AI** were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

2.3.3. Statistical Methods

Narrative comparison of included studies was performed with emphasis on mechanistic pathways, psychobiotic strains, biomarkers, treatment duration, and clinical outcomes

3. Research Results

3.1. Neuroinflammation and Microglial Activation

One of the central mechanisms linking gut dysbiosis and psychiatric disorders is chronic low-grade neuroinflammation [16]. Altered intestinal permeability, frequently referred to as "leaky gut," allows the translocation of lipopolysaccharides (LPS), bacterial metabolites, and pro-inflammatory molecules into the systemic circulation [17]. These molecules activate peripheral immune pathways and stimulate microglial activation in the central nervous system.

Activated microglia release pro-inflammatory cytokines, including IL-1β, IL-6, TNF-α, and interferon-γ, which interfere with neurotransmitter metabolism and neuroplasticity [18]. Elevated inflammatory markers have consistently been observed in patients with major depressive disorder [19].

Several psychobiotic strains can attenuate neuroinflammatory signaling. Lactobacillus rhamnosus, Bifidobacterium longum, and Lactobacillus plantarum have demonstrated anti-inflammatory effects by modulating NF-κB signaling and reducing pro-inflammatory cytokines [20–22].

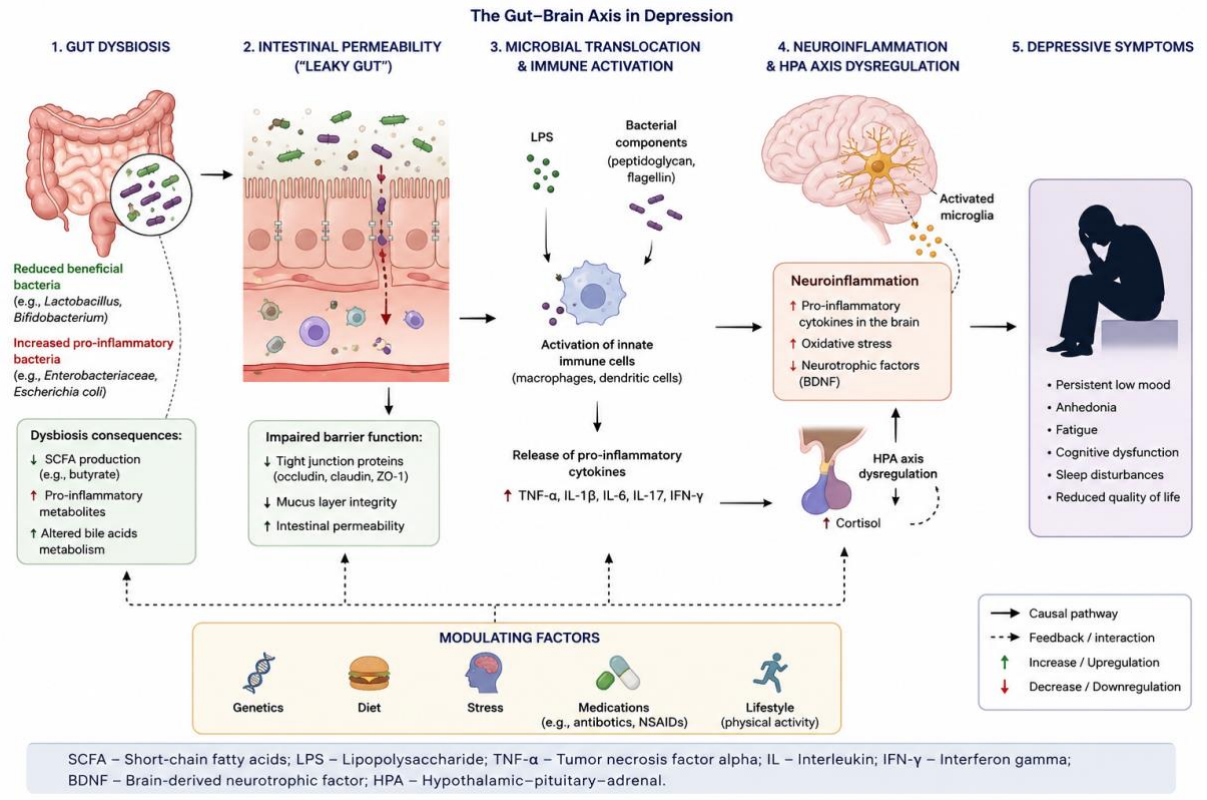


Fig. 1. *Mechanisms linking gut dysbiosis, intestinal permeability, neuroinflammation, and depressive symptoms.*

Source: own elaboration based on [16–22].

Recent evidence also indicates that gut-derived metabolites influence mitochondrial function and oxidative stress pathways in neurons [23]. Mitochondrial dysfunction may impair neuronal energy metabolism and contribute to emotional dysregulation.

3.2. HPA-Axis Dysregulation and Stress Response

The hypothalamic–pituitary–adrenal (HPA) axis is one of the principal communication pathways between the gut and brain [24]. Chronic stress induces excessive cortisol release, which negatively affects hippocampal neurogenesis, intestinal barrier integrity, and microbiota composition [25].

Patients with depression frequently demonstrate hyperactivation of the HPA axis and elevated cortisol concentrations [26]. Animal studies suggest that germ-free mice exhibit exaggerated stress responses that normalize after colonization by the microbiota [27].

Selected psychobiotic strains may modulate the HPA-axis activity. Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 were associated with reduced cortisol levels and improved stress resilience [28]. Similar effects have been observed for Lactobacillus casei and Bifidobacterium breve in stress-related models [29].

The vagus nerve appears to play a major role in this process. Experimental studies have indicated that psychobiotic-induced behavioral effects are partially abolished after vagotomy, suggesting direct gut-to-brain neural signaling [30].

3.3. Short-Chain Fatty Acids and Microbial Metabolites

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are bacterial metabolites produced through the fermentation of dietary fiber [31]. SCFAs participate in immune regulation, maintenance of intestinal barrier integrity, microglial maturation, and epigenetic modulation [32].

Butyrate is particularly important because of its anti-inflammatory and neuroprotective properties [33]. It acts as a histone deacetylase inhibitor and may enhance BDNF expression, neuroplasticity, and hippocampal function [34].

Reduced abundance of SCFA-producing bacteria, particularly Faecalibacterium prausnitzii and Roseburia species, has been identified in patients with depressive disorders [35]. Mediterranean dietary patterns rich in fiber, polyphenols, omega-3 fatty acids, and fermented foods appear to increase SCFA production and microbial diversity [36].

Table 1. Selected bacterial strains and metabolites associated with psychobiotic effects.

Bacterial strain	Major metabolites	Proposed mechanisms	Potential psychiatric effects
Lactobacillus rhamnosus	GABA	vagus nerve modulation	anxiolytic effects
Bifidobacterium longum	SCFAs	anti-inflammatory effects	reduction of stress symptoms
Lactobacillus plantarum	serotonin precursors	kynurenine pathway modulation	cognitive improvement
Faecalibacterium prausnitzii	butyrate	intestinal barrier support	anti-inflammatory activity
Bifidobacterium breve	acetate	immune modulation	reduction of depressive symptoms

Source: own elaboration based on [20–36].
Notes: GABA – γ-aminobutyric acid; SCFAs – short-chain fatty acids.

3.4. Tryptophan Metabolism and the Kynurenine Pathway

Tryptophan metabolism is another major pathway linking the gut microbiota to mental health [37]. Tryptophan serves as a precursor for serotonin synthesis; however, inflammatory activation shifts metabolism toward the kynurenine pathway [38].

Increased kynurenine production may lead to the accumulation of neurotoxic metabolites, such as quinolinic acid, which contributes to glutamatergic excitotoxicity and neuroinflammation [39]. Elevated kynurenine-to-tryptophan ratios have been observed in depressive disorders [40].

Certain psychobiotics may modulate tryptophan metabolism. Lactobacillus plantarum 299v and Bifidobacterium infantis have the potential to reduce kynurenine concentrations and improve cognitive function in patients with depression [41,42].

Furthermore, microbial metabolites may activate aryl hydrocarbon receptors (AhR), influencing immune homeostasis and neuroinflammatory pathways [43]. This interaction has recently emerged as a promising area of research in precision psychiatry.

3.5. Clinical evidence and psychobiotic supplementation

Recent randomized controlled trials and meta-analyses suggest that psychobiotic supplementation may provide modest but clinically meaningful improvements in depressive and anxiety symptoms [44–47].

The most frequently investigated strains include:

- Lactobacillus helveticus,
- Lactobacillus rhamnosus,
- Lactobacillus plantarum,
- Bifidobacterium longum,
- Bifidobacterium breve.

The treatment duration in most studies ranged from 4 to 12 weeks [48]. Clinical improvement is generally observed after approximately 4–8 weeks of continuous supplementation.

Synbiotic formulations combining probiotics with prebiotic substrates may demonstrate superior efficacy compared to probiotics alone because of improved bacterial colonization and metabolic support [49].

Table 2. Selected recent clinical studies evaluating psychobiotics in depression and anxiety disorders.

Author	Year	Population (n)	Intervention	Duration	Primary outcome	Main findings
Tian et al.	2022	MDD patients (n=45)	Bifidobacterium breve CCFM1025	4 weeks	Depression severity	Significant reduction in depressive symptoms and modulation of tryptophan metabolism
Haghighat et al.	2021	Adults with depression (n=110)	Synbiotic supplementation	12 weeks	Depression score, BDNF	Improved depressive symptoms and increased BDNF levels
Schneider et al.	2023	MDD patients (n=61)	Vivomixx formulation	4 weeks	Cognitive performance	Improvement in cognitive function and attention
Huang et al.	2023	Meta-analysis (14 studies)	Various probiotics	Variable	Depression and anxiety scores	Moderate improvement in depressive symptoms
Nikolova et al.	2024	Meta-analysis	Gut microbiota studies	Variable	Psychiatric outcomes	Confirmed associations between dysbiosis and psychiatric disorders
Malard et al.	2025	Narrative review	Psychobiotics	Variable	Mental health outcomes	Highlighted strain-specific therapeutic effects and need for biomarker-guided treatment

Source: own elaboration based on references [13,14,15,44–46].

Abbreviations: MDD – major depressive disorder; BDNF – brain-derived neurotrophic factor.

However, clinical responses to these agents are highly heterogeneous. Some studies failed to demonstrate statistically significant improvements compared with placebo, emphasizing the importance of strain specificity and patient selection [50].

3.6. Enteric nervous system, vagal pathway, and neuroplasticity

Beyond metabolic and immune pathways, direct neural interaction between the gut and the central nervous system plays a fundamental role in mood regulation [4, 5]. The enteric nervous system (ENS), often termed the "second brain," operates via an intricate network of neurons embedded in the gastrointestinal wall [4]. The vagus nerve serves as the primary neuroanatomical bridge, transmitting sensory signals directly from the gut lumen to the solitary tract nucleus in the brainstem, which subsequently projects to limbic structures including the amygdala and hippocampus [5, 7, 30].

Furthermore, gut microbiota composition directly influences brain-derived neurotrophic factor (BDNF) expression—a key regulator of synaptic plasticity, neuronal survival, and hippocampal neurogenesis [13, 18, 34]. Depressive disorders are frequently associated with reduced hippocampal BDNF levels and impaired neuroplasticity [3, 28]. Interventions with specific psychobiotic strains, as well as synbiotic formulations, have been shown to restore hippocampal BDNF expression, thereby supporting neuroplasticity and enhancing responsiveness to conventional psychiatric pharmacotherapy [14, 28, 49].

3.7. Drug-microbiome interactions and lifestyle determinants

The interaction between the intestinal microbiome and psychiatric interventions is inherently bidirectional [8, 10, 13]. Psychotropic medications, including selective serotonin reuptake inhibitors (SSRIs) and antipsychotics, exhibit antimicrobial properties that can alter gut bacterial composition and diversity [1, 3, 13]. Conversely, intestinal bacteria can metabolize psychotropic drugs, altering their bioavailability, therapeutic efficacy, and side-effect profile [7, 13, 51].

Lifestyle factors also exert a substantial influence on gut barrier integrity and microbial equilibrium [10, 17, 36]. Chronic psychological stress, irregular circadian rhythms, sleep deprivation, and diets high in ultra-processed foods exacerbate intestinal permeability ("leaky gut") and dysbiosis [9, 10, 17, 25]. Addressing these metabolic and lifestyle determinants alongside psychobiotic administration may provide a more comprehensive framework for managing mood disorders [36, 49].

4. Discussion

The gut–brain axis has become one of the most intensively investigated concepts in modern psychiatry. Current evidence suggests that the gut microbiota may influence emotional regulation through multiple interconnected pathways involving inflammation, neurotransmitter metabolism, neuroendocrine signaling, and microbial metabolite production [4,16].

One of the most clinically relevant observations is the consistent association between depressive disorders and systemic inflammation markers. Elevated cytokine levels, increased intestinal permeability, and altered microbial diversity have been reported repeatedly across multiple studies [18,19]. However, the exact causal relationship remains difficult to establish.

The available evidence concerning psychobiotics is promising but heterogeneous. Several randomized clinical trials have demonstrated improvements in depressive symptoms following supplementation with selected Lactobacillus and Bifidobacterium strains [44–47]. However, other studies have failed to replicate these findings [50]. This discrepancy may result from substantial differences in probiotic composition, dosage, treatment duration, dietary patterns, baseline microbiota composition, and severity of psychiatric symptoms.

An important limitation of current psychobiotic research is the strain-specific nature of its therapeutic effects. Not all probiotics possess psychobiotic properties, and findings associated with one bacterial formulation cannot be generalized to others [11,12]. Furthermore, many studies are limited by their small sample sizes and short intervention periods.

Another rapidly developing field is precision psychiatry and microbiome-derived biomarkers. Future studies should identify specific microbial signatures associated with treatment response, inflammatory phenotypes, and cognitive dysfunction [51]. Such approaches could facilitate personalized psychobiotic interventions.

Dietary modulation also appears to be clinically relevant. Mediterranean-style dietary patterns rich in fiber, fermented foods, omega-3 fatty acids, and polyphenols may support microbial diversity and SCFA

production [36]. Therefore, psychobiotics should likely be viewed as part of a broader microbiota-centered therapeutic strategy rather than isolated supplementation.

Although psychobiotics have favorable safety profiles, their clinical implementation requires caution. However, the standardization of strains, dosing regimens, treatment duration, and diagnostic biomarkers remains insufficient. Large multicenter randomized trials are still needed before psychobiotics can become a routine component of psychiatric treatment.

4.1. Precision Psychiatry and Microbiome-Based Biomarkers

A major challenge in contemporary biological psychiatry is patient heterogeneity [3, 11, 50]. Current clinical data demonstrate variable responses to psychobiotic interventions, largely due to baseline individual differences in gut microbiota composition, dietary habits, and systemic inflammatory profiles [11, 12, 36, 50]. Precision psychiatry aims to overcome these limitations by integrating high-throughput metagenomic sequencing and metabolomic profiling to identify specific microbially derived biomarkers [46, 51]. Establishing baseline microbial signatures—such as ratios of short-chain fatty acid producers or specific inflammatory bacterial markers—could allow clinicians to predict which patient subgroups are most likely to benefit from targeted psychobiotic or synbiotic therapies [1, 35, 46, 51].

4.2. Limitations of Current Evidence

Despite the growing interest in psychobiotics and the gut–brain axis, several limitations should be acknowledged. First, substantial heterogeneity exists among available studies regarding psychobiotic strains, dosages, treatment duration, patient populations, and outcome measures. Second, many clinical trials include relatively small sample sizes and short intervention periods, limiting the generalizability of findings. Third, most currently available evidence focuses on depressive and anxiety symptoms rather than long-term psychiatric outcomes. Furthermore, differences in baseline microbiota composition, dietary habits, concomitant medications, and lifestyle factors may significantly influence treatment response. Finally, although mechanistic studies provide important biological insights, causal relationships between microbiota alterations and psychiatric disorders remain incompletely understood. Future large-scale multicenter randomized controlled trials with standardized methodologies are required to establish clinically applicable recommendations.

Several critical limitations must be taken into account when interpreting current evidence [11, 46, 50]. First, a significant portion of mechanistic understanding originates from preclinical animal models, such as germ-free mice, which do not fully replicate human gut physiology, complex microbial ecosystems, or psychiatric symptom phenotypes [7, 27, 30]. Second, clinical translation is hindered by a lack of standardization in product manufacturing and clinical protocols [12, 48]. Commercial probiotic formulations vary widely in strain viability, colony-forming unit (CFU) counts, storage stability, and gastrointestinal survival [11, 12, 48]. Finally, since psychobiotic effects are strictly strain-specific, findings from one clinical strain cannot be extrapolated to other strains within the same species [11, 46]. Long-term, large-scale multicenter trials with rigorous biomarker monitoring remain necessary to establish optimal dosages, delivery vehicles, and treatment durations [46, 50].

5. Conclusions

The gut–brain axis constitutes a complex bidirectional communication network that is significantly involved in emotional regulation and psychiatric disorders.

Current evidence indicates that gut dysbiosis, neuroinflammation, HPA-axis dysregulation, impaired intestinal barrier integrity, altered SCFA production, and abnormal tryptophan metabolism may contribute to the pathophysiology of depression and anxiety disorders.

Selected psychobiotic strains have demonstrated potential therapeutic benefits through the modulation of inflammatory pathways, neurotransmitter synthesis, vagus nerve signaling, and neuroplasticity. Nevertheless, the efficacy of psychobiotics appears to be strain-specific and remains incompletely standardized.

Future research should focus on precision psychiatry approaches, microbiome-derived biomarkers, standardized clinical protocols, and large-scale randomized controlled trials.

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