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Review

Role of the Gut Microbiota in Anxiety and Mental Health Regulation: A Comprehensive Review

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ABSTRACT:

The gut microbiota has emerged as an important contributor to mental health through its bidirectional communication with the central nervous system via the microbiota gut brain axis. Dysbiosis has increasingly been associated with anxiety, depression, and other neuropsychiatric disorders, although the causal nature of these associations remains under investigation. The MGB axis operates through multiple interconnected pathways, including neural (vagus nerve, enteric nervous system), endocrine (hypothalamic–pituitary–adrenal axis), immune (cytokine signaling), and metabolic (short-chain fatty acids, tryptophan metabolites, bile acids) mechanisms. Emerging evidence from preclinical and clinical studies have reported compositional changes in the gut microbiota is characterized by reductions in *Lactobacillus*, *Bifidobacterium*, and butyrate-producing genera alongside elevations in pro-inflammatory taxa are have frequently been associated with heightened anxiety and depressive symptomatology. Therapeutic modulation of the gut microbiota through psychobiotics, prebiotics, synbiotics, dietary interventions, and fecal microbiota transplantation (FMT) has emerged as a promising adjunctive approach, although clinical evidence remains heterogeneous. This review systematically synthesizes current evidence on the mechanistic underpinnings of the gut–brain axis in anxiety and mental health regulation, evaluates the therapeutic landscape of microbiota-targeted interventions, and identifies critical gaps requiring further investigation in the context of personalized psychiatry.

Keywords:
Gut microbiota; microbiota–gut–brain axis; anxiety; depression; psychobiotics; dysbiosis; short-chain fatty acids; tryptophan; HPA axis; neuroinflammation

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1. Introduction

Mental health disorders, particularly anxiety and depression, represent a formidable global public health challenge. According to the World Health Organization, an estimated 280 million people worldwide suffer from depression, and anxiety disorders rank among the most prevalent psychiatric conditions globally **(Głaz et al., 2023).** Despite significant advances in pharmacological and psychotherapeutic interventions, remission rates remain unsatisfactory, underscoring the urgent need for novel therapeutic paradigms **(Bautista, 2025**). The limitations of conventional antidepressant and anxiolytic therapies including drug resistance, systemic side effects, and poor blood–brain barrier permeability have catalyzed interest in alternative and complementary approaches **(Jafari, 2025).**

Over the past two decades, a paradigm shift has occurred in our understanding of the biological substrates of mental illness. The gut microbiota has increasingly been recognized as a potential modulator of brain function and behavior **(Sasso et al., 2023).** The human gastrointestinal tract harbors up to 10^{14} microbial cells, encompassing nearly 1,000–1,500 bacterial species alongside diverse fungal and viral communities **(Luqman et al., 2024; Wilczek et al., 2023).** This complex ecosystem, collectively termed the gut microbiota, engages in continuous bidirectional communication with the CNS through what is now designated the microbiota–gut–brain (MGB) axis **(Dziedzic et al., 2024; Dziedziak et al., 2025).**

Dysbiosis may alter signaling along the microbiota gut brain axis, leading to alterations in microbial composition and function that influence neuronal activity, immunity, and intestinal inflammation **(Dziedzic et al., 2024).** Emerging evidence suggests an connection between microbiota alterations and neurological and psychiatric disorders, including depression, anxiety, autism spectrum disorder (ASD), schizophrenia, bipolar disorder, and neurodegenerative diseases **(Dziedziak et al., 2025)**. The MGB axis is proposed to function not merely a passive conduit but an active regulatory network through which microbial communities modulate neurotransmitter synthesis, neuroendocrine signaling, immune activation, and metabolic homeostasis **(Bautista, 2025; Singh et al., 2022).**

This review aims to provide a comprehensive, systematic synthesis of the current evidence on the role of the gut microbiota in anxiety and mental health regulation. We examine the structural and functional architecture of the MGB axis, delineate the key mechanistic pathways through which gut microbiota influence brain function, review the microbial signatures associated with anxiety and depressive disorders, and evaluate the therapeutic potential of microbiota-targeted interventions. Special attention is given to quantitative and statistical evidence from clinical and preclinical studies, as well as emerging concepts such as circadian regulation of the gut–brain axis and precision psychiatry.

2. The Microbiota–Gut–Brain Axis: Structural and Functional Architecture

2.1 Overview and Bidirectionality

The MGB axis constitutes a complex, bidirectional communication network linking the gut, its resident microbiota, and the brain **(Dziedzic et al., 2024)**. This axis is thought to integrate neural, endocrine, immune, and metabolic signals to maintain homeostasis across multiple physiological systems **(Dziedziak et al., 2025).** The bidirectional nature of this communication implies

that the state of the gut microbiota may influence brain function and behavior, while the brain, through its neural properties, reciprocally influences gut function, motility, secretion, and microbial community structure **(Sasso et al., 2023; Wilczek et al., 2023).**

The gut–brain axis (GBA) is mediated through multiple direct and indirect pathways, including: (1) neural routes involving the enteric nervous system (ENS), vagus nerve, and spinal nerves; (2) neuroendocrine signaling, primarily via the hypothalamic–pituitary–adrenal (HPA) axis; (3) immune mechanisms involving cytokines such as IL-1β, IL-6, and TNF-α; and (4) microbiota-derived metabolites and neuroactive compounds, including short-chain fatty acids (SCFAs), neurotransmitters, vitamins, and tryptophan metabolites **(Dziedziak et al., 2025).** The brain can influence the structure and function of gut microbiota through the autonomic nervous system by regulating gut motility, intestinal transit, secretion, and gut permeability **(Sasso et al., 2023)**. The principal signaling pathways of the microbiota–gut–brain axis and their respective roles in neuropsychiatric regulation are summarized in Table 1.

The microbiota gut brain axis provides a useful conceptual framework for understanding communication between the gastrointestinal tract and the central nervous system. However, many mechanistic pathways remain incompletely understood, particularly in humans.

Most current knowledge is derived from experimental animal models, whereas direct evidence demonstrating equivalent mechanisms in clinical populations remains limited. Future studies integrating microbiome profiling with functional neuroimaging, metabolomics, and longitudinal clinical assessment are needed to clarify the relative contribution of each signaling pathway to psychiatric disorders. As illustrated in **Figure 1**, communication occurs through multiple interconnected pathways rather than a single linear mechanism.

2.2 The Enteric Nervous System and Vagus Nerve

The ENS, often referred to as the "gut brain," comprises an extensive network of neurons embedded within the gastrointestinal wall and is considered important in regulating stress and gastrointestinal activity. The ENS interacts closely with the gut microbiota, which includes neurotransmitter-producing bacteria capable of synthesizing GABA, serotonin, dopamine, and norepinephrine **(Mosquera et al., 2024).** The vagus nerve is considered one of the principal communication pathways between the gut and the brain, conveying microbial-derived chemicals and influencing brain function and behavior **(Almahal et al., 2025).**

Microbial metabolites are proposed to influence neurotransmitter production such as serotonin, GABA, and glutamate is influenced by the binding of microbial metabolites to specific receptors in vagal sensory neurons **(Dziedzic et al., 2024)**. Increased vagal activation occurs with probiotic supplementation; for example, with *Lactobacillus johnsonii* La1 and *Bifidobacterium infantis* and vagotomy has been shown to prevent the restorative effect of probiotics on anxiety in animal models. Specifically, vagotomy prevented the anxiolytic effects of *B. longum* NCC3001 and *L. rhamnosus* JB-1 in rodent studies, directly implicating the vagus nerve as a key mediator in the gut–brain axis **(Bear et al., 2021).**

Experimental evidence strongly supports the involvement of vagal signaling in microbiota brain communication. Nevertheless, direct assessment of vagal activity in human psychiatric disorders remains technically challenging. Consequently, the contribution

of neural signaling relative to endocrine, immune, and metabolic mechanisms remains uncertain. Future studies combining electrophysiological measurements with microbiome analyses may help clarify these relationships. The neural pathways highlighted in **Figure 1** emphasize the central role of vagal communication within the microbiota gut brain axis.

2.3 The Hypothalamic–Pituitary–Adrenal Axis

The HPA axis is considered a major neuroendocrine pathway through which the gut microbiota modulates stress responses and emotional regulation. Adrenocorticotropic hormone (ACTH) stimulates the adrenal glands to synthesize gluco-corticosteroid hormones (stress hormones), such as cortisol or corticosterone **(Chudzik et al., 2021).** Acting systemically, Stress hormones may increase intestinal permeability of tight junctions and thus increase the permeability of the intestinal barrier, leading to bacterial translocation, which causes HPA axis response and immune activation **(Chudzik et al., 2021).** Preclinical studies demonstrate that germ-free or dysbiotic states exaggerate HPA reactivity, remodel synaptic plasticity, and induce anxiety- and depression-like behaviors **(Bautista, 2025)**.

Exaggerated waking cortisol is a biomarker of emotional disturbances such as depression **(Cerdó et al., 2017).** Psychobiotics have been reported to improve symptoms in some studies by reducing inflammation, restoring gut permeability, restoring blood–brain barrier (BBB) integrity, modulating neurotransmitters, regulating the HPA axis, and raising SCFA levels **(Singh et al., 2022).** Some probiotics impair the HPA tension feedback, which controls mood and emotion, resulting in reduced corticosteroid levels **(Ugwu, 2025).** The integrated and bidirectional nature of microbiota–gut–brain communication across neural, endocrine, immune, and metabolic domains is illustrated in **Figure 1**. The intestinal microbiota communicates with the central nervous system through interconnected neural, endocrine, immune, and metabolic pathways while intestinal barrier integrity regulates the systemic exposure to microbial products. Disruptions in microbial homeostasis may alter signaling to brain regions involved in emotional regulation and cognition, potentially contributing to anxiety, depression, stress related disorders, and cognitive dysfunction. Communication is bidirectional, with central nervous system activity also influencing gut physiology and microbial composition. The figure summarizes the principal mechanisms discussed throughout this review and serves as a conceptual framework rather than a representation of a single biological pathway.

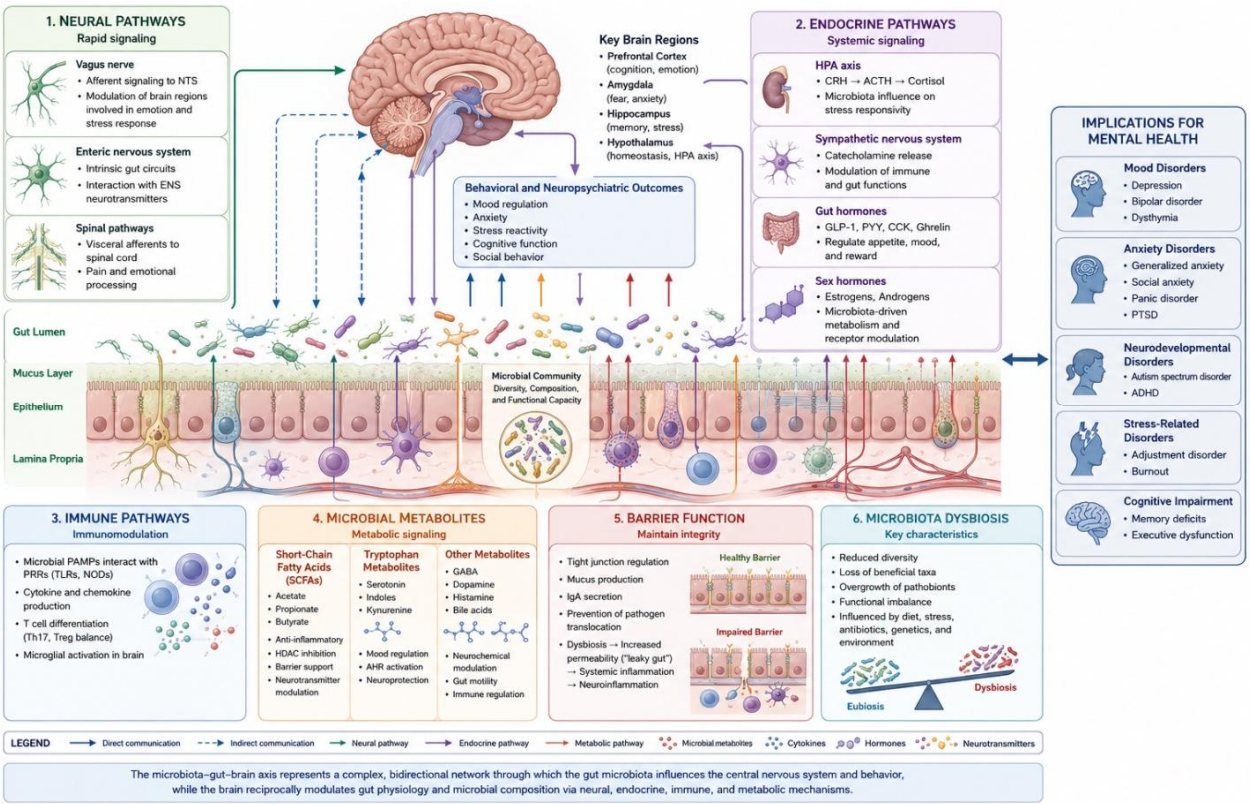
Although experimental models consistently demonstrate interactions between the gut microbiota and the hypothalamic pituitary adrenal axis, human evidence remains less consistent. Variability in stress exposure, lifestyle, medication use, and endocrine assessment contributes to conflicting findings across studies. These factors should be considered when interpreting the relationship between microbial composition and stress related disorders.

Table 1. Major signaling pathways of the microbiota–gut–brain axis with representative mechanisms and supporting references.

Pathway	Key Components	Mechanisms	Neuropsychiatric Impact	Key References

Neural	Vagus nerve, ENS	Microbial metabolites activate vagal afferents; neurotransmitter signaling (GABA, serotonin)	Anxiety modulation, behavioral changes	**Dziedzic et al., 2024; Almahal et al., 2025**
Endocrine	HPA axis (CRH, ACTH, cortisol)	Stress-induced cortisol alters gut permeability and microbiota composition	Stress disorders, depression	**Chudzik et al., 2021; Bautista, 2025**
Immune	Cytokines (IL-6, TNF-α, IL-1β)	Peripheral inflammation → BBB signaling → microglial activation	Neuroinflammation, mood dysregulation	**Randeni & Xu, 2025; Dziedziak et al., 2025**
Metabolic	SCFAs, tryptophan metabolites	SCFAs regulate epigenetics; tryptophan metabolism affects serotonin/kynurenine balance	Cognitive and emotional regulation	**Singh et al., 2022; Zeppa et al., 2022**
Barrier Integrity	Tight junctions, intestinal epithelium	Dysbiosis → increased permeability ("leaky gut") → LPS translocation	Systemic inflammation, anxiety	**Dziedzic et al., 2024; Mosquera et al., 2024**

Figure 1. Integrated overview of the microbiota gut brain axis and its proposed role in mental health.



2.4 Immune Pathways and Neuroinflammation

The gut microbiota may contribute to immune regulation, shaping inflammatory responses within the brain and orchestrating complex interactions that modulate immune responses, promote tolerance to commensal microorganisms, and contribute to the maintenance of immune homeostasis. A resilient and diverse gut microbiome is indispensable for robust immune function and appropriate immunoregulatory mechanisms **(Dziedzic et al., 2024).**

The gut–brain axis is mediated through immune mechanisms involving cytokines such as IL-1β, IL-6, and TNF-α **(Dziedziak et al., 2025).** Inflammatory cytokines produced within the gut may cross the BBB or signal through the vagus nerve to affect brain functions, influencing the development of mood disorders such as depression. Dysbiosis has been associated with increased intestinal permeability known as "leaky gut," which allows bacterial endotoxins to enter the bloodstream and induce systemic inflammation; this inflammation can then impact brain function and behavior. Dysbiosis also compromises intestinal barrier integrity, allowing endotoxins like lipopolysaccharide (LPS) to enter the bloodstream and trigger systemic inflammation, which may promote microglial activation; the brain's immune cells leading to neuroinflammation, a hallmark of neuropsychiatric disorders **(Randeni & Xu, 2025).**

Immune signaling represents one of the most plausible biological links between gut dysbiosis and psychiatric disorders. However, inflammatory markers are influenced by numerous environmental and clinical factors, making it difficult to isolate microbiota specific effects. Large prospective studies are required to determine whether immune alterations precede or follow changes in microbial composition.

3. Gut Microbiota Composition and Dysbiosis in Anxiety and Depression

3.1 Microbial Diversity and Mental Health

The composition of the gut microbiota is influenced by factors such as diet, age, lifestyle, and inflammatory status. A stable and diverse microbiota plays a crucial role in regulating metabolic and immune processes within the human body. In recent years, scientists have discovered a bidirectional communication between the gut microbiota and the brain, termed the gut microbiota–brain axis, and have demonstrated that disturbances in this ecosystem are associated with psychiatric and neurological diseases **(Wilczek et al., 2023).**

Multi-omics studies consistently demonstrate that microbial signatures in anxiety and depression are mirrored by metabolic shifts; reduced SCFAs, indoles, and serotonin precursors alongside elevated kynurenine pathway metabolites that converge to impair neurotransmitter balance and promote chronic neuroinflammation. Clinically, many patients with depression and anxiety also present with gastrointestinal comorbidities, highlighting the translational relevance of the microbiota–gut–brain axis **(Bautista, 2025).**

3.2 Dysbiosis Patterns in Anxiety and Depressive Disorders

Dysbiosis in major depressive disorder (MDD) is frequently characterized by reductions in butyrate-producing genera and elevations in pro-inflammatory taxa, which have been linked to neuroinflammation, impaired neurotransmitter synthesis, and HPA axis dysregulation **(Abidin et al., 2025).** Changes in the

composition of the gut microbiota are associated with conditions such as depression, schizophrenia, bipolar disorder, ASD, attention deficit hyperactivity disorder (ADHD), and neurodegenerative diseases such as Parkinson's and Alzheimer's **(Dziedziak et al., 2025).**

A landmark study demonstrated that fecal microbiota transplantation (FMT) from patients with major depression into germ-free rats induced alterations in tryptophan metabolism, anhedonia, and anxiety-like behavior, supporting a potential mechanistic link, gut microbiota composition to depressive-like symptoms **(Westfall & Pasinetti, 2019).** Similarly, when fecal samples from depressed people were transplanted into mice, an increase in fecal acetate and total SCFA concentrations was found along with increases in depression-like behavior **(Bear et al., 2021).** These findings provide experimental evidence supporting a causal contribution in animal models for the role of the gut microbiota in mental health regulation.

Several studies have reported that reduced abundance of GABA-producing taxa is associated with heightened amygdala reactivity and anxiety-like behavior, whereas probiotic supplementation that increases microbial GABA production correlates with decreased behavioral despair and reduced physiological stress markers in preclinical and clinical settings. In depressive phenotypes, dysbiosis diverts tryptophan away from 5-HT synthesis toward the kynurenine pathway, contributing to anhedonia and low mood; restoration of eubiotic communities or targeted psychobiotics increases 5-HT–related signaling and tracks with symptom improvement **(Bautista, 2025).** A consolidated overview of microbial compositional changes and their functional implications in anxiety and depressive disorders is presented in Table 2.

Table 2: Major Gut Microbiota, Biological Functions, and Proposed Roles in Anxiety and Mental Health

Gut Microbial Taxon	Principal Biological Function	Major Bioactive Metabolites	Proposed Mechanism in the Microbiota Gut Brain Axis	Clinical Associations	Representative References
Lactobacillus spp.	Carbohydrate fermentation; maintenance of intestinal homeostasis	GABA, lactate	Modulation of vagal signaling, neurotransmitter synthesis, and stress responses	Frequently reduced in anxiety and depression; commonly investigated as psychobiotics	**Bravo et al. (2011); Cryan et al. (2019); Liu et al. (2019)**
Bifidobacterium spp.	SCFA production; immune regulation	Acetate	Strengthens intestinal barrier, modulates immune responses, regulates emotional behavior	Reduced abundance reported in depressive disorders; therapeutic potential demonstrated in clinical trials	**Kelly et al. (2016); Ng et al. (2018); Liu et al. (2019)**
Faecalibacterium prausnitzii	Anti inflammatory activity	Butyrate	Suppresses inflammatory signaling, promotes	Frequently depleted in major depressive disorder	**Jiang et al. (2015); Dalile et al. (2019)**

			intestinal integrity		
Akkermansia muciniphila	Mucin degradation	Acetate, propionate	Maintains mucus layer and epithelial integrity	Reduced abundance associated with metabolic dysfunction and some psychiatric cohorts	**Cryan et al. (2019); Mayer et al. (2015)**
Roseburia spp.	Fermentation of dietary fiber	Butyrate	Anti inflammatory and neuroprotective functions	Reduced abundance associated with dysbiosis	**Dalile et al. (2019); Foster et al. (2017)**
Prevotella spp.	Complex carbohydrate metabolism	SCFAs	Influences host metabolism and immune regulation	Variable findings depending on dietary pattern and population	**Foster et al. (2017); Cryan et al. (2019)**

3.3 Specific Microbial Taxa and Psychiatric Outcomes

Among the most frequently studied psychobiotic bacteria are genera such as *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Streptococcus*, and *Enterococcus*, which influence the MGB axis through the production of SCFAs, neurotransmitters, and other bioactive metabolites. The predominant psychobiotic strains identified in systematic reviews belong to *Lactobacillus* (45.5%) and *Bifidobacterium* (29%) genera **(Śliwka et al., 2025).** *Lactobacillus* and *Bifidobacterium* are known to enhance serotonin synthesis and have been linked to reduced depressive symptoms. Individuals with depression have significantly altered gut microbiota composition, indicating that tryptophan-derived metabolites are impacted by gut microbiota diversity **(Abidin et al., 2025). Chojnacki et al. (2022)** reported altered tryptophan metabolism in depressive patients with small intestinal bacterial overgrowth (SIBO), showing increased urinary kynurenine and quinolinic acid levels alongside decreased tryptophan and kynurenic acid, suggesting enhanced activation of the neurotoxic kynurenine pathway. Additionally, SIBO patients scored higher on depression and anxiety scales (Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale) compared to controls **(Dziedziak et al., 2025)**. Clinical investigations consistently report associations between microbial alterations and psychiatric disorders. However, considerable heterogeneity exists across cohorts with respect to microbial composition, sequencing methodology, dietary patterns, medication exposure, and geographic variation. These methodological differences likely contribute to inconsistent findings and limit reproducibility. Animal studies provide strong mechanistic evidence supporting a role for the gut microbiota in behavioral regulation. Nevertheless, rodent models do not fully reproduce the complexity of human psychiatric disorders, including psychosocial influences, genetic diversity, and environmental exposures. Consequently, caution is warranted when extrapolating experimental findings directly to clinical practice.

4. Mechanistic Pathways: How Gut Microbiota Regulate Anxiety and Mental Health

4.1 Neurotransmitter Modulation

4.1.1 Serotonin and Tryptophan Metabolism

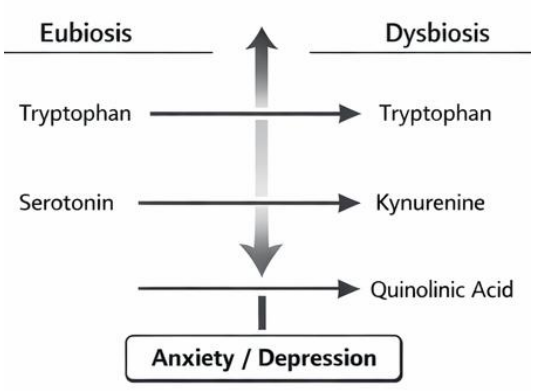
The gut microbiota is an abundant source of differentiated metabolites that serve as a chemical toolbox in the communication between the intestines and CNS *via* GBA pathways. These include tryptophan, γ-aminobutyric acid (GABA), histamine, serotonin, SCFAs, 5-hydroxytryptamine (5-HT), dopamine, and acetylcholine (ACh) **(Dziedzic et al., 2024).**

Approximately 90% of the body's serotonin is produced in the gut, and the gut microbiota contributes to the regulation in regulating this production **(Zeppa et al., 2022)**. Spore-forming bacteria have been shown to enhance serotonin production by up-regulating tryptophan hydroxylase 1 (TPH1) in enterochromaffin cells **(Abidin et al., 2025).** Approximately 10–20% of the tryptophan allocated toward serotonin development will directly pass through the BBB, initiating serotonin synthesis in the brain. The remaining tryptophan is metabolized along the kynurenine pathway, which forms several metabolites important for the pathophysiology of depression **(Westfall & Pasinetti, 2019).**

The activation of the kynurenine pathway may reduce tryptophan availability bioavailability for serotonin production and modulates brain functions, influencing neuropsychiatric disorders like depression **(Zeppa et al., 2022).** Inflammatory pathways, particularly the kynurenine pathway activated by cytokines like IL-6, divert tryptophan from serotonin synthesis toward neurotoxic metabolites contributing to depression **(Abidin et al., 2025).** Pro-inflammatory cytokines can affect serotonin concentration through activation of the kynurenine pathway, reducing levels of tryptophan and serotonin and exacerbating symptoms of affective disorders **(Mosquera et al., 2024).**

In germ-free and antibiotic-induced microbiota-depleted mice, despite increased circulating tryptophan levels, serotonin and kynurenine availabilities were decreased, suggesting that gut microbiota modulated kynurenine metabolism **(Cerdó et al., 2017).** Dysregulation of tryptophan metabolites due to dysbiosis has been associated to psychiatric disorders, including depression. Experimental evidence suggests that SCFAs, primarily butyrate, influence the activity of the enzyme indoleamine 2,3-dioxygenase (IDO), may reduce kynurenine production and help to alleviate neuroinflammation **(Almahal et al., 2025).** The main metabolites of tryptophan produced by gut microbiota are tryptamine and indolic compounds that can reach distant organs, including the brain. Indole has been proposed to contribute in the gut–brain axis; an accumulation of this molecule in the brain led to mood disorders and anxiety in animal models. Other microbial indolic derivatives from tryptophan catabolism exert anti-inflammatory action, suppressing CNS inflammation **(Zeppa et al., 2022).** The divergence of tryptophan metabolism under eubiotic and dysbiotic conditions and its implications for neuropsychiatric outcomes are depicted in Figure 3.

Figure 2. Divergent metabolic pathways of tryptophan under eubiosis versus dysbiosis and their implications for serotonin availability and neurotoxicity.



Mathematically, the kynurenine-to-tryptophan ratio (KTR) serves as a quantitative biomarker of IDO enzyme activity and tryptophan catabolism:

$$KTR = \frac{Kynurenine}{Tryptophan} X\ 1000$$

Elevated KTR values are consistently observed in patients with depression and anxiety, reflecting enhanced IDO activation and reduced serotonin precursor availability **(Westfall & Pasinetti, 2019; Głaz et al., 2023)**. A bolus dose of resveratrol (5 g) in humans significantly reduced tryptophan levels 2.5 and 5 hours after treatment in healthy volunteers, resulting in a 1.33- and 1.30-fold increase in the kynurenine-to-tryptophan ratio, respectively **(Westfall & Pasinetti, 2019).**

4.1.2 GABA and GABAergic Signaling

GABA is the primary inhibitory neurotransmitter in the CNS, reducing neuronal excitability and playing a role in stress responses and mood regulation. Certain gut bacteria, including *Lactobacillus* and *Bifidobacterium* species, can produce GABA by converting glutamate, an excitatory neurotransmitter into GABA through the action of glutamate decarboxylase. GABAergic signaling in the brain is essential for regulating anxiety, stress, and mood, and the dysregulation of GABA production may contribute to psychiatric conditions such as depression and anxiety disorders **(Randeni & Xu, 2025).**

Depression and anxiety disorders are associated with decreased GABA levels in the brain. Among GABA-regulating bacteria, food-derived *Lactobacillus* strains such as *L. plantarum*, *L. paracasei*, *L. rhamnosus*, and *L. brevis* have been identified. **Yunes et al. (2020)** screened 135 human-derived *Bifidobacterium* and *Lactobacillus* strains for their ability to produce GABA, identifying significant inter-strain variability in GABA-producing capacity **(Chudzik et al., 2021).** Reduced abundance of GABA-producing taxa is associated with heightened amygdala reactivity and anxiety-like behavior **(Bautista, 2025).**

4.1.3 Dopamine and Other Neurotransmitters

Distinct gut microbial species affect host physiology by producing diverse neuromolecules involved in mood regulation. *Lactobacillus* and *Bifidobacterium* spp. generate GABA, while other bacterial species contribute to the synthesis of dopamine, norepinephrine, and acetylcholine **(Cerdó et al., 2017; Dziedziak et al., 2025).** Bacterial metabolites produced by gut microbiota such as GABA, acetylcholine, serotonin, and norepinephrine may influence synaptic signaling and play a crucial role in mood and behavior regulation. These neurotransmitters modulate signaling pathways of the local ENS and then the gut–brain axis **(Jach et al., 2023).**

4.2 Short-Chain Fatty Acids (SCFAs) and Neuroactive Metabolites

SCFAs, including acetate, propionate, and butyrate, are metabolites produced by a healthy gut microbiota during the fermentation of dietary fibers and resistant starch. These SCFAs play a crucial role in immune modulation. Butyrate, in particular, is thought to influence the gut–brain axis, potentially by enhancing colonic serotonin production, a key neurotransmitter involved in mood and behavior regulation **(Abidin et al., 2025).**

Experimental studies suggest that certain SCFAs may influence blood brain barrier integrity, although their direct penetration into the human brain remains incompletely understood. **(Singh et al., 2022).** Butyrate can cross the BBB and produce a dose-dependent

increase in neuronal and glial nuclear histone H3 acetylation in mice due to its potential to inhibit histone deacetylation **(Cerdó et al., 2017)**. Gut bacteria also produce SCFAs such as butyrate, which contribute to maintenance of intestinal barrier integrity, reduce systemic inflammation, and promote proper serotonergic signaling in the CNS **(Dziedziak et al., 2025).**

In male mice, daily oral supplementation of SCFAs (67.5 mmol acetate, 25 mmol propionate, and 40 mmol butyrate) decreased stress-related increases in anxiety-like behaviors in the open field test, and increased sucrose preference and decreased urine sniffing; both markers of depression-like behavior. The SCFA supplement was associated with changes in gene expression in the brain related to dopamine receptors, part of the mesolimbic reward pathway, which can be altered in depression. Prebiotic supplementation in mice increased SCFA concentrations, many of which were negatively correlated with depression-like and anxiety-like behaviors **(Bear et al., 2021).**

Metabolites produced by the gut microbiota can significantly influence the brain–gut axis. For example, SCFAs like butyrate, produced by the microbiota, inhibit histone deacetylases, supporting memory and neural plasticity. Butyrate may have mood-stabilizing effects in rodent models, such as reducing depressive-like behavior induced by chronic psychosocial stress and reversing anhedonia and sociability impairments **(Dziedziak et al., 2025).**

Short chain fatty acids represent one of the best characterized classes of microbiota derived metabolites. Despite compelling experimental evidence, the extent to which circulating concentrations influence human brain function remains uncertain. Standardized metabolomic analyses may improve understanding of their clinical relevance.

4.3 Brain-Derived Neurotrophic Factor (BDNF)

The microbiome may influence concentrations of brain-derived neurotrophic factor (BDNF) in the brain. BDNF is a widely expressed neurotrophin serving several functions within the CNS, including neuronal differentiation and survival, and regulation of BDNF concentration is involved in depression and anxiety. BDNF levels have been observed to be lower in the cortex and hippocampus of germ-free (GF) mice compared to controls, suggesting that the gut microbiota appears to contribute to the elevation of brain BDNF and may modulate behavior through changes in BDNF levels **(Chudzik et al., 2021).**

Prebiotic administration has been shown to enhance expression of BDNF and improve cognition in animal studies **(Jach et al., 2023).** The probiotic reversed anxiety as well as a number of biochemical changes produced by stress, including reversal of decreased brain levels of BDNF and serotonin and restoration of plasma levels of tryptophan and several of its metabolites, the Firmicutes-to-Bacteroidetes ratio, and fecal levels of SCFAs **(MacKay et al., 2024).**

Although increased intestinal permeability has been proposed as a mechanism linking gut dysbiosis with neuroinflammation, evidence remains inconsistent across clinical populations. Standardized biomarkers of intestinal barrier integrity are required before this hypothesis can be translated into routine clinical practice.

4.4 Intestinal Permeability and the Leaky Gut Syndrome

One of the proposed contributors of the systemic inflammatory response is enhanced intestinal permeability, a condition commonly known as leaky gut syndrome (LGS). The mechanisms engaged for LGS development are primarily gut microflora disturbances, breakdown of the intestinal barrier, and damage of enterocytes, leading to systemic inflammation, which is critical for depression pathophysiology **(Dziedzic et al., 2024).** Increased intestinal permeability, known as LGS, plays a major role in the systemic inflammatory response, caused by intestinal dysbiosis, damage to enterocytes, and stress, contributing to the pathophysiology of depression **(Mosquera et al., 2024).** Glucocorticoids may impair the intestinal barrier function, reduce epithelial integrity, move bacteria outward, and provoke an inflammatory immune response **(Singh et al., 2022)**. Gut bacteria can also influence the expression and function of tight junction proteins that regulate intestinal permeability. Dysbiosis compromises intestinal barrier integrity, resulting in a "leaky gut," allowing endotoxins like LPS to enter the bloodstream and trigger systemic inflammation **(Randeni & Xu, 2025).** The sequential biological cascade linking gut dysbiosis to neuroinflammation and behavioral manifestations is conceptually illustrated in Figure 2.

4.5 Circadian Rhythmicity and the Gut–Brain–Circadian Axis

An underappreciated yet critical dimension of the MGB axis model is circadian rhythmicity. Both host endocrine cycles and microbial communities exhibit diurnal oscillations that synchronize metabolism, immune activity, and neural signaling. Disruption of these rhythms through factors such as sleep disturbance, irregular feeding, or shift work alters microbial diversity, dampens metabolite oscillations, destabilizes HPA regulation, and enhances neuroinflammation, thereby amplifying vulnerability to psychiatric disorders **(Bautista, 2025).**

Collectively, evidence supports a model in which anxiety and depression are systemic conditions arising from integrated neural, immune, endocrine, metabolic, and circadian dysregulation, rather than isolated brain-based pathologies. This reconceptualization positions microbial taxa and metabolites as candidate biomarkers and therapeutic targets **(Bautista, 2025).**

The influence of the gut microbiota on neurotransmitter metabolism is biologically plausible and supported by extensive experimental evidence. However, microbial production of neurotransmitters does not necessarily translate into direct central nervous system effects because many neurotransmitters do not readily cross the blood brain barrier. Indirect signaling through neural, endocrine, and immune pathways is therefore considered more likely.

Figure 3. Mechanistic Pathways Linking Gut MIcrobiota to Anxiety and Mental Health Regulation

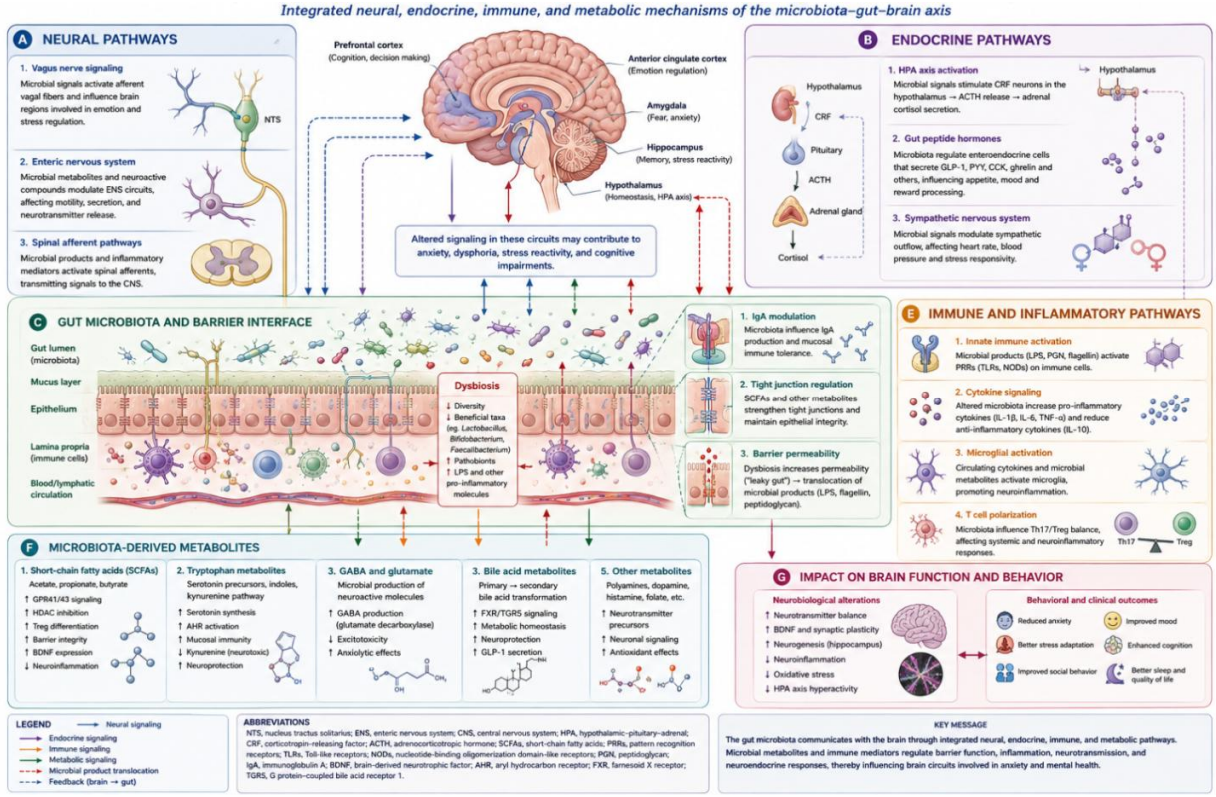


Table 2: Mechanistic Pathways Linking Gut Microbiota to Anxiety and Mental Health: Biological Basis, Evidence, and Translational Significance

Mechanistic Pathway	Principal Mediators	Biological Consequences	Evidence from Animal Studies	Evidence from Human Studies	Overall Strength of Evidence	Representative References
Neural signaling	Vagus nerve, enteric nervous system	Modulation of stress responses and emotional regulation	Strong	Moderate	Moderate to Strong	**Bravo et al. (2011); Cryan & Dinan (2012)**
Endocrine regulation	Hypothalamic pituitary adrenal axis, cortisol	Stress adaptation and neuroendocrine regulation	Strong	Moderate	Moderate	**Sudo et al. (2004); Foster et al. (2017)**
Immune	IL-6, TNF-α, IL-1β,	Neuroinflammation,	Strong	Strong	Strong	**Dantzer et al.**

modulation	IL-10	microglial activation				**(2008); Miller & Raison (2016)**
Microbial metabolites	SCFAs, indoles, bile acids	Neuroprotection, immune regulation, barrier maintenance	Strong	Moderate	Moderate	**Dalile et al. (2019); Kennedy et al. (2017)**
Tryptophan metabolism	Serotonin, kynurenine metabolites	Neurotransmission and stress regulation	Strong	Moderate	Moderate	**Kennedy et al. (2017); Cryan et al. (2019)**
Intestinal barrier dysfunction	Lipopolysaccharide, tight junction proteins	Systemic inflammation and altered gut permeability	Moderate	Emerging	Emerging	**Moloney et al. (2016); Cryan et al. (2019)**
Neuroplasticity	Brain derived neurotrophic factor	Synaptic plasticity and neuronal survival	Moderate	Limited	Emerging	**Bercik et al. (2011); Cryan et al. (2019)**

Scale

- Strong = consistent mechanistic evidence with substantial supporting studies
- Moderate = biologically plausible with moderate clinical support
- Emerging = promising evidence but limited human validation

5. Gut Microbiota Signatures in Specific Anxiety-Related Disorders

5.1 Generalized Anxiety Disorder and Social Anxiety

A large body of research supports the role of stress in several psychiatric disorders in which anxiety is a prominent symptom. The gut microbiome–immune system–brain axis is involved in a large number of disorders, and this axis is affected by various stressors **(MacKay et al., 2024).** Preclinical studies demonstrate that germ-free or dysbiotic states exaggerate HPA reactivity, remodel synaptic plasticity, and induce anxiety- and depression-like behaviors **(Bautista, 2025).** Mice fed with prebiotics showed diminished stressor-induced anxiety-like behavior. In a mouse model of ASD, a maternal high-fat diet reduced the number of oxytocin immunoreactive neurons in the hypothalamus and induced dysbiosis that was restored by a commensal *Lactobacillus reuteri* strain **(Cerdó et al., 2017).** These findings underscore the role of specific microbial taxa in modulating anxiety-related neural circuits.

5.2 Post-Traumatic Stress Disorder (PTSD) and Obsessive-Compulsive Disorder (OCD)

The gut microbiome has been implicated in the pathophysiology of PTSD and OCD, with dysbiosis

contributing to altered stress reactivity and immune dysregulation. Matters to be considered in future research include longer-term studies with factors such as sex of the subjects, drug use, comorbidity, ethnicity/race, environmental effects, diet, and exercise taken into account. The translatability of studies on animal models to clinical situations and the effects on the gut microbiome of drugs currently used to treat these disorders represent important research priorities **(MacKay et al., 2024).**

5.3 Environmental Pollutants and Gut–Brain Axis Disruption

Humans are exposed to a wide range of pollutants in everyday life that impact intestinal microbiota and manipulate the bidirectional communication between the gut and the brain, resulting in predisposition to psychiatric or neurological disorders. Acute methylmercury (Me-Hg) exposure changed the structure and function of the gut microbiota in rats, including *Desulfovibrionales*, *Peptococcaceae*, and *Helicobacter*, all of which are linked to particular neurometabolites like glutamate and GABA. In the mature CNS, glutamate and GABA are the primary excitatory and inhibitory neurotransmitters, respectively **(Singh et al., 2022).**

6. Dietary Influences on the Gut Microbiota and Mental Health

6.1 Dietary Patterns and Microbial Diversity

The complex relationship between diet, the gut microbiota, and mental health has become a focal point of contemporary research. Specific dietary components such as fiber, proteins, fats, vitamins, minerals, and bioactive compounds shape the gut microbiome and influence microbial metabolism to regulate depressive outcomes. These dietary-induced changes in the gut microbiota can modulate the production of microbial metabolites, which play vital roles in gut–brain communication **(Randeni & Xu, 2025).**

The resulting imbalance in the gut microbiome from poor dietary patterns can enhance intestinal permeability, promote systemic inflammation, and adversely affect the gut–brain axis. In contrast, the Mediterranean diet rich in fruits, vegetables, whole grains, nuts, seeds, and olive oil, along with moderate consumption of fish and poultry has been shown to promote a healthy gut microbiome and support mental health **(Randeni & Xu, 2025).** Trials have demonstrated robust improvements in depression following structured dietary modifications **(Bautista, 2025).**

6.2 Prebiotics and Dietary Fiber

Prebiotics are defined as nondigestible dietary fibers (e.g., inulin, fructo-oligosaccharides, and galacto-oligosaccharides) that stimulate the growth and/or activity of certain gut bacteria such as *Lactobacillus* and *Bifidobacteria*. This modulation of the gut environment may offer new avenues for reducing depression-like behavior and anxiety. Prebiotics may influence serotonin production by providing SCFAs, which can stimulate TPH1 gene expression in cells and through the gut–brain axis, thereby exerting anxiolytic or antidepressant-like effects **(Tang et al., 2025).**

In clinical trials, prebiotic supplementation enhanced the levels of SCFAs, improved social behavior symptoms and sleep patterns in ASD, and caused a reduction in anxiety scores in irritable bowel syndrome (IBS). In other clinical studies, administration of a diet high in prebiotic fibers improved mood, anxiety, stress, and

sleep in adults with moderate mental stress and low prebiotic intake. Metabolites formed after prebiotic degradation influenced brain function, decreased BBB permeability, and reduced neuroinflammation **(Jach et al., 2023).**

When prebiotic galactooligosaccharide (GOS) was tested in a clinical trial (ISRCTN54052375), it increased the probiotic bacteria *Bifidobacteria* within the gut, helping to alleviate symptoms of IBS **(Sasso et al. 2023).** B-GOS attenuated vigilance to negative stimuli; a behavioral marker of anxiety and depression suggesting a reduction in anxiety and depression **(Cerdó et al., 2017).** Recommended prebiotic doses range from 5–15 g/day of fibers such as inulin, fructooligosaccharides, and galactooligosaccharides, with a duration of at least 4 weeks **(Tang et al., 2025).**

Current microbiota based interventions demonstrate encouraging but modest therapeutic effects. Considerable heterogeneity in intervention protocols, microbial strains, treatment duration, and outcome measures limits direct comparison across studies. Future randomized controlled trials should prioritize standardized methodologies and mechanistic outcome measures in addition to clinical endpoints.

6.3 Polyphenols and Synbiotics

The gut microbiota manages the bioaccessibility of phenolic metabolites from dietary polyphenols, whose multiple beneficial properties have known therapeutic efficacy against depression. Synbiotics is a term combining probiotics with dietary polyphenols may provide a novel therapeutic strategy for depression. Synbiotics have the potential to alleviate neuroinflammation by modulating microglial and inflammasome activation, reduce oxidative stress, and balance serotonin metabolism, thereby simultaneously targeting several of the major pathological risk factors of depression **(Westfall & Pasinetti, 2019).**

Polyphenols, through their probiotic effects on the gut microbiota such as *Bacteroidetes* and *Firmicutes*, induce the formation of SCFAs. Chlorogenic acid, caffeic acid, rutin, and quercetin have all been shown to promote the formation of SCFAs such as propionate, butyrate, and acetate **(Zeppa et al., 2022).** Quercetin (60 mg/kg) alleviated anxiety and depressive behaviors while attenuating brain oxidative stress and suppressing excessive corticosterone induction in rats treated with adriamycin **(Westfall & Pasinetti, 2019)**.

7. Therapeutic Interventions Targeting the Gut Microbiota

7.1 Probiotics and Psychobiotics

7.1.1 Definition and Classification

Psychobiotics are defined as live organisms that, when ingested in adequate amounts, produce beneficial health effects in patients suffering from psychiatric illness **(Cerdó et al., 2017).** Unlike conventional probiotics, psychobiotics have the potential to positively affect mental health by influencing the production of neurotransmitters, SCFAs, and enteroendocrine hormones **(Mosquera et al., 2024).** The definition has been expanded in recent years to include prebiotics whose effect on the brain is bacteria-mediated, and a wider definition encompasses any substance that exerts a microbiome-mediated psychological effect, including probiotics, prebiotics, synbiotics, and postbiotics **(Sasso et al., 2023).**

Psychobiotic mechanisms of action include neurotransmitter regulation (27.1%), modulation of the gut microbiota (27.1%), SCFA production (16.9%), and

control of inflammatory responses (15.3%). Psychobiotic microorganisms can be found in fermented foods such as yogurt, sauerkraut, and kimchi. Healthy dietary patterns rich in pro- and prebiotics play a crucial role in mood regulation through their impact on the gut microbiome **(Śliwka et al., 2025).**

7.1.2 Preclinical Evidence

Several probiotic strains have been reported as psychobiotics from animal studies, having psychotropic effects on depression, anxiety, and stress, due to their ability to produce and deliver neuroactive substances such as GABA and serotonin, which act on the brain–gut axis **(Zeppa et al., 2022)**. Supplementation with the probiotic *Lactobacillus reuteri* ATCC 23272 decreased depression-like behavior, seemingly via the production of H_2O_2, which inhibits the enzyme IDO1 and restores the balance of serotonin/kynurenine pathways. IDO1 is activated by inflammation and LPS **(Bear et al., 2021).**

A probiotic (*L. rhamnosus* GG), prebiotic mix (polydextrose and galacto-oligosaccharide), or combined synbiotic mix, following maternal separation stress in male and female Sprague Dawley rats, reduced stress-induced increases in anxiety-like behavior. The synbiotic had the greatest effect and was also able to ameliorate stress-induced memory changes. Increases in cortisol, gut permeability, and bacterial adherence/penetration were prevented by probiotic supplementation **(Bear et al., 2021).**

Lactobacillus plantarum, *Bifidobacterium breve*, and *Akkermansia muciniphila* demonstrated particularly promising effects in systematic reviews of psychobiotic interventions. Psychobiotics such as *B. breve* CCFM1025 also modulate tryptophan metabolism by influencing the kynurenine and indole pathways, which translates into the regulation of serotonin levels **(Śliwka et al., 2025).**

7.1.3 Clinical Evidence

In a study by **Dinan and Cryan (2013)**, 124 healthy volunteers (mean age 62 years), those who consumed a mix of psychobiotics (*L. helveticus* and *B. longum*) exhibited less anxiety and depression than controls **(Westfall & Pasinetti, 2019)**. A probiotic combination of *L. helveticus* R0052 plus *B. longum* R0175 reduced anxiety and depression in healthy subjects compared with control ones **(Zeppa et al., 2022). Messaoudi et al. (2011)** showed that consumption of these probiotics reduced anxiety and depression scores in subjects with reduced urinary free cortisol **(Sasso et al., 2023)**. **Akkasheh et al. (2016)** showed that the consumption of a probiotics were associated with reduced Beck Depression Inventory (BDI) scores, indicating overall improved symptoms including mood, in 40 patients diagnosed with depression. **Marcos et al. (2004)** reported that probiotics decreased levels of stress and anxiety assessed using the state-trait anxiety inventory (STAI) that remained unchanged in subjects under academic examination stress **(Cerdó et al., 2017).** In a large cohort of pregnant women, supplementation with *L. rhamnosus* HN001 led to less postpartum depression and anxiety compared to placebo controls **(Westfall & Pasinetti, 2019)**. In a randomized controlled trial evaluating the effect of probiotic and synbiotic supplementation on reducing symptoms of depression and anxiety in 75 hemodialysis patients aged 30–65 years, results showed a significant reduction in depression severity according to the Hospital Depression and Anxiety Scale (HADS) in the synbiotic supplement group compared to controls **(Głaz et al., 2023).**

A systematic review by **Liu et al. (2019)** analyzed 34 controlled clinical trials in which the effects of pre- and probiotics on depression and anxiety were studied; they concluded that prebiotics showed no significant differences from placebo for depression or anxiety, but probiotics showed small significant effects for both depression and anxiety. **Chao et al. (2020)** in a meta-analysis of 10 randomized controlled trials, found that probiotics reduced depressive symptoms in patients with anxiety and depression and in healthy people under stress, but there was no reduction in anxiety scores. **Smith et al. (2021)** conducted a systematic review of 12 studies in which participants consumed probiotics, prebiotics, or synbiotics and were evaluated for mood or stress levels; 6 reported reduced depression with probiotics and 2 reported reduced anxiety with probiotics **(MacKay et al., 2024).** Results from recent randomized controlled trials suggest that daily probiotic supplementation significantly reduces the severity of depression compared to placebo ($p < 0.05$). Additionally, this effect may be enhanced by the combined use of a probiotic with a prebiotic **(Głaz et al., 2023).**

For the effectiveness of antidepressant therapy, psychobiotics should be administered at a dose higher than 1 billion CFU/day (10^9 CFU/day) for at least 8 weeks **(Jach et al., 2023).** Recommended doses for psychobiotics in clinical studies range from 10^9 to 10^{10} CFU/day, with a duration of at least 4 weeks **(Tang et al., 2025).**

7.1.4 Strain-Specific Effects and Mechanisms

Probiotic supplementation, particularly with strains of *Lactobacillus* and *Bifidobacterium*, has shown beneficial effects in some clinical trials; however, findings regarding anxiety are more variable, likely due to differences in study design, probiotic strains, and sample sizes. Emerging evidence suggests that personalized biomarkers could help predict who will benefit most from probiotic interventions. Baseline microbiota diversity, higher levels of *Lactobacillus* and *Bifidobacterium*, and lower abundance of pro-inflammatory taxa appear linked to better outcomes in neurological and psychiatric disorders. Reductions in inflammatory markers such as IL-6, TNF-α, IL-17, and CRP, along with favorable metabolomic profiles like elevated SCFAs and balanced tryptophan metabolism, correlate with improved cognition and mood **(Jafari, 2025).** Through modulation of the kynurenine pathway, probiotics may promote the synthesis of neuroprotective kynurenic acid (KYNA) over neurotoxic quinolinic acid (QUIN). A multi-strain probiotic formulation significantly reduced circulating IL-6 and TNF-α levels in patients with Parkinson's disease, suggesting a decrease in neuroinflammation relevant to conditions such as depression, Alzheimer's disease, Parkinson's disease, MS, and ASD **(Jafari, 2025).**

7.2 Prebiotics

Several studies have demonstrated the potential of prebiotics to influence stress, anxiety, and depression, possibly through a reduction in perceived stress associated with changes in *Bifidobacterium* spp. or other gut microbiota taxa **(Abidin et al., 2025).** Prebiotic supplementation in mice increased SCFA concentrations, many of which were negatively correlated with depression-like and anxiety-like behaviors **(Bear et al., 2021).** Animal studies have demonstrated that prebiotic administration reduces stress responsiveness, anxiety, and depressive-like behavior, enhances expression of BDNF, and improves cognition **(Jach et al., 2023).**

Nurturing a beneficial gut microbiome with prebiotics such as fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) is an appealing but under-investigated microbiota manipulation **(Zeppa et al., 2022).** Prebiotic fibers, probiotics, and fermented foods increase SCFAs with alterations in tryptophan metabolism toward TPH1-dependent serotonin production, linking nutrition-driven gut microbiota shifts to symptoms across mood disorders and metabolic disease along the microbiota–gut–brain axis **(Tang et al., 2025).**

7.3 Synbiotics and Postbiotics

A synergic combination of probiotics and prebiotics is referred to as a synbiotic, and prebiotics specifically have a role in promoting probiotic colonization of the gut **(Luqman et al., 2024).** Synbiotics synergistically combine probiotics and prebiotics. The synbiotic had the greatest effect in reducing stress-induced anxiety-like behavior and was also able to ameliorate stress-induced memory changes in animal models **(Bear et al., 2021).**

Postbiotics deliberately inactivated whole cells or their components offer health advantages mediated by changes in the microbiota, improved intestinal barrier function, modulation of metabolic or immunological responses, or nervous system signaling. Several studies on humans and animal models have shown the anti-depressive and anxiolytic effects of postbiotics **(Singh et al., 2022).** Postbiotics have therapeutic benefits comparable to those of probiotics in that they maintain the integrity of the epithelial barrier function, restore the variety and composition of the microbiota, manage immune reactions, and modulate signaling along the gut–brain axis **(Luqman et al., 2024).**

According to studies, regulating the gut–brain axis protected mice against *Salmonella*-induced depressive-like behavior by pretreatment with heat-killed probiotic *L. plantarum*-derived postbiotics, notably their metabolites. Some bacterial metabolites, including SCFAs and bile acids, have postbiotic properties **(Luqman et al., 2024).** When examining clinical trials utilizing postbiotics for the treatment of mental disorders, anxiety is the only disorder studied in current clinical trial registries **(Sasso et al. (2023).** The mechanisms, evidence base, and clinical implications of microbiota-targeted therapeutic strategies are comparatively summarized in Table 3.

Table 3: Clinical Evidence, Therapeutic Strategies, Current Limitations, and Future Research Priorities

Intervention / Research Area	Mechanism of Action	Current Clinical Evidence	Major Limitations	Clinical Readiness	Future Research Priorities	Representative References
Probiotics (Psychobiotics)	Modulation of microbial composition, immune signaling, neurotransmission	Small to moderate improvements in depressive symptoms; inconsistent	Strain heterogeneity, dosage variability, short follow up	Adjunctive therapy	Large multicenter randomized trials and standardized formulations	**Ng et al. (2018); Liu et al. (2019)**

		findings for anxiety				
Prebiotics	Increased SCFA production and beneficial bacterial growth	Limited but encouraging evidence	Small sample sizes and inconsistent outcomes	Experimental	Identification of optimal substrates and dosing strategies	**Schmidt et al. (2015); Liu et al. (2019)**
Synbiotics	Combined probiotic and prebiotic activity	Emerging evidence	Few high quality clinical trials	Experimental	Comparative effectiveness studies	**Liu et al. (2019)**
Dietary interventions	Global modulation of microbial diversity and metabolism	Moderate evidence for improvement in depressive symptoms	Dietary adherence and confounding lifestyle factors	High	Longitudinal mechanistic studies integrating microbiome and metabolomics	**Jacka et al. (2017); Cryan et al. (2019)**
Fecal microbiota transplantation	Restoration of microbial community structure	Strong preclinical evidence; limited clinical evidence in psychiatry	Safety concerns, donor variability, lack of standardized protocols	Research only	Well controlled clinical trials in psychiatric populations	**Kelly et al. (2016); Zheng et al. (2016)**
Precision microbiome therapeutics	Personalized microbial interventions	Preliminary	Biomarker validation and reproducibility	Future application	Multiomics integration, artificial intelligence assisted prediction, precision psychiatry	**Cryan et al. (2019); Foster et al. (2017)**

Clinical readiness categories

- **High:** Supported by multiple clinical studies and suitable as an adjunct to standard care.

- **Adjunctive:** May complement established treatments but is not recommended as monotherapy.
- **Experimental:** Requires additional clinical validation before routine use.
- **Research only:** Currently limited to experimental or investigational settings.

7.4 Fecal Microbiota Transplantation (FMT)

Animal FMT studies support a causal contribution of the gut microbiota to behavioural phenotypes **(Bautista, 2025).** FMT may provide antidepressant microbiota to depressed people, and anxiety is transmissible via FMT in mice. By using FMT, one may supplement harmful gut bacteria with healthy ones **(Luqman et al., 2024).** Therapeutic strategies aimed at the gut microbiota, such as probiotics, dietary modifications, prebiotics, and FMT, may offer future therapeutic opportunities **(Ugwu, 2025).**

Initial studies suggest that the microbiome may be utilized to predict treatment outcomes and diagnose psychological problems. Clinical study outcomes support the use of probiotics as an adjunct in MDD treatment and determine the efficacy of psychobiotic therapy in populations with psychiatric conditions. However, there have been no clinical trials on the use of FMT to treat depression specifically, representing a significant gap in the literature **(Luqman et al., 2024).**

7.5 Physical Exercise as a Microbiota-Modulating Intervention

Physical exercise may exert a role in alleviating depression-like symptoms by inducing changes in the gut microbiota composition. These modifications have an impact on the microbiota–gut–brain axis through different mechanisms, such as activation of the vagus nerve, modulation of neurotransmitter metabolism (i.e., tryptophan, which is converted and produces over 90% of the serotonin in the gut), regulation of the HPA axis, an increase in SCFA production (and thus inflammation reduction), and gut hormones (i.e., GABA, neuropeptide Y, and dopamine, that act locally on the ENS). A possible mechanism through which exercise might be beneficial in the control and treatment of depression is the ability of the gut microbiota to regulate tryptophan metabolism via the kynurenine pathway, which is strongly associated with depression **(Zeppa et al., 2022).**

8. Quantitative and Statistical Perspectives

8.1 Epidemiological Burden

Almost 4% of people in the world suffer from depressive disorders, and the forecasts of further increase in incidence are alarming **(Wilczek et al., 2023).** According to current data from the World Health Organization, an estimated 280 million people worldwide suffer from depression **(Głaz et al. (2023).** The prevalence of schizophrenia, affecting approximately 1% of the global population, underscores the urgency for innovative therapeutic strategies **(Mosquera et al., 2024).** Anxiety and depressive disorders rank among the most prevalent psychiatric conditions worldwide, yet remission rates remain unsatisfactory despite advances in pharmacological and psychotherapeutic interventions **(Bautista, 2025).**

8.2 Clinical Trial Metrics

When examining clinical trials utilizing probiotics for the treatment of mental disorders, there are currently a total of 52 clinical trials covering all stages between

2004 and 2022 listed on the US NIH clinical trials website. The most studied mental health disorders are stress, followed by depression, anxiety, cognition impairment, and sleep disorders. Postbiotic and FMT are the least researched among all clinical trial categories explored **(Sasso et al., 2023).**

A systematic review following PRISMA guidelines identified 369 articles, of which 45 met inclusion criteria for psychobiotic interventions in depression. The predominant psychobiotic strains belonged to *Lactobacillus* (45.5%) and *Bifidobacterium* (29%) genera. Strain sources included commercial preparations (24%), human-derived (16%), and food-derived (16%) strains **(Śliwka et al., 2025).** In a meta-analysis by **Liu et al. (2019),** 34 controlled clinical trials, probiotics showed small but significant effects for both depression and anxiety, while prebiotics showed no significant differences from placebo. A meta-analysis by **Chao et al. (2020)** consisting of 10 randomized controlled trials found that probiotics reduced depressive symptoms in patients with anxiety and depression and in healthy people under stress, but there was no reduction in anxiety scores **(MacKay et al., 2024).**

8.3 Dose–Response Relationships

For the effectiveness of antidepressant therapy, psychobiotics should be administered at a dose higher than 1 billion CFU/day (10^9 CFU/day) for at least 8 weeks **(Jach et al., 2023).** Recommended doses for psychobiotics in clinical studies range from 10^9 to 10^{10} CFU/day, with a duration of at least 4 weeks. Prebiotic doses range from 5–15 g/day of fibers such as inulin, fructo-oligosaccharides, and galacto-oligosaccharides, with a duration of at least 4 weeks **(Tang et al., 2025).**

The dose–response relationship for psychobiotics can be conceptualized as follows.

$$E = \frac{E_{max} \cdot D}{ED_{50} + D}$$

Where:

- E = clinical effect
- E_{max} = maximum achievable effect
- D = dose (CFU/day)
- ED_{50} = dose producing 50% of the maximum effect

where ED_{50} is the dose producing 50% of the maximum effect. Current evidence suggests that doses below 10^9 CFU/day are generally insufficient to produce clinically meaningful effects, while doses of 10^9–10^{10} CFU/day over 4–8 weeks represent the therapeutic window for most psychobiotic strains **(Tang et al., 2025; Jach et al., 2023).**

9. Gut Microbiota in Neurodevelopmental and Neurodegenerative Disorders

9.1 Autism Spectrum Disorder

In a mouse model of ASD, a maternal high-fat diet reduced the number of oxytocin immunoreactive neurons in the hypothalamus and induced dysbiosis that was restored by a commensal *Lactobacillus reuteri* strain. In humans, evidence of microbiome–gut–brain axis interactions have been obtained from the association of shifts in gut microbiota composition with central nervous disorders including ASD and anxiety and depressive behaviors **(Cerdó et al., 2017).** In clinical trials, prebiotic supplementation improved social behavior symptoms and sleep patterns in ASD **(Jach et al., 2023).**

9.2 Alzheimer's Disease and Parkinson's Disease

The microbiota–gut–brain axis has emerged as a potential focus for the enhancement of cognitive abilities and the improvement of Alzheimer's disease (AD). Probiotics and prebiotics can improve the imbalance associated with AD. SLAB51 and Lab4b, two mixed probiotic formulations, have respectively shown potential in in vitro models of Parkinson's disease and neuronal protection. Although these "psychobiotics" are effective in reducing neuronal damage and inhibiting brain inflammation, direct clinical evidence for AD patients is still lacking**.**

In the domain of mental and brain health, psychobiotics such as *Lactobacillus rhamnosus*, *Lactobacillus lactis*, and *Lactobacillus casei* differ in their effects on improving cognitive function and all reduce the response to stress. This form of treatment not only rectifies the imbalance of intestinal flora but is also closely associated with the restoration of the intestinal barrier **(Zhang et al., 2025).**

9.3 Schizophrenia

The prevalence of schizophrenia, affecting approximately 1% of the global population, underscores the urgency for innovative therapeutic strategies. Recent insights into the role of neuroinflammation, the gut–brain axis, and the microbiota in schizophrenia pathogenesis have paved the way for the exploration of psychobiotics as a novel treatment avenue. These interventions, targeting the gut microbiome, offer a promising approach to ameliorating psychiatric symptoms. Probiotics and psychobiotics, including specific strains of *Lactobacillus* and *Bifidobacterium*, have shown promising effects in reducing depressive and anxiety symptoms in both animal models and human trials **(Mosquera et al., 2024).**

10. Methodological Considerations and Limitations

10.1 Heterogeneity in Study Design

The results of MGB axis studies do not always agree, and the results from animal studies do not always translate well to human research. This has been a concern with MGB axis research **(Bear et al., 2021).** Heterogeneity in study design, small sample sizes, and limited causal evidence underscore the need for rigorous, large-scale trials **(Abidin et al., 2025).** Findings remain heterogeneous due to strain specificity, individual microbiome diversity, and methodological differences across studies **(Jafari, 2025).**

10.2 Translational Challenges

Matters to be considered in future research include longer-term studies with factors such as sex of the subjects, drug use, comorbidity, ethnicity/race, environmental effects, diet, and exercise taken into account. The translatability of studies on animal models to clinical situations and the effects on the gut microbiome of drugs currently used to treat these disorders represent important research priorities. Based on animal work, supplementation with SCFAs looks promising for improving anxiety-like and depression-like symptoms, but more information about translatability to humans, particularly across the lifespan, must be obtained **(MacKay et al., 2024).**

10.3 Nuance and Disagreement in the Literature

It is important to note that not all studies report consistent findings. In a study by **Romijn et al. (2017)** with a cohort of 79 participants with self-reported mood measures, a probiotic preparation containing *L. helveticus* and *B. longum* did not significantly alter the

mood or depression scores compared to the placebo group; however, this could be from the heterogeneity, severity, or chronicity of the treatment cohort **(Westfall & Pasinetti, 2019).** Some researchers indicate that probiotics may lead to significant improvements in cognitive function in patients suffering from depressive disorders, while others find no significant effect **(Głaz et al., 2023).** The exact mechanisms of action and the specific roles of psychobiotic microorganisms in modulating the microbiota–gut–brain axis are still not fully understood **(Śliwka et al., 2025).**

11. Future Directions and Precision Psychiatry

11.1 Personalized Microbiome-Based Therapies

Precision interventions ranging from diet and psychobiotics to FMT, chrononutrition, and immune-modulatory strategies offer promising avenues for personalized psychiatry **(Bautista, 2025).** Future directions should prioritize identification of microbial biomarkers, optimization of strain-specific and dose–response data, and integration of gut-targeted approaches into personalized mental healthcare **(Abidin et al., 2025).** The understanding of the gut microbiota and its activities is essential for the generation of future personalized healthcare strategies **(Cerdó et al., 2017).**

Innovative drug carriers, such as microbially-derived nanoparticles and probiotics that target particular parts of the gut or microbial communities, may improve pharmaceutical treatment efficacy and specificity **(Ugwu, 2025).** Advancements in artificial intelligence and nanotechnology are set to revolutionize psychobiotic development and application, promising to enhance their production, precision, and effectiveness **(Mosquera et al., 2024).**

11.2 Biomarker Development

Initial studies suggest that the microbiome may be utilized to predict treatment outcomes and diagnose psychological problems **(Luqman et al., 2024).** Emerging evidence suggests that personalized biomarkers could help predict who will benefit most from probiotic interventions. Baseline microbiota diversity, higher levels of *Lactobacillus* and *Bifidobacterium*, and lower abundance of pro-inflammatory taxa appear linked to better outcomes in neurological and psychiatric disorders. Reductions in inflammatory markers such as IL-6, TNF-α, IL-17, and CRP, along with favorable metabolomic profiles like elevated SCFAs and balanced tryptophan metabolism, correlate with improved cognition and mood **(Jafari, 2025).**

11.3 Integration with Conventional Therapies

Administration of probiotics labeled as psychobiotics and their metabolites as metabiotics, especially as an adjuvant to antidepressants, improves mental disorders **(Jach et al., 2023).** Microbial modulation offers a novel adjunctive strategy for depression management, particularly in treatment-resistant cases or to reduce the side effects of conventional drugs **(Abidin et al., 2025).** Nutritional interventions should be used cautiously for the medical management of significant depressive disorders; they ought to be paired with other therapies such as behavioral therapy, medication for depression, and habitual modifications **(Luqman et al., 2024).**

Studies suggest that probiotics may serve as an adjunct therapy for depression, especially in treatment-resistant cases. The increasing acceptance of the expanded concept of the MGB axis underscores the importance of microorganisms in mental well-being. As our

understanding of the microbiome's role in health and disease grows, probiotics emerge as promising agents for addressing mental health issues, providing new avenues for therapeutic interventions in depressive disorders **(Dziedzic et al., 2024).**

Despite substantial progress during the past decade, the field remains in an early stage of clinical translation. Future advances will depend not only on identifying disease associated microbial signatures but also on establishing reproducible mechanistic pathways and clinically meaningful therapeutic targets.

12. Conclusion

The gut microbiota plays a multifaceted and increasingly recognized role in the regulation of anxiety and mental health through its complex bidirectional interactions with the CNS via the MGB axis. The mechanistic underpinnings of this relationship encompass neural (vagus nerve, ENS), endocrine (HPA axis), immune (cytokine signaling, neuroinflammation), and metabolic (SCFAs, tryptophan metabolites, GABA, BDNF) pathways that collectively modulate neurotransmitter synthesis, stress reactivity, intestinal permeability, and neuroplasticity.

Dysbiosis has frequently been characterized by reductions in *Lactobacillus*, *Bifidobacterium*, and butyrate-producing genera alongside elevations in pro-inflammatory taxa are consistently associated with heightened anxiety and depressive symptomatology across preclinical and clinical studies. Potential causal role supported by animal studies of the gut microbiota in mental health is supported by FMT experiments demonstrating the transmissibility of depressive and anxiety-like phenotypes through microbial communities. Therapeutic modulation of the gut microbiota through psychobiotics (10^9–10^{10} CFU/day for ≥4–8 weeks), prebiotics (5–15 g/day), synbiotics, postbiotics, dietary interventions, and FMT represents a promising area for future therapeutic development. Meta-analyses of randomized controlled trials demonstrate small but significant effects of probiotics on both depression and anxiety, with strain-specific effects being a critical determinant of therapeutic efficacy. *Lactobacillus plantarum*, *Bifidobacterium breve*, and *Akkermansia muciniphila* have demonstrated particularly promising effects.

Despite these advances, significant challenges remain, including heterogeneity in study design, small sample sizes, limited causal evidence in humans, and the complexity of individual microbiome variability. Future research must prioritize large-scale, well-designed randomized controlled trials; identification of microbial biomarkers for treatment response prediction; optimization of strain-specific and dose–response data; and integration of gut-targeted approaches into personalized mental healthcare frameworks. The reconceptualization of anxiety and depression as systemic conditions arising from integrated neural, immune, endocrine, metabolic, and circadian dysregulation rather than isolated brain-based pathologies positions the gut microbiota as a central therapeutic target in the evolving field of precision psychiatry.

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