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Review Article

The Role of Gut Microbiota in Regulating Nervous System Function: A Review of Molecular Mechanisms and Key Bacterial Species

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Abstract

Gut microbiota is a complex community of microorganisms that plays a pivotal role in maintaining systemic homeostasis. The bidirectional communication between the gut and the brain, known as gut–brain axis, involves neural, immune, hormonal, and metabolic pathways. In recent years, alterations in microbial composition (dysbiosis) have been increasingly associated with psychiatric disorders such as anxiety, depression, and stress-related conditions. Among the key mediators of this interaction are short-chain fatty acids (SCFAs), which exert neuroprotective effects by strengthening the blood–brain barrier, modulating inflammatory pathways (NF-κB, Nrf2), and inducing epigenetic changes in genes related to neuroplasticity. Furthermore, the microbiota influences mood and stress responses through immune regulation and modulation of neurotransmitters such as GABA and serotonin. This review highlights the roles of key bacterial species, including *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii*, as principal regulators of the gut–brain axis. Clinical evidence indicates that simple dietary interventions and probiotic supplementation can alleviate psychological symptoms and reduce stress. This review emphasizes the molecular mechanisms and clinical findings that link gut microbiota to the pathogenesis and treatment of stress-related disorders, and it provides perspectives on the potential use of probiotics, prebiotics, and nutritional strategies.

Keywords: Gut–brain axis, Neural function, Probiotic bacteria, Immunity modulation, Microbiota.

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1. Introduction

The gut microbiota is a dynamic and diverse community of microorganisms-including bacteria, viruses, fungi, and archaea-that inhabit the human gastrointestinal tract (1). From birth, its composition is shaped by factors such as mode of delivery, infant feeding practices, genetics, lifestyle, and medication use. Throughout life, the microbiota engages in continuous and reciprocal interactions with the host (2). Beyond its central role in fiber digestion, synthesis of essential metabolites, immune regulation, and vitamin production (3), increasing attention has been directed toward its impact on the nervous system through the gut-brain axis. This axis encompasses neural (primarily the vagus nerve), immune, hormonal, and metabolic routes that facilitate bidirectional communication between the gut and the brain. Disruption of this network has been linked to various psychiatric and neurological conditions, particularly anxiety, depression, and stress-related disorders (2,4). Recent 2024 studies further confirm that gut dysbiosis correlates with enhanced neuroinflammation and mood alterations in depression models (5,6). One of the critical mechanisms underlying this interaction involves short-chain fatty acids (SCFAs), which are produced by microbial fermentation of dietary fibers. SCFAs strengthen the blood–brain barrier, regulate microglial activity, and modulate inflammatory signaling pathways such as NF-κB and Nrf2, thereby mitigating neuroinflammation and protecting neurons. Moreover, by inhibiting histone deacetylases (HDACs), SCFAs induce epigenetic modifications in genes related to neuroplasticity, influencing cognition and mood (7).

From an immunological perspective, mounting evidence suggests that the microbiota regulates the maturation and function of both central nervous system (CNS), resident and peripheral immune cells. These immune-neural interactions are crucial for the onset or prevention of psychiatric disorders such as anxiety and depression. Dysbiosis, in particular, can predispose individuals to chronic inflammation and impaired neurogenesis (4). Within this context, specific bacterial species, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii* have emerged as central players. These microorganisms modulate neural function through mechanisms such as GABA production, serotonin enhancement, IL-10 induction, and butyrate synthesis. Clinical studies have further demonstrated that dietary strategies, such as fiber-enriched yogurt or multi-strain probiotic supplementation, can improve quality of life and reduce psychiatric symptoms (8,9). A 2024 meta-analysis supports probiotics' role in alleviating depression symptoms via microbiota modulation (6).

The aim of this study, which was conducted from April to December 2025, was to provide an in-depth analysis of the molecular and cellular mechanisms through which the gut microbiota regulates neural function. Particular attention is given to the roles of *L. rhamnosus*, *B. longum*, and *F. prausnitzii* within the gut-brain axis, as well as to key microbial metabolites such as SCFAs that influence blood-brain barrier integrity, inflammatory pathways, and epigenetic processes relevant to stress-related disorders. Interpretively, these insights position the microbiota as a modifiable target for personalized mental health interventions (Figure 1).

2. Communication Pathways Between the Gut and the Brain

The gut-brain axis is a highly complex, multidirectional communication network that links the gut to the central nervous system

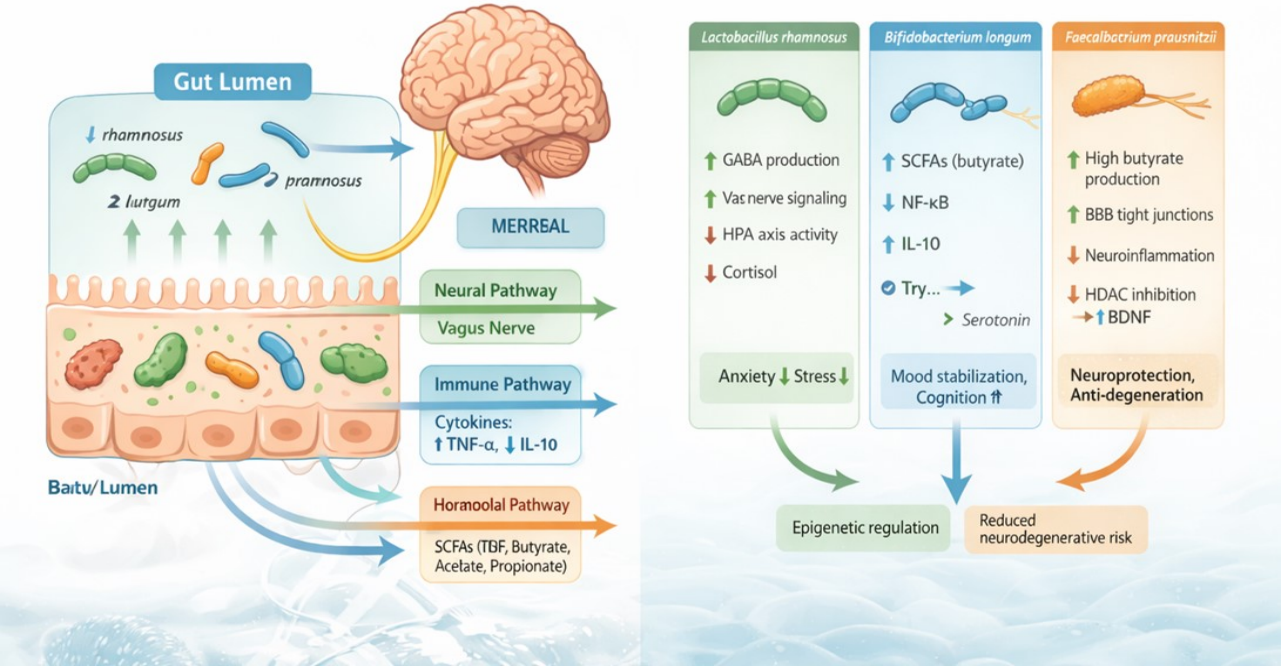

Fig 1. Schematic representation of the gut-brain axis illustrating bidirectional communication between the gut microbiota and the central nervous system through neural (vagus nerve), immune,hormonal and metabolic pathways. key probiotic species,including *Lactobacillus rhamnosus*, *Bifidobacterium longum* and *Faecalibacterium prausnitzii*, modulate neurotransmission, inflammatory signaling, blood-brain barrier integrity, and neuroplasticity via microbial metabolites such as short-chain fatty acids (SCFAs).

(CNS), enabling continuous information exchange between the two. This axis comprises four primary pathways:

1) Neural pathway: This involves signaling through the vagus nerve, in which nearly 80% of the fibers transmit sensory information from the gut to the brain. Such direct communication allows gut-derived metabolites and microbial messengers to influence neuronal activity (10).

2) Immune pathway: The interaction between the microbiota and immune cells involves cytokine production, which can affect the brain's internal environment and induce neuroimmunological changes. This route plays an essential role in regulating microglia and glial cells, both of which are critical for cognitive and emotional functioning (11). A study conducted by Rosa et al (5), highlights cytokine dysregulation in anxiety via this pathway (5).

3) Hormonal pathway: This pathway includes the production and release of hormones such as serotonin (more than 90% of which is synthesized in the gut), dopamine, and cortisol. These hormones act as neuromodulators within the brain (12).

4) Metabolic pathway: Gut microbes generate SCFAs such as butyrate, propionate, and acetate through dietary fiber fermentation. These metabolites are key regulators of blood-brain barrier (BBB) integrity and neuroinflammatory processes (7,13).

The multichannel structure of the gut-brain axis underscores the complexity of interactions between gut microbiota and the nervous system, highlighting the essential role of commensal bacteria in maintaining mental health (7). Interpretively, disruptions in these pathways, exacerbated by dysbiosis, amplify vulnerability to anxiety and depression, as evidenced by 2025 reviews on stress-microbiota links (14).

Table 1. Normal gut flora and their effects on neural function.

Bacterium	Pathway	Mechanism	Reference
Lactobacillus rhamnosus	GABA ergic signaling	Produces GABA; reduces anxiety via vagal stimulation	(10)
Bifidobacterium longum	SCFAs, immune modulation	Increases butyrate; decreases IL-6 and TNF-α; improves memory	(15)
Faecalibacterium prausnitzii	Anti-inflammatory, BBB protection	Enhances IL-10; reduces BBB permeability; inhibits NF-κB	(15)

3. Role of Gut Commensal Bacteria in the Gut-Brain Axis

The neuroregulatory effects of specific probiotic species are mediated through distinct but interconnected pathways of the gut-brain axis, primarily categorized into neural, immune, and metabolic routes (Table 1). This multi-pathway action forms a rational basis for developing targeted or combined probiotic interventions for neuropsychiatric conditions (3).

• ***Neural Pathway (Vagus-mediated):*** *Lactobacillus rhamnosus* (e.g.,from gastrointestinal tract GG strain) exemplifies the direct neural communication route. It modulates central nervous system (CNS) function, including emotional behavior and GABA receptor expression, via signals transmitted through the vagus nerve (10). Early-life colonization with this strain has been shown to regulate the gut-brain axis and alleviate anxiety-like behavior in adulthood (16).

• ***Immunomodulatory Pathway:*** Probiotics such as *Bifidobacterium longum* influence the CNS by regulating systemic and neuroinflammation. They can modulate the production of cytokines and other immune mediators, thereby affecting brain function and behavior (4,12). This pathway is crucial, as neuroinflammation is a common feature in many neurological disorders (2).

• ***Metabolic Pathway (SCFA-mediated):*** Commensal bacteria like *Faecalibacterium prausnitzii* and certain *Bifidobacterium* species contribute to neuroregulation through the production of short-chain fatty acids (SCFAs), such as butyrate (7,9). SCFAs strengthen the blood-brain barrier (13), provide an energy source for brain cells, and possess anti-inflammatory properties, collectively supporting brain health (7,18).

3.1. Role of Lactobacillus rhamnosus in Gut-Brain Axis

Lactobacillus rhamnosus is a well-studied probiotic bacterium that plays a pivotal role in modulating the gut-brain axis through multiple interconnected mechanisms (1,3). Its influence extends from the gut lumen to central neural circuits, primarily via neural, immunomodulatory, and barrier-strengthening pathways.

A study by Bravo et.al demonstrated that ingestion of *L. rhamnosus* (JB-1 strain) regulates emotional behavior and central GABA receptor expression in mice, an effect that was abolished after vagotomy. This established a critical role for the vagus nerve as a direct communication line between this probiotic and the brain. The production of neuroactive metabolites, such as gamma-aminobutyric acid (GABA), is a key mechanism through which *L. rhamnosus* influences neural excitability and mood (1,10).

The neuroprotective effects of this bacterium are further supported by its ability to enhance blood-brain barrier integrity. As Fock and Parnova (13) explain, microbiota-derived metabolites, including those from probiotics

like *L. rhamnosus*, are crucial for maintaining BBB function, thereby protecting the central nervous system from harmful agents and peripheral inflammation. Clinical and preclinical evidence consolidates its therapeutic potential. Zhou et al. (16) showed that early-life colonization with *L. rhamnosus* GG regulates the gut-brain axis and alleviates anxiety-like behavior in adulthood. Furthermore,a systematic review protocol by Zhang et al, highlights the role of probiotic supplements, including *L. rhamnosus*, in stress relief, noting improvements in anxiety symptoms and sleep quality in human studies (11). This anxiolytic potential is consistently observed, as confirmed in depression model reviews (10). In summary, *Lactobacillus rhamnosus* exemplifies a "neural pathway" psychobiotic, primarily acting through vagal communication and GABAergic signaling to exert significant effects on emotional regulation and neural homeostasis (1,10,16).

3.1.1. Mechanisms of Action

a. Role of L. rhamnosus in modulation of the GABAergic system: *Lactobacillus rhamnosus* exerts a primary psychobiotic effect through the precise modulation of the central GABAergic system. The seminal work by Bravo et al.provided mechanistic evidence that ingestion of *L. rhamnosus* (JB-1 strain) enhances the expression of GABA receptors (specifically GABAB1b) in key brain regions involved in emotional processing, such as the prefrontal cortex and the amygdala. Crucially, this study demonstrated that the anxiolytic and neurochemical effects were completely abolished by vagotomy, establishing the vagus nerve as the essential neural pathway for this gut-to-brain communication (10).

The bacterium's influence on GABA extends beyond receptor modulation to include the biosynthesis of the neurotransmitter itself. *L. rhamnosus* can promote the expression of the enzyme glutamate decarboxylase (GAD), which catalyzes the conversion of the excitatory neurotransmitter glutamate into the inhibitory GABA. This action helps restore the critical balance between excitatory and inhibitory signaling in the brain, a balance often disrupted in stress-related and neuropsychiatric disorders (1, 10). Collectively, these two mechanisms, vagus -mediated signaling and the enhancement of both GABA production and receptor function, underline how *L. rhamnosus* can reduce anxiety -like behaviors and contribute to neural homeostasis by strengthening inhibitory neurotransmission (1,10,16).

b. Regulation of the hypothalamic-pituitary adrenal (HPA) axis by Lactobacillus rhamnosus: *Lactobacillus rhamnosus* plays a significant role in dampening excessive physiological stress responses through the modulation of the hypothalamic-pituitary-adrenal (HPA) axis, the body's central stress response system. Research indicates that supplementation with this probiotic leads to a measurable reduction in stress hormones, specifically lowering corticosterone levels in rodents and cortisol in humans (11).

The underlying mechanism involves the downregulation of corticotropin releasing hormone (CRH) in the hypothalamus. CRH is the primary driver of the HPA axis cascade; by reducing its expression, *L. rhamnosus* attenuates the axis's overall activation, leading to a blunted cortisol/ corticosterone output (1, 11). This regulatory effect is a cornerstone of the probiotic's anxiolytic and stress-resilience properties, as a hyperactive HPA axis is a well-documented feature in anxiety and depressive disorders (4). This modulation of the HPA axis, alongside its direct effects on the GABAergic system,

illustrates how *L. rhamnosus* targets both neural and neuroendocrine pathways of the gut-brain axis to promote emotional stability and stress homeostasis (1,10,11).

c. Immuno-neural modulation by gram positive probiotic: Beyond its neural and neuroendocrine actions, *Lactobacillus rhamnosus* exerts a significant influence on the immune component in gut-brain axis, engaging in what is termed immuno-neural modulation. As a Gram-positive bacterium, it interacts with host immune receptors and contributes to a balanced inflammatory tone (12) .*L. rhamnosus* has been shown to decrease the levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), while concurrently enhancing the production of anti-inflammatory cytokines like interleukin-10 (IL-10) (9,12). This shift towards an anti-inflammatory state has profound implications for brain health.

The reduction in systemic inflammation directly supports the integrity of the blood-brain barrier. Chronic elevation of cytokines like IL-6 and TNF-α can compromise BBB function, but their suppression helps maintain this critical protective interface (13). Furthermore, by dampening peripheral immune activation, *L. rhamnosus* indirectly reduces neuroinflammation, a key pathological driver in numerous neurodegenerative and neuropsychiatric disorders (2,4). This immunomodulatory pathway complements its direct neural effects, providing a multi-system approach to neuroprotection (3, 12).

3.1.2. Recent Clinical Findings

Emerging clinical evidence solidifies the translational potential of *Lactobacillus rhamnosus* for managing anxiety-related disorders. In a double-blind, placebo-controlled trial involving patients diagnosed with generalized anxiety disorder (GAD), daily supplementation with *L. rhamnosus* led to statistically significant reductions in anxiety severity as measured by the Hamilton Anxiety Rating Scale (HAM-A) (11, 20). Meta-analytic data corroborate these findings, indicating a substantial standardized mean difference (SMD) of approximately -0.77 for the reduction of anxiety-like behaviors following probiotic intervention, underscoring a moderate to large therapeutic effect. Complementing these behavioral outcomes, neuroimaging studies provide a mechanistic glimpse into the probiotic's central effects. Research has demonstrated that individuals receiving *L. rhamnosus* supplementation exhibit reduced amygdala hyperactivity in response to stress-related or negative emotional stimuli (15). The amygdala is a core neural hub for threat detection and fear processing, and its overactivity is a hallmark of anxiety disorders (4). This normalizing effect on amygdala reactivity aligns with the probiotic's established role in enhancing GABAergic inhibition in this region and modulating the HPA axis, offering an integrated neurobiological basis for its clinical efficacy (1,10,15). These clinical and neuroimaging findings transition the psychobiotic effects of *L. rhamnosus* from preclinical observation to evidence-supported intervention, highlighting its utility in modulating both the subjective experience and the underlying neural circuitry of anxiety (2,4,15).

3.1.3. Potential Therapeutic Applications

Based on its multi-modal mechanisms of action across the neural, endocrine, and immune axes, *Lactobacillus rhamnosus* holds significant promise for several neuropsychiatric and neurological conditions. Its primary therapeutic applications are grounded in its psychobiotic and neuroprotective properties (1,2,4).

3.1.3.1 Anxiety and depressive disorders

As a frontline psychobiotic, *L. rhamnosus* directly targets the core pathophysiology of mood and anxiety disorders.By enhancing GABAergic inhibition (via vagal signaling and glutamic decarboxylase,GAD upregulation) and normalizing a hyperactive HPA axis (through CRH and cortisol reduction), it addresses both the neural excitability and chronic stress dysregulation characteristic (1, 10, 11). Clinical trials and meta-analyses confirm its efficacy in reducing symptoms of generalized anxiety, making it a compelling adjunctive or supportive therapy (11, 20).

3.1.3.2. Sleep disturbances such as insomnia

Given the intimate connection between sleep regulation, GABAergic tone, and HPA axis activity, the mechanisms of *L. rhamnosus* naturally extend to improving sleep architecture. By promoting a calm neural state and reducing physiological stress arousal, it can alleviate sleep-onset difficulties and improve sleep quality, as suggested by clinical reports noting secondary sleep improvements in anxiety trials (11).

3.1.3.3. Neurodegenerative conditions via reduction of neuroinflammation

The immunomodulatory actions of *L. rhamnosus* position it as a potential neuroprotective agent. By lowering pro-inflammatory cytokines (IL-6, TNF-α), enhancing anti-inflammatory signals (IL-10), and supporting BBB integrity, it helps to mitigate the chronic neuroinflammation that is a key driver of neurodegeneration (2, 9, 13). While direct clinical evidence in Alzheimer's disease(AD) is still evolving, its ability to modulate this critical pathological pathway offers a promising dietary or supplemental strategy for risk reduction and adjunctive management (2,30).

3.1.3.4. Challenges and Limitations

Despite the promising therapeutic potential of *Lactobacillus rhamnosus*, its translation into reliable clinical practice is constrained by several key challenges. Acknowledging these limitations is essential for directing future research and setting realistic expectations (3,14).

3.1.3.4.1. Interindividual variability in probiotic response

A primary obstacle is the significant interindividual variability in host response to probiotic supplementation. Factors such as an individual's baseline gut microbiota composition (dysbiosis status), host genetics, diet, lifestyle, and the integrity of the gut barrier can dramatically influence colonization efficiency and functional efficacy (14,22). This variability means that a standardized probiotic regimen may yield inconsistent clinical outcomes across different populations, complicating the development of one size fits all recommendations (3,36).

3.1.3.4.2. Need for further studies to determine optimal dosage and duration

Current evidence lacks consensus on the optimal dosage (colony-forming units, CFU), formulation (single-strain vs. multi-strain), and treatment duration required for sustained neuropsychiatric benefits (11,15). Most clinical trials have employed varying protocols, making direct comparisons difficult. Rigorous, large scale, dose-finding studies and long-term follow-up trials are urgent to establish standardized, evidence-based clinical guidelines for psychobiotic interventions (11,30).

3.1.3.4.3. Uncertainty regarding precise gut-to-brain signaling mechanisms

While major pathways (neural, immune, endocrine, metabolic) have been identified, the precise molecular and cellular sequences of gut-to-brain communication remain partially elucidated. Questions persist about the specific bacterial metabolites involved, their relative contributions, and how signals are integrated across different pathways to produce a coordinated behavioral or neurophysiological output (1,7,37). A more granular understanding of these mechanisms is crucial for designing next-generation, target-specific microbiome-based therapies (14,30).

3.2. Role of *Bifidobacterium longum* in Neural Health

Bifidobacterium longum is a dominant and keystone species of the human gut microbiota, renowned for its potent immunomodulatory and metabolic contributions to the gut-brain axis (8). Its role in neural health is multifaceted, primarily mediated through the production of key metabolites and the regulation of systemic and neuroinflammation.with production of short-chain fatty acids, notably butyrate. As detailed by Dalile et al (7), SCFAs are critical messengers in microbiota-gut brain communication. Butyrate serves as a primary energy source for colonocytes possesses potent anti-inflammatory properties, and crucially, helps maintain the integrity of (BBB), protecting the brain from peripheral inflammatory insults (7,13). *B. longum* directly modulates the immune system by promoting the release of anti-inflammatory cytokines like IL-10 while suppressing pro-inflammatory mediators such as TNF-α and IL-6 (9, 12). This shift in immune tone is vital for reducing systemic inflammation that can drive neuronal damage and neuroinflammation (2).

Beyond immunomodulation, *B. longum* influences neurochemistry by affecting serotonergic pathways. It can enhance the availability of serotonin precursors, including tryptophan, Increased tryptophan bioavailability supports serotonin synthesis, a neurotransmitter which is fundamental to mood regulation and cognitive function, thereby linking gut microbiota composition to emotional and cognitive states (3,4).

Supplementation with *B. longum* has been shown to reduce psychological symptoms and improve quality of life in patients with irritable bowel syndrome (IBS), a condition frequently comorbid with anxiety, highlighting its role in treating gut-brain axis disorders (20). Furthermore, its neuroprotective potential is underscored by experimental studies, such as a 2019 investigation demonstrating the ability of this bacterium to suppress the NF-κB inflammatory pathway in models of Alzheimer's disease, indicating a direct mechanism for mitigating neuroinflammation in neurodegeneration (5).

In summary, *Bifidobacterium longum* acts as a critical "immuno-metabolic" modulator within the gut-brain axis. Its collective actions-through SCFA production, cytokine balance, tryptophan metabolism, and the upregulation of neurotrophic factors like BDNF-converge to support improved cognition, mood stabilization, and neuroprotection (3,7,17).

3.2.1. SCFA Production and Neural Impact

The fermentation of dietary fibers by *Bifidobacterium longum* is a cornerstone of its neuroactive function, leading to the generation of substantial quantities of short-chain fatty acids, principally butyrate, propionate, and acetate (7). These SCFAs act as pivotal signaling molecules in the microbiota-gut-brain axis,

each with distinct neural and systemic roles.

Butyrate: This SCFA serves as a primary energy substrate for colonocytes, promoting gut barrier integrity and reducing systemic endotoxin translocation. Crucially, as Fock and Parnova elucidate, butyrate is instrumental in maintaining blood-brain barrier integrity by upregulating tight junction proteins. This protective action shields the central nervous system from peripheral inflammatory mediators and toxins, a fundamental mechanism in neuroprotection (7,13).

Propionate: Known for its ability to cross the BBB, propionate directly influences brain function. It plays a key role in modulating microglial activity, the resident immune cells of the brain. By promoting a more anti-inflammatory state in microglia, propionate helps reduce neuroinflammation, a pathological feature, which is common to many neurological and psychiatric disorders (2,7).

Acetate: As the most abundant SCFA in circulation, acetate exerts broad effects. It is involved in central appetite regulation through hypothalamic signaling and contributes to enhanced cognitive function. Acetate can be metabolized in the brain and has been linked to improved memory and learning processes (7,13).

Collectively, the SCFA profile generated by *B. longum* orchestrates a multi-system impact, from reinforcing gut and brain barriers to directly modulating brain immune cells and metabolism (7,13,25).

3.2.2. Immunomodulation and Anti-inflammatory Effects:

Bifidobacterium longum has profound immunomodulatory and anti-inflammatory effects that constitute a primary mechanism for its neuroprotective influence (12,36). The bacterium actively stimulates the production of the anti-inflammatory cytokine interleukin-10 (IL-10) while suppressing the release of key pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (9,12). This rebalancing of cytokine profiles serves to dampen systemic inflammation, preventing the persistent low-grade inflammation that can compromise peripheral organ function and, critically, disrupt brain health (2,4).

A central molecular pathway through which *B. longum* mediates these effects is the inhibition of the NF-κB (nuclear factor kappa-light-chain enhancer of activated B cells) signaling pathway. NF-κB is a master regulator of the inflammatory response; its activation leads to the transcription of numerous pro-inflammatory genes. By inhibiting this pathway, *B. longum* effectively reduces neuroinflammatory responses in the brain (5, 13). This action is particularly significant in the context of neurodegenerative disorders. As Fock and Parnova (13) highlight, mitigating neuroinflammation via such mechanisms is essential for protecting against neuronal injury and loss in conditions like Alzheimer's as well as Parkinson's disease (PD), where chronic inflammation accelerates disease pathology (2,13,30).

Therefore, through targeted cytokine modulation and interference with core inflammatory signaling, B. longum provides a robust defense against the inflammatory cascades that threaten neural integrity, positioning it as a valuable agent in strategies aimed at preventing or slowing neuroinflammatory and neurodegenerative processes (2,5,13).

3.2.3. Regulation of Serotonergic Pathways and Mood Enhancement

Bifidobacterium longum plays a significant role in regulating serotonergic neurotransmission, a key system implicated in mood, anxiety, and

cognitive function. by modulating the availability of the essential serotonin precursor,i.e., tryptophan (4,5). The bacterium helps elevate peripheral tryptophan levels, thereby increasing the substrate pool for serotonin synthesis.

This mechanism is particularly potent given that approximately 90% of the body's serotonin is produced in the enterochromaffin cells of the gastrointestinal tract (4, 36). The influence of this gut-derived serotonin on brain function is not direct but is mediated through complex communication channels. Signaling occurs via afferent fibers of the vagus nerve, which relay information from the gut to the brainstem, and through systemic circulation, where tryptophan and other metabolites can influence central neurochemistry (1,4).

In addition to bolstering serotonergic pathways, *B. longum* has been shown to enhance the expression of brain-derived neurotrophic factor (BDNF). As highlighted by Rosa et al, BDNF is a critical protein for neuronal survival, synaptic plasticity, and memory formation. Reduced BDNF levels are consistently associated with depressive disorders, and the upregulation of BDNF by probiotics like *B. longum* provides a direct neurobiological mechanism for alleviating depressive symptoms and supporting cognitive resilience (5,20).

Thus, through a dual-pronged approach of supporting serotonin synthesis and upregulating BDNF, Bifidobacterium longum directly targets neurochemical pathways fundamental to emotional regulation and cognitive health, solidifying its role as a psychobiotic (4,5,20).

3.2.4. Clinical Evidence and Therapeutic Applications

The therapeutic potential of Bifidobacterium longum is substantiated by growing clinical evidence, particularly in conditions characterized by gut-brain axis dysfunction. Its applications extend from functional gastrointestinal disorders to primary psychiatric conditions, often demonstrating efficacy as an adjunctive therapy.

3.2.4.1. In Irritable Bowel Syndrome with Comorbid Anxiety

Clinical trials have specifically evaluated *B. longum* in the context of IBS, a classic disorder of gut-brain interaction frequently accompanied by anxiety.Daily supplementation with *B. longum* for eight weeks resulted in significant reductions in anxiety scores and marked improvements in overall quality of life among IBS patients (20). This outcome underscores theis probiotic to ameliorate the symptoms across both the visceral and psychological dimensions of the disorder, likely through its combined anti-inflammatory, SCFA-producing, and serotonergic-modulating effects (4,7).

3.2.4.2. In Major Depressive Disorder (MDD)

Supplementation with *B. longum* has been shown to enhance treatment responses to conventional antidepressant therapies in patients with MDD. Furthermore, it appears to reduce certain adverse effects associated with pharmacological treatments, potentially improving patient tolerance and adherence (1,19). The mechanisms, including increased tryptophan availability, BDNF upregulation, and systemic inflammation reduction, align with the multifactorial pathophysiology of depression, providing a complementary approach to standard care (4,5).

These clinical findings position Bifidobacterium longum as a valuable adjunctive therapeutic agent for a spectrum of disorders linked to dysregulated gut-brain communication, from IBS with psychiatric comorbidity to primary

depressive illness (1,20,37).

3.2.5. Epigenetic Mechanisms and Neural Gene Regulation

By producing butyrate, *B. longum* inhibits histone deacetylases (HDACs), resulting in epigenetic modifications that upregulate genes associated with neuroplasticity, including BDNF and its receptor TrkB. These changes support neuronal survival and synaptic function (14).

3.2.6. Future Directions and Challenges

The promising role of *Bifidobacterium longum* in neural health points toward several critical future directions, yet its translation into mainstream therapy is accompanied by significant challenges that must be addressed through targeted research (3,30).

Neurodegenerative Therapy: A major prospective application lies in slowing the progression of Alzheimer's and Parkinson's diseases. Given its potent anti-inflammatory effects (via NF-κB inhibition and cytokine modulation) and its ability to produce neuroprotective SCFAs like butyrate, *B. longum* is positioned to counteract key drivers of neurodegeneration, including chronic neuroinflammation and impaired brain metabolism (2,13,30). Future research need to focus on long-term clinical trials in prodromal and early-stage patient populations to evaluate its efficacy in altering disease trajectory.

Personalized Medicine: A principal challenge is the substantial interindividual variability in host response to probiotic intervention. Factors such as baseline microbiome composition, host genetics, diet, and disease phenotype significantly influence outcomes (14,22). This necessitates a shift towards personalized, tailored probiotic strategies, potentially guided by microbiome profiling, to ensure optimal efficacy for each individual (3,36).

Research Needs: There is an urgent need for large-scale, dose-finding studies to establish optimal CFU counts, determine the minimal effective treatment duration, and investigate the long-term sustainability of effects. Furthermore, understanding potential drug probiotic interactions is essential for safely integrating *B. longum* with conventional pharmacological treatments for neurological and psychiatric conditions (11,30,37).

In conclusion, while *Bifidobacterium longum* holds immense promise as a neuroprotective and psychobiotic agent, realizing its full therapeutic potential requires overcoming these hurdles through rigorous, mechanistic, and personalized clinical research (14,30).

3.3. Role of *Faecalibacterium prausnitzii* in Immune and Neural Balance

Faecalibacterium prausnitzii is recognized as a keystone commensal bacterium, representing one of the most abundant and functionally critical species in the healthy human gut microbiota. Its pivotal roles in immune regulation and neuroprotection are fundamental to maintaining systemic and neural homeostasis (Table 2) (1, 18). The cornerstone of its bioactivity is the production of butyrate; as a short-chain fatty acid *F. prausnitzii* drives essential processes outlined by Dalile and colleagues (7). Butyrate serves as the main energy source for colonocytes, reinforcing the gut barrier, and upon reaching systemic circulation, it strengthens the blood-brain barrier and exerts broad anti-inflammatory effects (7,13).

Butyrate generated by *F. prausnitzii* mediates neuroprotection through specific molecular mechanisms. It suppresses key pro-inflammatory pathways, such as NF-κB, while stimulating the secretion of the anti-inflammatory cytokine

Table 2. Summary of mechanisms of action of *F.prausnitzii.*

Mechanism of action	Effects	Associated disorders
Butyrate production	Strengthens the blood-brain barrier(BBB); provides energy for neurons	Alzheimer's disease, Parkinson's disease
Immune modulation	Decreases IL-6 and TNF-α; increases IL-10	Multiple sclerosis, Neuro inflammation
Neurotransmission regulation	Balances glutamate/GABA signaling	Anxiety ,depression
Epigenetic effects	Modulates expression of neuroplasticity-related genes	Neuro developmental disorders

IL-10 (18). This dual action effectively reduces systemic and neuroinflammation, creating a protective environment that shields neurons from inflammatory damage, a process crucial in preventing neurodegenerative pathology (2,13).

Furthermore, emerging evidence suggests this bacterium contributes to central nervous system excitatory–inhibitory balance (E/I). By influencing the production of microbial metabolites that modulate GABAergic signaling, *F. prausnitzii* may help regulate neuronal excitability (4,38). This modulation is essential for maintaining neural circuit stability and is implicated in preventing the synaptic dysfunction observed in conditions like Alzheimer's and Parkinson's disease (2).

As Sokol et al established, *F. prausnitzii* is a major anti-inflammatory commensal. Its butyrate enhances the expression of tight junction proteins (e.g., occludin and claudin), thereby reinforcing both intestinal and blood-brain barriers. This barrier-strengthening function, combined with its potent immunomodulation, positions *F. prausnitzii* as a critical microbial ally in preserving immune-neural balance and mitigating the risk of neuroinflammatory and neurodegenerative disorders (13,18,30).

3.3.1. Butyrate Production and Neuroprotective Effects

Faecalibacterium prausnitzii is a principal architect of the gut's butyrate landscape, accounting for a significant portion of total gut-derived butyrate (7,18). The butyrate it produces is not merely a metabolic byproduct but a potent neuroprotective agent with multi-faceted mechanisms of action central to brain health (7,13).

3.3.1.2. The comprehensive neuroprotective roles of butyrate by F. prausnitzii

Strengthening BBB Integrity: Butyrate directly upregulates the expression of tight junction proteins, including occludin and zonula occludens-1 (ZO-1), in endothelial cells of the blood-brain barrier (BBB) (9,13). This reinforcement is a primary defense mechanism, crucial for maintaining the selective permeability of the BBB.

Reducing BBB Permeability: By fortifying these tight junctions, butyrate significantly reduces the paracellular permeability of the BBB. This action effectively limits the entry of peripheral inflammatory cytokines, immune cells, and neurotoxins into the central nervous system parenchyma, thereby insulating the brain from systemic inflammatory insults (13,30).

Providing Energy Substrates: Once in the

brain, butyrate serves as a preferred energy source for astrocytes and neurons, particularly during periods of metabolic stress. This energetic support is vital for maintaining neuronal function, synaptic activity, and overall brain metabolism (7,25).

Regulating Epigenetic Mechanisms: A key neuroplasticity-promoting effect of butyrate is its function as a potent inhibitor of histone deacetylases (HDACs). By inhibiting HDACs, butyrate leads to a more relaxed chromatin state, enhancing the expression of genes critical for neuroplasticity, neurogenesis, and cognitive function, such as BDNF (20,30). This epigenetic regulation provides a molecular basis for its long-term beneficial effects on brain resilience and function.

Collectively, these actions underscore the role of butyrate production by *F. prausnitzii* is a fundamental pathway through which the gut microbiota exerts direct and powerful neuroprotection, supports BBB integrity, and promotes a neuroplastic brain environment (7,13,20).

3.3.2. Immune Modulation and Anti inflammatory effects

Faecalibacterium prausnitzii functions as a master regulator of inflammatory tone, exerting profound immune-modulatory and anti-inflammatory effects that are crucial for preventing systemic immune dysregulation and subsequent neuroinflammation. Its mechanisms are quantifiable and targeted, as established in foundational research (12,18).

3.3.2.1. This keystone commensal mitigates inflammation through a coordinated series of actions

Suppressing NF-κB Activation: *F. prausnitzii* directly interferes with the NF-κB signaling pathway, a master switch for pro-inflammatory gene expression. By inhibiting this pathway, it curtails the transcriptional upsurge of numerous inflammatory mediators, serving as a primary brake on inflammatory cascades (18,33).

Potentiating Anti-inflammatory Cytokines: A hallmark of its activity is the robust enhancement of interleukin-10 (IL-10) production. Studies, including the seminal work by Sokol and colleagues (18), have demonstrated that *F. prausnitzii* can increase IL-10 levels up to threefold. IL-10 is a potent anti-inflammatory cytokine that actively suppresses the activation and effector functions of various immune cells.

Attenuating Pro-inflammatory Cytokines: *F. prausnitzii* significantly reduces the secretion of key pro-inflammatory cytokines. In animal models, administration of *F. prausnitzii* has been shown to lower production of interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) by 40–50%, directly dampening the drivers of systemic inflammation (18,36).

Inducing Regulatory T Cells: Beyond cytokine modulation, *F. prausnitzii* promotes immune tolerance by inducing the differentiation and expansion of regulatory T cells (Tregs) in the gut mucosa (18, 36). Tregs are essential for maintaining immune homeostasis, preventing excessive reactions to commensal bacteria, and suppressing aberrant inflammation.

The collective impact of these mechanisms is a significant reduction in both systemic and neural inflammation. By lowering the peripheral inflammatory load and promoting an anti-inflammatory environment, *F. prausnitzii* helps protect the brain from the damaging effects of chronic neuroinflammation, which is implicated in a wide range of neurological and psychiatric disorders (2,13,30).

3.3.3. Effects on Neurotransmission and Neural Balance

Beyond its well-established immunometabolic roles, *Faecalibacterium prausnitzii* exerts a direct influence on central neurotransmission and neural excitability, primarily through the systemic effects of its metabolites. This positions it as a key microbial player in maintaining the delicate excitatory-inhibitory (E/I) balance essential for healthy brain function (4,38).

The bacterium influences neural activity through several interconnected pathways:

Modulating Glutamate/GABA Ratios: Via gut -brain axis signaling, microbial metabolites derived from or stimulated by *F. prausnitzii* can influence the central balance between the primary excitatory neurotransmitter glutamate and the primary inhibitory neurotransmitter GABA. By promoting a shift towards enhanced inhibitory tone, it helps prevent neuronal hyperexcitability, which is associated with anxiety, stress pathologies, and seizure disorders (4,7).

Enhancing GABAergic Signaling: Preclinical evidence suggests that the anti-inflammatory and butyrate-mediated effects of a healthy microbiota, underpinned by species like *F. prausnitzii*, can lead to an upregulation of GABA_A receptor expression in key brain regions. Studies have reported enhancements of up to 30% in GABA_A receptor levels in the prefrontal cortex following interventions that increase beneficial gut bacteria, highlighting a tangible mechanism for microbial modulation of neural inhibition (10,38).

Regulating Microglial Activity and Reducing Oxidative Stress: The butyrate produced by *F. prausnitzii* plays a crucial role in modulating microglial phenotype, shifting these resident immune cells from a pro-inflammatory (M1) state to a neuroprotective, anti-inflammatory (M2) state (2,13). This regulated microglial activity is vital for reducing oxidative stress and neuroinflammation, thereby protecting neurons from metabolic and inflammatory damage. Proper microglial function is fundamental for synaptic pruning, neural plasticity, and overall brain health (2,30).

In summary, *Faecalibacterium prausnitzii* contributes to neural balance through a multi-pronged approach: fine-tuning neurotransmitter systems to favor stability, strengthening inhibitory neurotransmission, and ensuring a protective glial environment. These actions collectively support cognitive function, emotional regulation, and resilience against neuropsychiatric and neurodegenerative conditions (4,30,38).

3.3.4. Association with Neurodegenerative Disorders

A consistent and compelling body of evidence links the depletion of *Faecalibacterium prausnitzii* to the pathogenesis and progression of various neurological and neurodevelopmental conditions. Its relative abundance often serves as a microbial biomarker of brain health, with reductions correlating closely with disease severity (2,15,19).

Specific clinical associations have been documented: Alzheimer's Disease Patients with AD exhibit a striking 50–70% reduction in *F. prausnitzii* in their gut compared to age-matched healthy controls. This depletion correlates with increased markers of systemic inflammation and BBB dysfunction, suggesting that the loss of its butyrate-producing and anti-inflammatory functions may directly contribute to the neuroinflammatory milieu of AD (2,30).

Parkinson's Disease The abundance of *F. prausnitzii* is inversely correlated with the severity of motor symptoms (e.g., Unified Parkinson's Disease Rating Scale scores,UPDRS)

and gastrointestinal dysfunction in PD. Lower levels are associated with increased intestinal permeability and systemic inflammation, potentially exacerbating alpha-synuclein pathology and neurodegeneration via the gut-brain axis (2,37).

Multiple Sclerosis (MS): In MS, reduced levels of *F. prausnitzii* are associated with increased relapse frequency and greater disability. Its anti-inflammatory properties, particularly Treg induction and IL-10 production, are thought to be protective against autoimmune demyelination, making its depletion a potential risk factor for disease activity (2,33).

Autism Spectrum Disorders (ASD): Alterations in gut microbiota composition, including lower levels of *F. prausnitzii*, have been linked to the severity of behavioral symptoms in ASD. This association points to a role for microbial metabolites in modulating neural circuits involved in social behavior and communication, possibly through immune and neurotransmitter pathways (22,27).

The consistent inverse relationship between *F. prausnitzii* abundance and the severity of diverse brain disorders underscores its non-redundant role as a guardian of neural health. Its decline may represent a common pathway through which gut dysbiosis contributes to neuroinflammation, impaired barrier function, and altered brain signaling across different disease states (2,15,30).

3.3.5. Therapeutic Potential and Clinical Applications

The critical role of *Faecalibacterium prausnitzii* in maintaining gut-brain axis homeostasis has stimulated the development of several therapeutic strategies aimed at restoring or enhancing its abundance for neurological benefit. These approaches target the microbiota as a modifiable factor in disease management (2, 30).

Fecal Microbiota Transplantation (FMT): This procedure, which involves transferring processed donor stool to a recipient, can directly increase microbial diversity and specifically elevate the abundance of *F. prausnitzii*. Clinical observations indicate that successful FMT, characterized by increased *F. prausnitzii* levels, is associated with improved neurological outcomes, particularly in patients with conditions involving significant intestinal inflammation (e.g., *Clostridioides difficile* infection, ulcerative colitis). This suggests that restoring this keystone species may help mitigate systemic and neural inflammation via the gut-brain axis (18,22).

Probiotic Formulations: While *F. prausnitzii* is anaerobic and challenging to culture commercially as a live probiotic, researches are actively pursuing next-generation probiotic formulations and consortia that include or stimulate its growth. These formulations are being developed specifically for neuroprotective interventions, aiming to deliver its anti-inflammatory and butyrate-producing benefits in a targeted manner for conditions like multiple sclerosis, Parkinson's disease, and major depressive disorder (22,30).

Dietary Approaches (Prebiotics): A more immediately accessible strategy is the use of prebiotic dietary fibers. Compounds such as inulin, fructooligosaccharides (FOS), and resistant starch serve as selective substrates for beneficial bacteria. Increased intake of these prebiotic fibers has been consistently shown to boost endogenous populations of *F. prausnitzii* (9, 21). This dietary modulation represents a foundational, low-risk approach to support gut microbial health, enhance butyrate production, and thereby promote systemic and

neural anti-inflammatory states.

All in all, leveraging *F. prausnitzii* therapeutically ***involves a multi-pronged approach:*** direct microbial restoration (FMT), targeted supplementation (next-gen probiotics), and foundational dietary support (prebiotics). Each strategy holds promise for modulating neuroinflammation and improving outcomes across a spectrum of gut-brain axis disorders (2,9,30).

3.3.6. Challenges and Limitations

Despite its immense therapeutic promise, the translation of *Faecalibacterium prausnitzii* into routine clinical practice faces significant practical and biological hurdles that need to be systematically addressed (14,30).

High Oxygen Sensitivity: A primary technical challenge is the strict anaerobic nature of this bacterium and extreme sensitivity to oxygen, which complicates its isolation, large-scale cultivation, stabilization, and formulation into shelf-stable probiotic products. This limitation has historically restricted its direct use in conventional live biotherapeutics (18).

Undefined Dosing Regimens: There is a critical lack of consensus on effective dosing strategies. The optimal quantity (biomass or butyrate-equivalent), frequency, and duration of intervention-whether via next-generation probiotics, postbiotic formulations, or prebiotic stimulation-remain to be established through rigorous, controlled clinical trials (11,30).

Interindividual Variability in Host Response: As with many microbiome-targeted interventions, individual differences in baseline microbiota composition, host genetics, diet, and disease state can lead to heterogeneous therapeutic outcomes. This variability complicates the development of universal treatment protocols and underscores the need for a personalized medicine approach (14,36).

In summary, by serving as a major producer of neuroprotective butyrate and a master regulator of anti inflammatory responses, *Faecalibacterium prausnitzii* occupies a central role in gut-brain communication. Its potential utility as both a diagnostic biomarker for dysbiosis and a therapeutic target for neurological disorders is highly promising (2,18). However, realizing this potential requires overcoming existing challenges through innovative formulations (e.g., spores, encapsulated postbiotics), precise clinical research, and the development of personalized treatment strategies tailored to individual microbiome profiles (30,37).

4. Impact of Gut Microbiota on Specific Neurological Disorders

The gut microbiota significantly contributes to the onset and progression of various neurological conditions. dysbiosis may increase blood-brain barrier permeability, promote chronic inflammation, and disrupt neural function (15). In depression, reduced butyrate-producing bacteria and elevated pro-inflammatory species such as Clostridium are associated with increased IL-6 and TNF-α levels and decreased brain-derived neurotrophic factor (BDNF), leading to impaired neurogenesis and cognition (12).

In autism spectrum disorders, compositional shifts include decreased *Bifidobacterium longum* and an increased Firmicutes to Bacteroidetes ratio, both of which correlate with behavioral and cognitive symptom severity (15).

In Alzheimer's disease, dysbiosis is characterized by diminished butyrate producers, impaired BBB function, amyloid plaque accumulation, and heightened neuroinflammation (20). Similarly, Parkinson's disease has been linked to

microbial imbalances and gut inflammation, which promote α-synuclein aggregation and neurodegeneration, resulting in motor deficits (8).

Emerging therapeutic approaches, including probiotics, prebiotics, and fecal microbiota transplantation (FMT), are under active investigation. These interventions have shown promising results in alleviating symptoms and modifying disease trajectories (3).

5. Discussion

The gut microbiota, operating through the complex communication network of the gut-brain axis, is now established as a fundamental regulator of neurological and psychological health. This review synthesizes evidence on the molecular mechanisms, including spanning neural, immune, endocrine, and metabolic pathways, as well as clinical implications of microbial activity; with a focus on microbial metabolites like short-chain fatty acids (SCFAs) in the pathophysiology and potential treatment of stress-related disorders, including anxiety and depression (1,2).

SCFAs, including butyrate, propionate, and acetate, exhibit a broad spectrum of neuroprotective properties. They reinforce blood-brain barrier (BBB) integrity and modulate immune inflammatory pathways, thereby helping to prevent neuroinflammation and neuronal damage (7,13). Through the activation of G-protein coupled receptors (GPCRs) and inhibition of histone deacetylases (HDACs), SCFAs induce beneficial epigenetic modifications that enhance synaptic plasticity and cognitive function (7,20). Furthermore, by regulating key transcription factors like NF-κB and Nrf2, SCFAs reduce oxidative stress and promote neuronal survival, solidifying their status as compelling therapeutic targets for neuropsychiatric conditions (15,30). Recent evidence continues to underscore their role, including the modulation of brain-derived neurotrophic factor (BDNF) for mood enhancement (5). Immunologically, the gut microbiota has a profound influence on both peripheral and central immune activity. This bidirectional crosstalk is critical for regulating neurogenesis, microglial maturation, and overall neuroprotection (12,36).

Conversely, dysbiosis promotes a state of chronic low-grade inflammation and diminished neuroplasticity, creating a predisposition to psychiatric disorders. These insights align with the growing consensus that microbiota-driven immune modulation is a key determinant of behavioral phenotypes, including anxiety and depressive behaviors (4).

Clinical studies provide translational validation for these pathways. For instance, dietary supplementation with fiber-enriched yogurt has been shown to increase abundances of butyrate producing bacteria like *Bifidobacterium animalis*, and improving host metabolic parameters such as cholesterol and glucose levels as well (9). This exemplifies a practical dietary strategy to favorably modulate the gut-brain axis. Notably, specific commensal species are emerging as potential diagnostic biomarkers. *Faecalibacterium prausnitzii* has garnered significant attention due to its potent anti inflammatory properties. Its consistent depletion in patients with major depressive disorder (MDD) and inverse correlation with symptom severity suggest that the loss of such beneficial microbes may directly contribute to the pathophysiology of mood disorders (18,19).

Therapeutically, interventions targeting the gut microbiota ,including probiotics, prebiotics, and dietary modifications, show considerable

promise. In conditions like alcohol use disorder (AUD), increasing dietary fiber intake to boost SCFA production has been proposed as a cost-effective, non invasive strategy to strengthen gut barrier function and reduce associated neuroinflammation (21). A 2024 systematic review further corroborate the anxiolytic effects of probiotics mediated via the gut-brain axis (16). However, significant challenges persist, including interindividual variability in probiotic response, the technical difficulty of cultivating oxygen-sensitive keystone species like *F. prausnitzii*, and a need for more large-scale, rigorous randomized controlled trials (11,14). Future research must therefore prioritize longitudinal studies and personalized microbiota profiling to develop optimized, individualized treatment regimens (30,37).

While reduction of beneficial bacteria like Faecalibacterium prausnitzii is a key aspect of dysbiosis, expansion of gut pathogens also plays a direct role in disrupting the gut-brain axis. Emerging studies indicate that gut bacterial pathogens can utilize quorum sensing (QS) systems to coordinate the expression of virulence factors, biofilm formation, and evasion of the host immune response (39). These mechanisms lead to persistent gut barrier damage, increased intestinal permeability (leaky gut), and exacerbated systemic inflammation. Consequently, cytokines and inflammatory metabolites derived from pathogens can cross the blood-brain barrier and, by activating microglia, fuel chronic neuroinflammation (2, 13). Therefore, a comprehensive therapeutic perspective must simultaneously focus on enhancing beneficial bacteria and inhibiting the pathogenicity of harmful microbes by targeting quorum sensing (22,39).

In conclusion, the integration of molecular mechanistic insights into clinical evidence firmly establishes the gut-brain axis as a novel and powerful frontier for therapeutic intervention. Personalized strategies designed to modulate gut microbiota composition and functional output hold substantial potential for alleviating psychiatric symptoms, enhancing neuroprotection, and improving overall psychological well-being (1,2,30).

6. Conclusion

Recent studies clearly demonstrate that the gut microbiota exerts significant influence on central nervous system function through the gut –brain axis. Key bacterial species such as *Lactobacillus rhamnosus, Bifidobacterium longum*, and *Faecalibacterium prausnitzii* play crucial roles by producing metabolites, modulating immune responses, and regulating neural and hormonal signaling

Despite remarkable advances, further clinical and molecular research is required to elucidate precise mechanisms and optimize therapeutic interventions. The use of probiotics and strategies for microbiota modulation may serve as complementary and innovative approaches in treating psychiatric and neurological disorders. Ultimately, the evidence highlights the gut microbiota as a central regulator of brain health, and targeted manipulation of microbial species holds promise for developing personalized therapies.

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Conflict of Interest

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