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Review Article

Psychobiotics and the microbiota–gut–brain axis

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Abstract

Emerging evidence indicates that the microbiota–gut–brain axis plays a pivotal role in regulating brain function, behavior, and neurological homeostasis. Alterations in gut microbiota composition have been implicated in the pathogenesis of various mental, neurodevelopmental, and neurodegenerative disorders, leading to growing interest in psychobiotics as a promising therapeutic strategy. Psychobiotics, including probiotics, prebiotics, synbiotics, and other microbiota-targeted interventions, may exert beneficial effects by modulating gut microbial composition and activity, thereby influencing bidirectional communication along the microbiota–gut–brain axis. The beneficial effects of psychobiotics are thought to be mediated through multiple mechanisms, including regulation of the hypothalamic–pituitary–adrenal (HPA) axis, modulation of neurotransmitter synthesis, attenuation of systemic and neuroinflammation, enhancement of intestinal barrier integrity, production of microbial metabolites such as short-chain fatty acids, and interaction with the central nervous system through neural, endocrine, and immune pathways. This systematic review summarizes current evidence regarding the therapeutic potential of psychobiotics in mental disorders, including depression, anxiety, schizophrenia, and bipolar disorder, as well as neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, and neurodevelopmental disorders including autism spectrum disorder and attention-deficit/hyperactivity disorder. In addition, the underlying biological mechanisms through which psychobiotics influence the microbiota–gut–brain axis are comprehensively discussed.

Keywords: Gut microbiota, Psychobiotics, Mental disorders, Neurodegenerative disorders, Neurodevelopmental disorders

Introduction

In modern society, a substantial proportion of the population is affected by mental health problems (Jiménez-Pareyón *et al.,* 2025). Mental disorders are characterized by clinically significant disturbances in cognition, emotional regulation, or behavior that reflect dysfunctions in the psychological, biological, or developmental processes underlying mental functioning. Beyond their adverse effects on health and quality of life, mental disorders impose a considerable economic burden on society, as productivity losses and other indirect costs frequently exceed direct healthcare expenditures (WHO, 2022). According to the World Health Organization (WHO) (WHO, 2025), approximately 14% of the global population, corresponding to more than one billion individuals, were living with a mental disorder in 2021. Anxiety and depressive disorders are the most prevalent conditions and together account for more than two-thirds of all mental health disorders. Importantly, the number of individuals affected by mental disorders increased at a faster rate than the global population between 2011 and 2021. Although schizophrenia and bipolar disorder are less prevalent than anxiety and depression, they often have a more severe impact on daily functioning and remain major concerns for mental health services worldwide (Barrio *et al.,* 2022). The prevalence of mental disorders also differs by sex; depressive and anxiety disorders are generally more common among females, whereas autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are diagnosed more frequently in males throughout the life course (WHO, 2025). Accumulating evidence suggests that the gut microbiota influences a wide range of physiological, behavioral, and cognitive functions of the brain (Barrio *et al.,* 2022; Cheng *et al.,* 2022). The gut microbiota, defined as the community of microorganisms residing in the intestinal tract, contributes to numerous host functions, including the maturation of the central nervous system (CNS), the development of immune responses, and the modulation of neuroendocrine signaling. As a key component of the microbiota–gut–brain axis, it communicates bidirectionally with the brain through neural, endocrine, immune, and metabolic pathways (Barrio *et al.,* 2022).

Gut microbiota can modulate brain function and mental health through multiple mechanisms, including vagal signaling, regulation of neuroimmune responses, microbiota-mediated tryptophan metabolism, modulation of neuroendocrine activity, and the production of neuroactive compounds. Moreover, certain gut microorganisms are capable of synthesizing or regulating neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid (GABA), and glutamate, which play critical roles in neurological and immunological processes (Xiong *et al.,* 2023). In contrast, gut dysbiosis, defined as an imbalance in the composition and function of the intestinal microbiota, has been associated with several neuropsychiatric and neurodegenerative disorders, including autism, anxiety, depression, Alzheimer's disease (AD), and Parkinson's disease (PD) (Cheng *et al.,* 2022; Jiménez-Pareyón *et al.,* 2025). Increasing numbers of clinical and experimental studies emphasize the importance of targeting the microbiota–gut–brain axis in the management of neurological and psychiatric disorders. In this context, psychobiotics have emerged as a promising therapeutic approach for the development of novel microbiota-based interventions (Tian *et al.,* 2020; Dziedzic *et al.,* 2024; Merkouris *et al.,* 2024).

Psychobiotics encompass probiotics, prebiotics, synbiotics, and other microbiota-targeted interventions capable of modulating microbiota–gut–brain signaling and positively influencing emotional and cognitive health (Oroojzadeh *et al.,* 2022). These interventions have been investigated for their potential roles in the prevention, management, and alleviation of conditions such as PD, AD, ASD, ADHD, anxiety, and depression (Cui *et al.,* 2025). The present review summarizes current evidence regarding the mechanisms underlying psychobiotic action and evaluates their therapeutic potential in mental, neurodegenerative, and neurodevelopmental disorders.

The microbiota-gut-brain axis

The gut microbiota plays an essential role in maintaining host physiological homeostasis and contributes to numerous biological processes that are fundamental to human health (Kavvadia *et al.,* 2017). In addition to regulating gastrointestinal function, the gut microbiota influences the development and maturation of the CNS, modulates immune responses, regulates the hypothalamic–pituitary–adrenal (HPA) axis, contributes to the maintenance of blood–brain barrier integrity, affects neurotransmitter synthesis and signaling, promotes neurogenesis, and supports myelination. Consequently, maintaining a balanced gut microbial community is essential for preserving normal gut–brain communication and neurological function, whereas microbial dysbiosis has been associated with disturbances in immune, endocrine, and neural homeostasis (Liang *et al.,* 2018).

The gut–brain axis (GBA) is a complex bidirectional communication network linking the gastrointestinal tract and the CNS. This communication is mediated through interconnected neural, endocrine, immune, metabolic, and humoral pathways. The autonomic nervous system, the enteric nervous system, the vagus nerve (VN), and the hypothalamic–pituitary–adrenal (HPA) axis coordinate continuous signaling between the gut and the brain, enabling the CNS to regulate gastrointestinal physiology while allowing gut-derived signals to influence cognition, emotion, stress responses, and behavior (Appleton, 2018).

Given the fundamental role of intestinal microorganisms in this communication network, the term microbiota–gut–brain (MGB) axis has become widely accepted to emphasize the contribution of the gut microbiota to gut–brain signaling (Liang *et al.,* 2018). The MGB axis integrates neural, endocrine, immune, and metabolic pathways through which intestinal microorganisms communicate with the host. Microbial metabolites, immune mediators, neurotransmitters, and neural signaling collectively influence both gastrointestinal and brain function, highlighting the dynamic and reciprocal relationship between the gut microbiota and the CNS (Casertano *et al.,* 2022).

Disruption of gut microbial homeostasis may impair this bidirectional communication. Gut dysbiosis, characterized by alterations in the composition and functional capacity of the intestinal microbiota, has been associated with numerous neurological and psychiatric disorders, including depression, anxiety, ASD, AD, and PD (Cheng *et al.,* 2022; Jiménez-Pareyón *et al.,* 2025). Dysbiosis promotes the production of pro-inflammatory cytokines, microbial toxins, and other harmful metabolites that increase intestinal permeability and contribute to systemic inflammation, neuroinflammation, and altered neural signaling. Consequently, restoration of gut microbial balance has emerged as a promising therapeutic strategy for improving mental and neurological health (Imran *et al.,* 2025).

In this context, psychobiotics have attracted increasing scientific attention because of their ability to modulate the gut microbiota and restore microbiota–gut–brain axis homeostasis. By regulating microbial composition, enhancing intestinal barrier integrity, reducing inflammation, and influencing neurochemical signaling, psychobiotics may alleviate the detrimental effects of gut dysbiosis and contribute to the prevention and management of various mental, neurodevelopmental, and neurodegenerative disorders (Tremblay *et al.,* 2021).

Psychobiotics

Psychobiotics are a class of microbiota-targeted interventions that exert beneficial effects on mental health by modulating the microbiota–gut–brain axis. The concept was first introduced by Dinan *et al.* (2013), who defined psychobiotics as live microorganisms that, when administered in adequate amounts, confer mental health benefits in individuals with psychiatric disorders. Since then, the definition has evolved to include prebiotics, synbiotics, postbiotics, and other interventions capable of modifying the gut microbiota and influencing brain function.

Unlike conventional probiotics, psychobiotics possess the ability to regulate the production of neuroactive compounds, influence immune and neuroendocrine signaling, and modulate communication along the microbiota–gut–brain axis. These properties have generated considerable interest in their potential application as complementary therapeutic agents for a wide range of psychiatric, neurodevelopmental, and neurodegenerative disorders. Among the most extensively investigated psychobiotic microorganisms are members of the genera *Lactobacillus*, *Lacticaseibacillus*, *Lactiplantibacillus*, *Bifidobacterium*, *Streptococcus*, *Enterococcus*, and *Escherichia*. These microorganisms produce a variety of bioactive metabolites, including short-chain fatty acids (SCFAs), neurotransmitters, vitamins, and other signaling molecules that contribute to gut microbial homeostasis and influence CNS function (Kyei-Baffour *et al.,* 2025).

The concept of psychobiotics has expanded considerably over the past decade. Sarkar *et al.* (2016) proposed broadening the definition to include prebiotics and other dietary components capable of selectively stimulating beneficial microorganisms within the gut ecosystem. Prebiotics are non-digestible substrates that are selectively utilized by host microorganisms, resulting in health

benefits for the host. The most extensively investigated prebiotics include fructooligosaccharides (FOS) and galactooligosaccharides (GOS), which promote the growth of beneficial bacterial genera such as *Bifidobacterium* and *Lactobacillus* (Sarkar *et al.,* 2016; Bermúdez-Humarán *et al.,* 2019). Synbiotics, which combine probiotics and prebiotics, have also attracted considerable attention because of their synergistic effects on gut microbial composition, metabolic activity, and microbiota–gut–brain communication. Increasing evidence suggests that synbiotic interventions may enhance cognitive performance, improve emotional well-being, and alleviate symptoms associated with several neurological and psychiatric disorders (Dahiya & Nigam, 2022).

The beneficial effects of psychobiotics are mediated through multiple biological mechanisms. These include modulation of gut microbial composition, restoration of intestinal barrier integrity, regulation of immune and inflammatory responses, attenuation of hypothalamic–pituitary–adrenal (HPA) axis hyperactivity, enhancement of neurotransmitter biosynthesis, and increased production of microbial metabolites such as SCFAs. Through these interconnected pathways, psychobiotics may contribute to the maintenance of brain homeostasis and the prevention or amelioration of stress-related, psychiatric, neurodevelopmental, and neurodegenerative disorders (Binda *et al.,* 2024; Ķimse *et al.,* 2024). Although accumulating evidence supports the therapeutic potential of psychobiotics, their clinical application remains in its early stages. Considerable heterogeneity exists among published studies with respect to probiotic strains, dosages, treatment duration, participant characteristics, and clinical outcomes. Consequently, additional large-scale, well-designed randomized controlled trials are required before psychobiotics can be routinely recommended in clinical practice (Binda *et al.,* 2024).

Mechanisms of action

Although the precise mechanisms underlying the effects of psychobiotics have not yet been fully clarified, accumulating evidence indicates that these microorganisms exert beneficial effects through interactions with the enteric nervous system and the host immune system. These interactions subsequently influence CNS functions, including emotional regulation, cognitive performance, and behavioral responses. Current evidence suggests that the psychobiotic effects are mediated through three principal pathways: (i) modulation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to attenuation of the stress response and systemic inflammatory processes; (ii) regulation of immune function via immunomodulatory mechanisms; and (iii) production of bioactive metabolites, including neurotransmitters, proteins, and SCFAs, which contribute to gut–brain communication (Skowron *et al.,* 2022).

Hypothalamic-pituitary-adrenal (HPA) axis

HPA axis constitutes the principal neuroendocrine system responsible for coordinating the physiological response to stress. This complex network comprises the hypothalamus, pituitary gland, adrenal cortex, and the associated regulatory signals and hormones that collectively maintain stress homeostasis (Kavvadia *et al.,* 2017). Exposure to a stressor initiates the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which subsequently stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH then promotes cortisol synthesis and release from the adrenal cortex. Persistent activation of the HPA axis during chronic stress leads to sustained elevations in cortisol levels, a condition associated with increased threat perception, impaired emotional regulation, and deficits in learning, memory, and other cognitive functions (Ķimse *et al.,* 2024). Emerging evidence highlights a dynamic bidirectional relationship between the HPA axis and the gut microbiota. The establishment and maturation of the gut microbial community during early life play a pivotal role in shaping brain development, behavioral outcomes, and the regulation of the stress response. Conversely, alterations in HPA axis activity can modify the composition and function of the gut microbiota while simultaneously increasing intestinal permeability, thereby further influencing microbiota–gut–brain axis signaling (Del Toro-Barbosa *et al.,* 2020).

Increasing evidence supports a close functional interaction between the gut microbiota and the HPA axis. One of the landmark studies investigating this relationship compared stress-induced HPA axis responses in germ-free (GF), specific pathogen-free (SPF), and gnotobiotic mice. The findings demonstrated that GF mice exhibited an exaggerated HPA axis response to restraint stress compared with SPF mice, providing compelling evidence that the presence of a normal gut microbiota is essential for the appropriate regulation of neuroendocrine stress responses (Sudo *et al.,* 2004). Further experimental studies have also highlighted the therapeutic potential of psychobiotics in modulating HPA axis activity. Tian *et al.* (2020) reported that chronic stress disrupted the negative feedback regulation of corticosterone by downregulating the expression of glucocorticoid receptors (NR3C1), thereby promoting glucocorticoid resistance and a concomitant increase in systemic inflammatory responses. Remarkably, administration of *Bifidobacterium breve* CCFM1025 restored stress-induced alterations in brain *Nr3c1* expression, reduced circulating pro-inflammatory cytokine levels, and significantly alleviated depression-like behaviors in mice. These findings suggest that modulation of the gut microbiota may contribute to the normalization of HPA axis function while simultaneously attenuating neuroinflammation and stress-related behavioral abnormalities (Tian *et al.,* 2020).

Immune response and inflammation

Gut dysbiosis has been increasingly implicated in the development of dysregulated immune responses characterized by excessive production of pro-inflammatory cytokines. The gut microbiota plays a pivotal role in maintaining immune homeostasis by shaping both innate and adaptive immune functions, primarily through the synthesis of bioactive metabolites that mediate

host–microbiota interactions. Although the intestinal epithelial barrier effectively prevents the translocation of most microorganisms into the systemic circulation, microbial metabolites are able to cross this barrier and enter the bloodstream, where they influence the activity and function of various immune cell populations (Del Toro-Barbosa *et al.,* 2020). Furthermore, the gut microbiota regulates mucosal immune responses through bidirectional communication with the intestinal epithelium, thereby contributing to the maintenance of systemic immune homeostasis during infection, inflammation, and autoimmune conditions. Within the CNS, microglia serve as the resident immune cells and play a critical role in neuroimmune surveillance (Imran *et al.,* 2025). Accumulating evidence indicates that the intestinal microbiota is essential for the maturation, morphological development, and functional activity of microglia. These effects are largely mediated by microbiota-derived SCFAs, which act as key signaling molecules involved in regulating microglial development and preserving immune function within the brain (Erny *et al.,* 2015).

Neuroactive compounds

The gut microbiota contributes to microbiota–gut–brain axis communication by modulating the expression of central neurotransmitters and their corresponding receptors, while also producing a broad spectrum of neuroactive metabolites, including neurotransmitters and SCFAs. Neuroactive compounds are biologically active molecules synthesized by neurons or microorganisms that influence the activity of neurons, glial cells, and other target cells. These molecules function as neurotransmitters, neuromodulators, or neurohormones and play fundamental roles in regulating neural signaling and brain function (Casertano *et al.,* 2022).

A growing body of evidence indicates that several members of the gut microbiota are capable of synthesizing neurotransmitters involved in host neurophysiology. For example, *Bifidobacterium infantis*, *Candida* spp., *Streptococcus* spp., *Escherichia* spp., and *Enterococcus* spp. have been reported to produce serotonin, whereas *Bacillus* spp. and *Lactobacillus* spp. are associated with dopamine production. In addition, norepinephrine can be synthesized by *Escherichia* spp., *Bacillus* spp., and *Saccharomyces* spp., while GABA is produced by several *Lactobacillus* and *Bifidobacterium* species. Acetylcholine production has also been demonstrated in *Lactobacillus* species. Collectively, these microbiota-derived neuroactive molecules are thought to influence gut–brain signaling and may contribute to the regulation of emotional, cognitive, and behavioral functions (Skowron *et al.,* 2022).

Serotonin (5-hydroxytryptamine, 5-HT) is a multifunctional neurotransmitter that plays a central role in regulating a wide range of physiological and behavioral processes. In the CNS, serotonin is involved in the modulation of mood, cognition, learning, and emotional processing, whereas in peripheral tissues it contributes to the regulation of gastrointestinal function, bone metabolism, and other physiological processes. Although serotonin is commonly recognized for its role as a central neurotransmitter, the vast majority of the body's serotonin—approximately 95%—is synthesized, stored, and secreted by enterochromaffin (EC) cells located within the intestinal mucosa, highlighting the importance of the gastrointestinal tract as the principal site of serotonin production (Wu *et al.,* 2019).

Catecholamines, including dopamine, norepinephrine, and epinephrine, function as both neurotransmitters and hormones, thereby mediating communication between the nervous and endocrine systems. These bioactive molecules are involved in numerous physiological processes, including the regulation of emotional responses, cognitive performance, attention, motivation, and memory formation. Given their diverse neurobiological functions, alterations in catecholamine signaling have been implicated in the pathophysiology of several neuropsychiatric disorders (Kyei-Baffour *et al.,* 2025).

GABA is the principal inhibitory neurotransmitter in the CNS and is essential for maintaining the balance between neuronal excitation and inhibition. GABAergic signaling contributes to numerous physiological and psychological processes, including the regulation of stress responses, emotional behavior, sleep, and cognitive function. Disruption of the GABAergic system has been implicated in the pathogenesis of several neuropsychiatric disorders, particularly depression and anxiety-related conditions (Du *et al.,* 2020).

Acetylcholine (ACh) is another key neurotransmitter with diverse functions in both the central and peripheral nervous systems. Within the brain, ACh primarily acts as a neuromodulator by regulating neuronal network activity and modulating responses to both internal and external stimuli. In contrast, in the peripheral nervous system, acetylcholine serves as the principal excitatory neurotransmitter, mediating signal transmission at neuromuscular junctions and within the autonomic nervous system (Picciotto *et al.,* 2012).

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that plays a crucial role in neuronal survival, differentiation, synaptic plasticity, and functional maintenance of the CNS. By supporting neuronal growth and connectivity, BDNF contributes to learning, memory, and cognitive function. A growing body of evidence indicates that reduced BDNF expression is closely associated with the development and progression of neuropsychiatric disorders, with lower BDNF levels consistently linked to increased severity of depressive and anxiety symptoms (Ķimse *et al.,* 2024).

Short-chain fatty acids (SCFAs)

SCFAs are the major metabolites generated through the microbial fermentation of non-digestible carbohydrates in the colon and represent key mediators of microbiota–host interactions (Liu *et al.,* 2020). Beyond their well-established role in intestinal physiology, SCFAs have emerged as

critical signaling molecules within the microbiota–gut–brain axis, influencing both peripheral and central mechanisms involved in brain function. Current evidence suggests that their neuroprotective and psychobiological effects are mediated through multiple pathways, including the stimulation of neuropeptide secretion, activation of vagal signaling, modulation of peripheral immune responses, and direct effects on neural cells and brain function (Cheng *et al.,* 2022). In addition, SCFAs contribute to the maintenance of intestinal barrier integrity and gastrointestinal immune homeostasis, thereby limiting systemic inflammation and promoting immune regulation. Through these immunomodulatory actions, SCFAs may protect against a variety of pathological conditions. Experimental studies have further demonstrated that SCFAs influence HPA axis activity, thereby contributing to the regulation of physiological stress responses (O'Riordan *et al.,* 2022). For example, intraluminal administration of physiological concentrations of SCFAs into the proximal colon has been shown to stimulate the release of serotonin from enterochromaffin cells, providing further evidence of their involvement in gut–brain communication (Fukumoto *et al.,* 2003). Moreover, dietary fiber supplementation has been reported to attenuate stress-induced anxiety-like behaviors by promoting favorable alterations in gut microbial composition and increasing SCFA production (Tarr *et al.,* 2015). Collectively, these findings highlight SCFAs as pivotal mediators linking the gut microbiota with neuroendocrine, immune, and neurotransmitter pathways involved in mental health.

Vagus nerve (VN)

The VN, the tenth cranial nerve, is a major component of the parasympathetic nervous system and serves as a critical communication pathway between the gastrointestinal tract and the CNS. It is composed of both afferent (sensory) and efferent (motor) fibers that facilitate bidirectional signaling between peripheral organs and the brain. Sensory fibers of the VN transmit physiological information from visceral organs, including the heart, lungs, liver, pancreas, stomach, and intestines, to central brain regions involved in autonomic regulation and behavioral responses (Del Toro-Barbosa *et al.,* 2020). Vagal afferent endings are strategically positioned beneath the intestinal epithelium, enabling them to detect microbial metabolites and signaling molecules either directly or indirectly. Through this pathway, gut microbiota can influence CNS activity and modulate a wide range of host behaviors, including mood, anxiety, appetite, and sickness-related behaviors (Del Toro-Barbosa *et al.,* 2020). Although gut microorganisms communicate with the brain through multiple mechanisms, including endocrine and immune pathways, vagal signaling is considered the most rapid and direct route of microbiota–brain communication. Continuous bidirectional transmission of neural signals via the VN is essential for maintaining physiological homeostasis and coordinating autonomic responses, further emphasizing its pivotal role within the microbiota–gut–brain axis (Fülling *et al.,* 2019).

Therapeutic effects of psychobiotics in mental disorders

Depression and anxiety

Depression and anxiety are among the most prevalent psychiatric disorders worldwide and represent a substantial public health burden. These conditions frequently coexist, with approximately 45–67% of individuals diagnosed with major depressive disorder also meeting the diagnostic criteria for at least one anxiety disorder, thereby complicating clinical management and reducing treatment efficacy (Asad *et al.,* 2025). Beyond their psychological manifestations, depression and anxiety are associated with considerable functional impairment, disability, diminished quality of life, and significant socioeconomic consequences affecting patients, their families, and society (Rosas-Sánchez *et al.,* 2025).

The pathophysiology of depression and anxiety is multifactorial and involves complex interactions among genetic susceptibility, environmental factors, and neurobiological alterations. Dysregulation of the HPA axis, chronic low-grade inflammation, neurotransmitter imbalance, impaired neuroplasticity, and disturbances in the microbiota–gut–brain axis have all been implicated in disease development and progression (Cui *et al.,* 2025).

Stress is considered one of the major environmental risk factors for both depression and anxiety. Persistent or excessive stress promotes HPA axis hyperactivity, disrupts emotional regulation, and contributes to cognitive dysfunction, thereby increasing susceptibility to mood disorders (Smith *et al.,* 2021). Moreover, accumulating evidence indicates that chronic stress induces profound alterations in gut microbial composition, including reductions in beneficial genera such as *Lactobacillus* and *Bifidobacterium*. These microbial changes are associated with impaired serotonin metabolism, increased intestinal permeability, gastrointestinal dysfunction, and heightened systemic inflammation, ultimately contributing to the development of anxiety, depression, post-traumatic stress disorder, and other stress-related disorders (Kavvadia *et al.,* 2017; Góralczyk-Bińkowska *et al.,* 2022; Ross, 2023).

Increasing evidence suggests that psychobiotics may counteract these pathological processes by restoring gut microbial homeostasis and improving microbiota–gut–brain communication. Experimental studies have demonstrated that *Lactobacillus johnsonii* BS15 prevents restraint stress-induced hippocampal dysfunction by reducing intestinal inflammation and preserving gut barrier integrity, thereby improving cognitive performance (Wang *et al.,* 2021). Similarly, a short-term psychobiotic dietary intervention significantly reduced perceived stress and induced beneficial metabolic alterations in the gut microbiota of healthy adults, highlighting the therapeutic potential of dietary strategies targeting the microbiota–gut–brain axis (Berding *et al.,* 2023).

Distinct alterations in gut microbial composition have consistently been reported in individuals with depression and anxiety. These alterations are generally characterized by increased abundances of *Bacteroidetes*, *Proteobacteria*, and *Alistipes*, together with reduced levels of beneficial taxa, including *Firmicutes*, *Lactobacillus*, *Bifidobacterium*, *Lachnospiraceae*, and *Faecalibacterium*. In particular, enrichment of *Alistipes* species has repeatedly been associated with depressive and anxiety disorders, suggesting their potential role as microbial biomarkers (Ross, 2023).

Mechanistically, gut dysbiosis contributes to psychiatric disorders through multiple interconnected pathways, including excessive inflammatory responses, altered production of neurotransmitters and microbial metabolites, increased intestinal permeability, and dysregulation of HPA axis activity. Microbial metabolites, particularly SCFAs and tryptophan-derived metabolites, participate in serotonin biosynthesis and neuroimmune signaling, thereby influencing emotional and cognitive functions. Consequently, modulation of the gut microbiota through psychobiotic interventions may simultaneously attenuate inflammation, restore neurotransmitter homeostasis, normalize HPA axis function, and improve mood-related symptoms (Cui *et al.,* 2025; Rosas-Sánchez *et al.,* 2025).

Preclinical studies provide substantial evidence supporting the antidepressant and anxiolytic effects of psychobiotics. Administration of *Bifidobacterium breve* CCFM1025 significantly reduced anxiety- and depression-like behaviors in chronically stressed mice while restoring HPA axis activity, decreasing inflammatory responses, increasing BDNF expression, and correcting stress-induced microbial dysbiosis accompanied by elevated SCFA and 5-hydroxytryptophan (5-HTP) levels (Tian *et al.,* 2020). Likewise, *Lactiplantibacillus plantarum* D-9 alleviated anxiety- and depression-like behaviors in mice by regulating tryptophan metabolism, suppressing inflammation, restoring HPA axis function, and remodeling the gut microbial community (Jia *et al.,* 2024a). In another experimental study, *Lactobacillus plantarum* JYLP-326 ameliorated anxiety, depression, and insomnia in examination-stressed college students while simultaneously improving gut microbial composition and fecal metabolomic profiles, suggesting that microbial and metabolic signatures may serve as potential biomarkers of stress-related psychiatric disorders (Zhu *et al.,* 2023). Furthermore, multi-strain probiotics isolated from Thai fermented foods exhibited anxiolytic, antioxidant, and neuroprotective properties in animal models, accompanied by improvements in locomotor activity and short-term memory (Luang-In *et al.,* 2020).

Clinical evidence also supports the therapeutic potential of psychobiotics. Adjunctive probiotic therapy has been shown to improve depressive symptoms while inducing favorable alterations in both gut microbiota composition and brain function in patients with major depressive disorder (Schaub *et al.,* 2022). Similarly, multi-strain probiotic supplementation significantly reduced depression severity and improved gastrointestinal function compared with placebo, suggesting additional benefits for patients presenting with both depressive symptoms and gastrointestinal disturbances (Tian *et al.,* 2023). Moreover, supplementation with *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 for eight weeks improved depressive symptoms, potentially through increasing circulating BDNF levels (Heidarzadeh-Rad *et al.,* 2020). High-prebiotic dietary interventions have likewise demonstrated beneficial effects on mood, anxiety, perceived stress, and sleep quality in adults experiencing psychological distress (Freijy *et al.,* 2023).

Evidence from systematic reviews and meta-analyses further supports the clinical relevance of microbiota-targeted interventions. A meta-analysis including 13 randomized controlled trials involving 786 participants demonstrated that prebiotics, probiotics, and synbiotics significantly improved depressive symptoms compared with placebo (Zhang *et al.,* 2023). More recent meta-analyses suggest that probiotics may also alleviate anxiety and cognitive symptoms, although the magnitude of these effects varies among studies owing to differences in probiotic strains, intervention duration, dosage, and study populations (Le Morvan de Sequeira *et al.,* 2022; Merkouris *et al.,* 2024; Zandifar *et al.,* 2025).

Overall, current evidence indicates that psychobiotics represent a promising adjunctive strategy for the prevention and management of depression and anxiety by modulating the microbiota–gut–brain axis. Nevertheless, considerable heterogeneity among clinical studies remains regarding probiotic strains, treatment protocols, patient characteristics, and outcome measures. Therefore, large-scale, well-designed randomized controlled trials are warranted to establish standardized psychobiotic interventions and to further elucidate the molecular mechanisms underlying their beneficial effects on mental health.

Schizophrenia

Schizophrenia is a severe and chronic psychiatric disorder characterized by profound impairments in cognitive, emotional, and social functioning, often resulting in long-term disability. Clinically, the disorder encompasses positive symptoms, including hallucinations and delusions; negative symptoms, such as anhedonia, avolition, alogia, and social withdrawal; and cognitive deficits affecting attention, working memory, executive function, processing speed, and learning abilities (Orsolini *et al.,* 2022). According to the WHO, schizophrenia affected approximately 23 million people worldwide in 2021, corresponding to nearly 1 in every 200 adults aged 20 years and older, and remains one of the leading causes of disability among psychiatric disorders (WHO, 2025).

Emerging evidence suggests that alterations in gut microbial composition may contribute to the pathophysiology of schizophrenia through the microbiota–gut–brain axis. Comparative microbiome studies have consistently demonstrated significant differences between individuals

with schizophrenia and healthy controls, indicating disease-specific microbial signatures (Manchia *et al.,* 2021). Increased abundances of *Lactobacillus*, *Succinivibrio*, *Collinsella*, and *Klebsiella*, together with reduced levels of *Bacteroides*, *Roseburia*, and *Faecalibacterium*, have been reported in patients with schizophrenia, supporting the presence of gut microbial dysbiosis in this disorder (Gao *et al.,* 2022).

Given the close relationship between gut dysbiosis, immune dysfunction, and metabolic abnormalities in schizophrenia, psychobiotics have attracted increasing attention as adjunctive therapeutic agents. A systematic review by Soleimani *et al.* (2023) suggested that probiotic supplementation may improve triglyceride, total cholesterol, and fasting blood glucose concentrations while reducing antipsychotic-associated metabolic disturbances, highlighting its potential role as an adjunct to conventional antipsychotic therapy. Furthermore, supplementation with *Bifidobacterium breve* A-1 was shown to alleviate anxiety and depressive symptoms in patients with schizophrenia, indicating that psychobiotics may also provide benefits for comorbid affective symptoms (Okubo *et al.,* 2019). In addition to their metabolic effects, psychobiotics appear to exert immunomodulatory actions that may be relevant to schizophrenia pathogenesis. Tomasik *et al.* (2015) demonstrated that adjunctive probiotic therapy in patients with chronic schizophrenia significantly reduced circulating von Willebrand factor (vWF) levels while increasing BDNF and several immune mediators, including monocyte chemoattractant protein-1 (MCP-1), RANTES, and macrophage inflammatory protein-1β (MIP-1β). These findings suggest that probiotics may influence immune regulation and intestinal barrier function, potentially through modulation of IL-17-related signaling pathways.

Several randomized clinical trials have further demonstrated the therapeutic potential of combined nutritional interventions. Co-supplementation with probiotics and selenium for 12 weeks significantly improved Positive and Negative Syndrome Scale (PANSS) scores and metabolic parameters in patients with chronic schizophrenia (Jamilian & Ghaderi, 2021). Similarly, combined supplementation with probiotics and vitamin D resulted in significant improvements in both total and general PANSS scores, together with favorable metabolic outcomes (Ghaderi *et al.,* 2019).

Overall, current evidence indicates that psychobiotics may represent a promising adjunctive strategy for schizophrenia by targeting gut microbial dysbiosis, immune dysregulation, and metabolic disturbances while potentially improving psychiatric symptom severity. Nevertheless, the available clinical evidence remains limited by relatively small sample sizes, heterogeneous study designs, and variability in probiotic strains and treatment protocols. Therefore, larger, well-designed randomized controlled trials are required to establish the clinical efficacy of psychobiotics and to clarify the mechanisms through which they influence schizophrenia pathophysiology.

Bipolar disorder (BP)

BD is a chronic and recurrent mood disorder characterized by alternating episodes of depression and mania or hypomania. Affecting approximately 2–3% of the global population, BD is associated with substantial morbidity and is frequently accompanied by impairments in cognitive performance, psychosocial functioning, and overall quality of life (Lai *et al.,* 2020).

Growing interest in the microbiota–gut–brain axis has prompted investigations into the potential role of psychobiotics as adjunctive interventions for bipolar disorder. Preliminary clinical evidence suggests that probiotic supplementation may improve cognitive and psychological outcomes in patients with BD. In a pilot study, three months of daily probiotic supplementation enhanced attention, psychomotor processing speed, and executive function in euthymic individuals with bipolar disorder (Reininghaus *et al.,* 2018). In a subsequent study, supplementation with a multi-strain probiotic formulation containing nine *Bifidobacterium* and *Lactobacillus* strains was associated with improvements in gastrointestinal symptoms and reductions in negative cognitive reactivity among euthymic patients (Reininghaus *et al.,* 2020). However, the available evidence remains inconsistent. Sabouri *et al.* (2022) reported that eight weeks of probiotic supplementation did not produce significant improvements in inflammatory or oxidative stress biomarkers in patients with bipolar I disorder, indicating that the biological effects of psychobiotics may vary according to study design, intervention characteristics, or patient-related factors. In contrast, Dickerson *et al.* (2018) demonstrated that adjunctive treatment with *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* Bb12 significantly reduced rehospitalization rates among patients recently discharged following hospitalization for a manic episode, suggesting potential benefits in relapse prevention.

Overall, current findings indicate that psychobiotics may offer therapeutic benefits in bipolar disorder, particularly with respect to cognitive function, gastrointestinal health, and relapse prevention. Nevertheless, the existing evidence is derived from a limited number of relatively small clinical studies, and the results remain heterogeneous. Therefore, larger randomized controlled trials are required to establish the efficacy of psychobiotic interventions, identify the most effective probiotic strains and treatment regimens, and elucidate the mechanisms underlying their effects in bipolar disorder.

Therapeutic effects of psychobiotics in neurodegenerative disorders

Parkinson's disease (PD)

PD is the second most common neurodegenerative disorder and affects approximately 2–3% of individuals older than 65 years. Clinically, PD is characterized by progressive motor manifestations, including bradykinesia, resting tremor, rigidity, and gait disturbances, together

with a wide spectrum of non-motor symptoms such as hyposmia, cognitive impairment, orthostatic hypotension, rapid eye movement sleep behavior disorder (RBD), constipation, and delayed gastric emptying (Elfil *et al.,* 2020; Williams-Gray & Worth, 2023).

Accumulating evidence indicates that alterations in the microbiota–gut–brain axis contribute to the pathogenesis and progression of PD. Gut microbial dysbiosis in PD is typically characterized by a reduction in beneficial short-chain fatty acid (SCFA)-producing bacteria, particularly butyrate-producing taxa that are essential for maintaining intestinal barrier integrity, regulating immune responses, and supporting neuronal health. Conversely, an increased abundance of pro-inflammatory microorganisms has been consistently reported, suggesting that microbial imbalance may promote chronic inflammation and neurodegeneration (Elfil *et al.,* 2020; X. Jia *et al.,* 2024b).

Given the central role of the gut microbiota in PD, psychobiotics have emerged as promising adjunctive therapeutic agents capable of modulating microbiota–gut–brain axis signaling. Experimental studies have demonstrated that *Clostridium butyricum* exerts neuroprotective effects by restoring gut microbial homeostasis and regulating microbiota–gut–brain communication, thereby attenuating pathological processes associated with PD (Tan *et al.,* 2020; Sun *et al.,* 2021).

Clinical studies further support the beneficial effects of microbiota-targeted interventions in PD. Early investigations showed that supplementation with *Lactobacillus acidophilus* and *Bifidobacterium infantis* alleviated abdominal pain and bloating, although improvements in constipation were modest (Georgescu *et al.,* 2016). In contrast, consumption of fermented milk enriched with multiple probiotic strains and prebiotic fiber significantly improved constipation in patients with PD (Barichella *et al.,* 2016).

More recent clinical trials have demonstrated broader therapeutic benefits. Twelve weeks of supplementation with *Lactobacillus plantarum* PS128 significantly improved motor performance, as reflected by reductions in Unified Parkinson's Disease Rating Scale (UPDRS) scores during both OFF and ON medication states. In addition, PS128 prolonged ON periods, shortened OFF periods, improved quality of life measured by the 39-item PD Questionnaire (PDQ-39), and reduced circulating markers of oxidative stress, including plasma myeloperoxidase (Lu *et al.,* 2021).

Similarly, a 12-week synbiotic intervention containing *Lacticaseibacillus paracasei* DG and the prebiotic inulin significantly improved constipation as well as several non-motor symptoms, including anxiety, alexithymia, and autonomic dysfunction affecting gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual functions (Andreozzi *et al.,* 2024). These clinical improvements were accompanied by favorable alterations in gut microbial composition, particularly an increased abundance of *Faecalibacterium prausnitzii* and other members of the order *Oscillospirales*. Furthermore, probiotic supplementation has been shown to modulate the expression of inflammatory and immunoregulatory genes, including *IL-1*, *IL-8*, *TNF-α*, *TGF-β*, and *PPAR-γ*, highlighting the anti-inflammatory potential of psychobiotic therapy in PD (Borzabadi *et al.,* 2018).

Collectively, current evidence suggests that psychobiotics may provide multiple therapeutic benefits in PD by restoring gut microbial balance, reducing intestinal and systemic inflammation, improving gastrointestinal dysfunction, alleviating motor and non-motor symptoms, and exerting neuroprotective effects through modulation of the microbiota–gut–brain axis. Nevertheless, the available clinical evidence remains limited by relatively small sample sizes and short intervention periods. Therefore, large-scale, long-term randomized controlled trials are warranted to establish the efficacy, optimal formulations, and safety of psychobiotic therapies in patients with PD.

Alzheimer's disease (AD)

AD is the most common cause of dementia and a progressive neurodegenerative disorder characterized by deterioration of memory, cognition, behavior, and functional capacity, ultimately compromising patients' independence and quality of life. The neuropathological hallmarks of AD include extracellular deposition of amyloid-β (Aβ) plaques and intracellular accumulation of hyperphosphorylated tau protein in the form of neurofibrillary tangles. Disease development is influenced by multiple factors, including aging, genetic susceptibility, and environmental exposures (Kesika *et al.,* 2021; Ağagündüz *et al.,* 2022). AD accounts for approximately 80% of dementia cases worldwide, and its prevalence continues to rise with population aging. According to the Global Burden of Disease Study, approximately 43.8 million individuals were living with AD in 2016, while projections estimate that this number will increase to 74.7 million by 2030 and exceed 130 million by 2050, representing a major global public health challenge (Kesika *et al.,* 2021).

Increasing evidence implicates the microbiota–gut–brain axis in the pathogenesis of AD and identifies gut microbial dysbiosis as a potential therapeutic target. Alterations in gut microbial composition have been associated with enhanced neuroinflammation, disruption of intestinal barrier integrity, abnormal amyloid deposition, and impaired neuronal function, suggesting that modulation of the gut microbiota may influence disease progression (Zhu *et al.,* 2021; Ağagündüz *et al.,* 2022). Consequently, psychobiotics have emerged as promising adjunctive interventions capable of modifying several pathological mechanisms involved in AD.

Both experimental and clinical studies have demonstrated beneficial effects of psychobiotics on cognitive function and disease-related pathology. In one of

the first clinical trials, daily consumption of probiotic milk containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* for 12 weeks significantly improved cognitive performance and several metabolic parameters in patients with AD (Akbari *et al.,* 2016). Similarly, supplementation with a multispecies probiotic formulation was shown to alter gut microbial composition and modulate circulating tryptophan metabolism, supporting a role for microbiota-targeted interventions in AD (Leblhuber *et al.,* 2018). However, another clinical study reported no significant improvements in cognitive or biochemical outcomes among patients with severe AD, suggesting that treatment efficacy may depend on disease stage, probiotic formulation, dosage, and intervention timing (Agahi *et al.,* 2018).

Experimental evidence further supports the neuroprotective potential of psychobiotics. The SLAB51 probiotic formulation reduced oxidative stress in the brains of AD mouse models through activation of SIRT1-dependent pathways, indicating its potential as an adjunctive therapeutic approach (Bonfili *et al.,* 2018). Likewise, *Lactobacillus plantarum* MTCC 1325 ameliorated cognitive impairment and restored acetylcholine levels in a D-galactose-induced rat model of AD (Nimgampalle & Kuna, 2017).

More recent studies have demonstrated that advanced psychobiotic formulations exert broader therapeutic effects. Layer-by-layer encapsulated *Lactiplantibacillus plantarum* ($(CS/SP)_2$-LP) significantly improved cognitive deficits in APP/PS1 transgenic mice by reducing Aβ deposition, attenuating neuroinflammation, limiting neuronal damage, restoring intestinal barrier integrity, improving tau phosphorylation, increasing postsynaptic density protein-95 (PSD-95) expression, normalizing gut microbial composition, and enhancing short-chain fatty acid (SCFA) production (Hu *et al.,* 2024). Similarly, combined prebiotic and probiotic supplementation decreased amyloid plaque accumulation, promoted neuroprotection, and modulated astrocyte and microglial phenotypes within the hippocampus of APP/PS1 mice (Lana *et al.,* 2024). In another preclinical study, multi-strain probiotic treatment improved cognitive performance while attenuating neuronal injury, amyloid and tau pathology, and neuroinflammatory responses in senescence-accelerated mouse prone 8 (SAMP8) mice (Xiao-hang *et al.,* 2024).

Collectively, current evidence suggests that psychobiotics may influence multiple pathological pathways involved in AD, including gut microbial dysbiosis, neuroinflammation, intestinal barrier dysfunction, oxidative stress, amyloid and tau pathology, and neurotransmitter dysregulation. Although preclinical findings are highly encouraging, clinical evidence remains limited and inconsistent. Therefore, adequately powered, long-term randomized controlled trials are needed to determine the efficacy, safety, optimal formulations, and mechanisms of psychobiotic interventions in patients with AD.

Therapeutic effects of psychobiotics in neurodevelopmental disorders

Autism spectrum disorder (ASD)

ASD is a heterogeneous neurodevelopmental disorder characterized by persistent impairments in social communication and social interaction, together with restricted, repetitive patterns of behavior, interests, or activities (Martínez-González & Andreo-Martínez, 2023). The global prevalence of ASD has increased markedly over recent decades, making it an important public health concern (Chiarotti & Venerosi, 2020). In addition to its core behavioral manifestations, ASD is frequently accompanied by gastrointestinal (GI) disorders, with an estimated prevalence ranging from 46% to 84% among affected children. Common gastrointestinal manifestations include chronic constipation, diarrhea, gastroesophageal reflux, abdominal pain, flatulence, nausea, inflammatory bowel disease, food intolerance, and impaired growth (Al-Beltagi, 2021). Increasing evidence suggests that these gastrointestinal abnormalities are closely associated with alterations in gut microbial composition and function. Children with ASD exhibit distinct patterns of gut dysbiosis together with changes in microbial metabolites, particularly SCFAs, which have been implicated in the pathophysiology of the disorder (Wang *et al.,* 2020; Duque *et al.,* 2021).

The growing recognition of the microbiota–gut–brain axis has stimulated interest in psychobiotics as potential adjunctive interventions for ASD. Both preclinical and clinical studies indicate that psychobiotics may alleviate gastrointestinal dysfunction while improving behavioral and cognitive outcomes through modulation of gut microbial communities and microbial metabolism. In an experimental study, *Bifidobacterium animalis* subsp. *lactis* Probio-M8 attenuated autism-like behaviors in mice by enhancing gut microbial diversity and restoring metabolic homeostasis (Miao *et al.,* 2024). Likewise, probiotic supplementation in children with ASD significantly increased fecal *Bifidobacterium* and *Lactobacillus* abundance, accompanied by improvements in gastrointestinal symptoms, reductions in autism severity, and favorable changes in body weight (Shaaban *et al.,* 2018). Furthermore, treatment with SB-121, a formulation containing *Limosilactobacillus reuteri*, Sephadex®, and maltose, improved adaptive behavior and social preference in individuals with ASD, suggesting beneficial effects on core behavioral manifestations (Schmitt *et al.,* 2023).

Additional evidence supports the potential benefits of microbiota-targeted interventions in ASD. Duque *et al.* (2021) reported that probiotic, prebiotic, and synbiotic therapies beneficially modified gut microbial composition and metabolic activity in children with ASD. Specifically, probiotic supplementation increased the relative abundance of *Lactobacillus*, whereas prebiotic treatment promoted *Bifidobacterium* growth and reduced *Lachnoclostridium* abundance. These microbial changes were accompanied by increased SCFA production and reduced ammonium

concentrations, particularly following prebiotic and synbiotic interventions. Similarly, supplementation with probiotics combined with fructo-oligosaccharides modulated gut microbiota composition, SCFA production, serotonin metabolism, and dopaminergic signaling, leading to improvements in ASD-related symptoms (Wang *et al.,* 2020). Consistent with these findings, precision synbiotic therapy increased microbial α-diversity, altered microbial metabolic pathways, and improved gastrointestinal discomfort, language ability, cognition, and communication skills in children with ASD (Phan *et al.,* 2024).

Recent randomized controlled trials have further strengthened the clinical evidence supporting psychobiotic interventions. In a double-blind parallel-group study involving 182 children with ASD, supplementation with a microencapsulated kefir-derived probiotic formulation (K11), either alone or enriched with zinc, selenium, magnesium, and vitamin A (K11-TMAX), significantly improved adaptive behavior and autism-related symptoms over a 90-day intervention period. These clinical improvements were accompanied by reductions in insulin, C-reactive protein, cortisol, and fecal calprotectin concentrations, together with increased *Lactobacillus* abundance and decreased *Escherichia coli* levels, suggesting simultaneous modulation of metabolic, inflammatory, and microbial pathways (de Queiroz *et al.,* 2026).

Overall, accumulating evidence indicates that psychobiotics may represent a promising adjunctive strategy for ASD by restoring gut microbial homeostasis, improving gastrointestinal function, regulating microbial metabolites, and alleviating behavioral symptoms through the microbiota–gut–brain axis. Nevertheless, current clinical evidence remains limited by heterogeneity in study design, probiotic formulations, intervention duration, and outcome measures. Therefore, large-scale, well-controlled clinical trials are needed to establish standardized psychobiotic therapies and to clarify the mechanisms underlying their effects in individuals with ASD.

Attention deficit/hyperactivity disorder (ADHD)

ADHD is the most common neurodevelopmental disorder among children and adolescents, with an estimated global prevalence ranging from 3.4% to 7.2% (Boonchooduang *et al.,* 2020). ADHD is characterized by persistent symptoms of inattention, hyperactivity, and impulsivity that interfere with academic achievement, social relationships, and overall quality of life. Pharmacological management primarily relies on medications that modulate dopaminergic, noradrenergic, and serotonergic neurotransmission. However, treatment adherence is often limited by adverse effects, concerns regarding long-term medication use, social stigma, and poor compliance, particularly during adolescence (Cocean & Vodnar, 2024).

Increasing evidence suggests that alterations in the gut microbiota may contribute to the pathophysiology of ADHD through interactions within the microbiota–gut–brain axis. Several studies have reported differences in gut microbial composition between children with ADHD and healthy controls, supporting a potential role of gut dysbiosis in disease development (Boonchooduang *et al.,* 2020; Lawrence *et al.,* 2025). Notably, a prospective randomized study demonstrated that children who later developed ADHD had lower fecal abundances of *Bifidobacterium* species during the first six months of life. Early supplementation with *Lactobacillus rhamnosus* GG was associated with a reduced risk of developing ADHD and Asperger syndrome, suggesting that modulation of the gut microbiota during early life may exert long-term neurodevelopmental effects (Pärtty *et al.,* 2015).

Clinical studies have increasingly explored the therapeutic potential of psychobiotics in ADHD. Supplementation with *Bifidobacterium bifidum* Bf-688 significantly improved core ADHD symptoms, promoted healthy weight gain, and favorably modified gut microbial composition in affected children (Wang *et al.,* 2022). In a subsequent study, the same probiotic strain enhanced neuropsychological performance, with these improvements being associated with microbiota remodeling and reduced N-glycan biosynthesis, suggesting a potential metabolic mechanism underlying its beneficial effects (Wang *et al.,* 2024). Similarly, supplementation with *Lactobacillus rhamnosus* GG improved physical, emotional, social, and school-related functioning in children and adolescents with ADHD in a pilot randomized controlled trial (Kumperscak *et al.,* 2020).

Adjunctive psychobiotic therapy has also shown encouraging results when combined with conventional pharmacological treatment. Co-administration of *Lactobacillus acidophilus* LB with atomoxetine for three months significantly improved ADHD symptom severity and cognitive performance compared with pharmacotherapy alone (Elhossiny *et al.,* 2023). Likewise, a double-blind, placebo-controlled randomized clinical trial demonstrated that supplementation with a 14-strain probiotic formulation in combination with weight-adjusted methylphenidate (Ritalin) significantly reduced symptom severity in children aged 6–12 years with ADHD (Ghanaatgar *et al.,* 2023).

Synbiotic interventions have also demonstrated potential benefits in ADHD. Treatment with Synbiotic 2000 was associated with reductions in subclinical autism-related repetitive behaviors in children and improved emotional regulation in adults (Skott *et al.,* 2020). Furthermore, Synbiotic 2000 significantly reduced circulating inflammatory markers, including IL-12/IL-23p40 and soluble intercellular adhesion molecule-1 (sICAM-1), while increasing fecal propionic acid concentrations, suggesting that modulation of immune function and microbial metabolism may contribute to its therapeutic effects (Yang *et al.,* 2023).

Overall, current evidence indicates that psychobiotics may represent a promising adjunctive strategy for ADHD by modulating gut microbial composition, improving neuropsychological function, regulating inflammatory pathways, and enhancing the effectiveness

of conventional therapies through the microbiota–gut–brain axis. Nevertheless, the available evidence remains limited by relatively small sample sizes, heterogeneous intervention protocols, and variability in probiotic formulations. Therefore, large, well-designed randomized controlled trials are needed to establish standardized psychobiotic therapies and clarify their long-term efficacy and underlying mechanisms in ADHD.

Limitations and future perspectives

Despite the growing body of evidence supporting the therapeutic potential of psychobiotics, several important limitations currently hinder their translation into routine clinical practice. Much of the available evidence is derived from preclinical studies or clinical trials with relatively small sample sizes, limiting the robustness and generalizability of the findings. Moreover, substantial heterogeneity exists across studies with respect to participant characteristics, disease severity, baseline gut microbiota composition, probiotic strains, dosages, intervention duration, and clinical outcome measures. This variability complicates comparisons between studies, reduces reproducibility, and limits the development of standardized psychobiotic treatment strategies.

Another major challenge is the incomplete understanding of the molecular and cellular mechanisms through which psychobiotics influence the microbiota–gut–brain axis. Although modulation of immune responses, neurotransmitter production, microbial metabolites, intestinal barrier integrity, and neuroendocrine signaling has been proposed, the relative contribution of these pathways and their interactions remain insufficiently characterized. Furthermore, reliable biomarkers capable of predicting treatment response or identifying individuals most likely to benefit from psychobiotic interventions have yet to be established.

The long-term efficacy and safety of psychobiotic supplementation also require further investigation. Although probiotics and related microbiota-targeted interventions are generally considered safe, their effects are highly strain-specific, and concerns remain regarding potential microbial translocation, unintended immunological responses, and other adverse events, particularly in immunocompromised or medically vulnerable populations. Consequently, comprehensive long-term safety assessments are necessary before widespread clinical implementation can be recommended.

Future research should focus on integrating advanced multi-omics technologies, host–microbiome interaction analyses, metabolomics, and neuroimmune profiling to elucidate the biological mechanisms underlying psychobiotic activity and to identify predictive biomarkers of treatment response. In parallel, large-scale, multicenter, randomized controlled trials employing standardized psychobiotic formulations, optimized dosing regimens, harmonized study protocols, and clearly defined clinical endpoints are essential to establish the efficacy, safety, and clinical applicability of psychobiotics in the prevention and treatment of psychiatric, neurodegenerative, and neurodevelopmental disorders.

Conclusion

In conclusion, accumulating evidence indicates that psychobiotics represent a promising microbiota-targeted approach for the prevention and adjunctive management of a broad spectrum of psychiatric, neurodegenerative, and neurodevelopmental disorders, including depression, anxiety, bipolar disorder, schizophrenia, AD, PD, ASD, and ADHD. By modulating the microbiota–gut–brain axis, psychobiotics have been associated with improvements in cognitive performance, emotional regulation, behavioral symptoms, gastrointestinal function, and overall quality of life. Their therapeutic effects appear to be mediated through multiple interconnected mechanisms, including regulation of the hypothalamic–pituitary–adrenal (HPA) axis, modulation of immune and inflammatory responses, production of neuroactive compounds and microbial metabolites, and restoration of gut microbial homeostasis.

Despite these encouraging findings, the current evidence base remains limited by methodological heterogeneity, relatively small clinical trials, and an incomplete understanding of the mechanisms underlying psychobiotic action. Consequently, additional well-designed, large-scale, multicenter randomized controlled trials are required to establish the efficacy, long-term safety, optimal probiotic strains, dosing strategies, and treatment duration of psychobiotic interventions. Advancing mechanistic knowledge and identifying reliable biomarkers of treatment response will be essential for translating psychobiotics into evidence-based, personalized therapeutic strategies for disorders involving the microbiota–gut–brain axis.

Author contributions

All authors contributed equally to the conception and design of the study. All authors approved the final version of the manuscript.

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