REVIEW article

Engineering the gut-brain connection for the future of mental health with psychobiotics

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Abstract: The gut-brain axis is a dynamic, bidirectional communication system connecting the central nervous system with the enteric nervous system. It regulates digestion, cognition, mood, and immune responses and plays an important role in neuropsychiatric and gastrointestinal disorders. Psychobiotics are described as live organisms that interact with the gut-brain axis to improve mental health in the host when consumed in sufficient amounts. This review outlines the mechanism through which psychobiotics will exert their effects, including neurotransmitter modulation (e.g., serotonin, GABA), regulation of the hypothalamic-pituitary-adrenal axis, inhibition of neuroinflammation and oxidative stress, restoration of intestinal barrier integrity, and production of neuroactive microbial metabolites such as short-chain fatty acids and tryptophan derivatives. Advances in psychobiotics include engineered microbial strains, targeted delivery systems, personalized therapies, and combination therapies improving mental health. Despite these advances, challenges such as individual differences, regulatory issues, and ethical concerns persist. Continued clinical research is needed to confirm that the psychobiotics are safe and effective for the treatment of psychiatric and neurodevelopmental disorders.

Introduction

The gut-brain axis (GBA) is a complex, bidirectional communication system that connects the brain's emotional and cognitive centres with peripheral intestinal functions. It consists of interactions between the central nervous system and the enteric nervous system, and includes neuronal, endocrine, immune, and metabolic signalling pathways [1]. It is known that disruptions in this communication network play an important role in the pathogenesis of a number of neurodevelopmental and psychiatric disorders, such as anxiety, depression, and autism spectrum disorders [2]. According to World Health Organization, over 970 million individuals were diagnosed with mental illness, having anxiety and depression being the most prominent in 2019 [3, 4]. Preliminary estimates revealed that the major depressive disorder and anxiety disorders have increased by 28% and 26%, respectively, with a past year. The majority of persons with mental illnesses do not have access to quality care, despite the existence of effective preventative and treatment options. Furthermore, a lot of people experience discrimination, stigma, and violation of their human rights [3]. Recent studies have shown that the gut flora plays a significant role in mental health due to its effect on GBA. Gut flora produces various neuroactive substances like serotonin, GABA, and short-chain fatty acids that affect behaviour, mood, and cognitive functions. Any imbalance or disruption in the natural composition of gut microorganisms (dysbiosis) may lead to mental illnesses like autism, anxiety, and depression. Hence,

targeting the gut microbiota may provide novel strategies for treating psychiatric disorders [5]. Psychobiotics, the class of probiotics known to have a positive effect on mental health by influencing the GBA. These are the living microorganisms, when taken in sufficient quantities, shown to improve mental health, particularly in those with psychiatric disorders. Through the GBA, these beneficial microbes will produce neuroactive chemicals like serotonin and GABA that help control brain activity [6, 7]. This review aims to explore the mechanisms by which the GBA influences mental health, discuss the emerging therapeutic potential of psychobiotics, and highlight recent innovations in engineering microbial systems for targeted neuropsychiatric interventions.

The GBA: a bidirectional communication network: The GBA is a dynamic, bidirectional communication system connecting the CNS with the enteric nervous system (ENS), **Figure 1**. It regulates digestion, cognition, mood, and immune responses and plays an important role in neuropsychiatric and gut disorders [8].

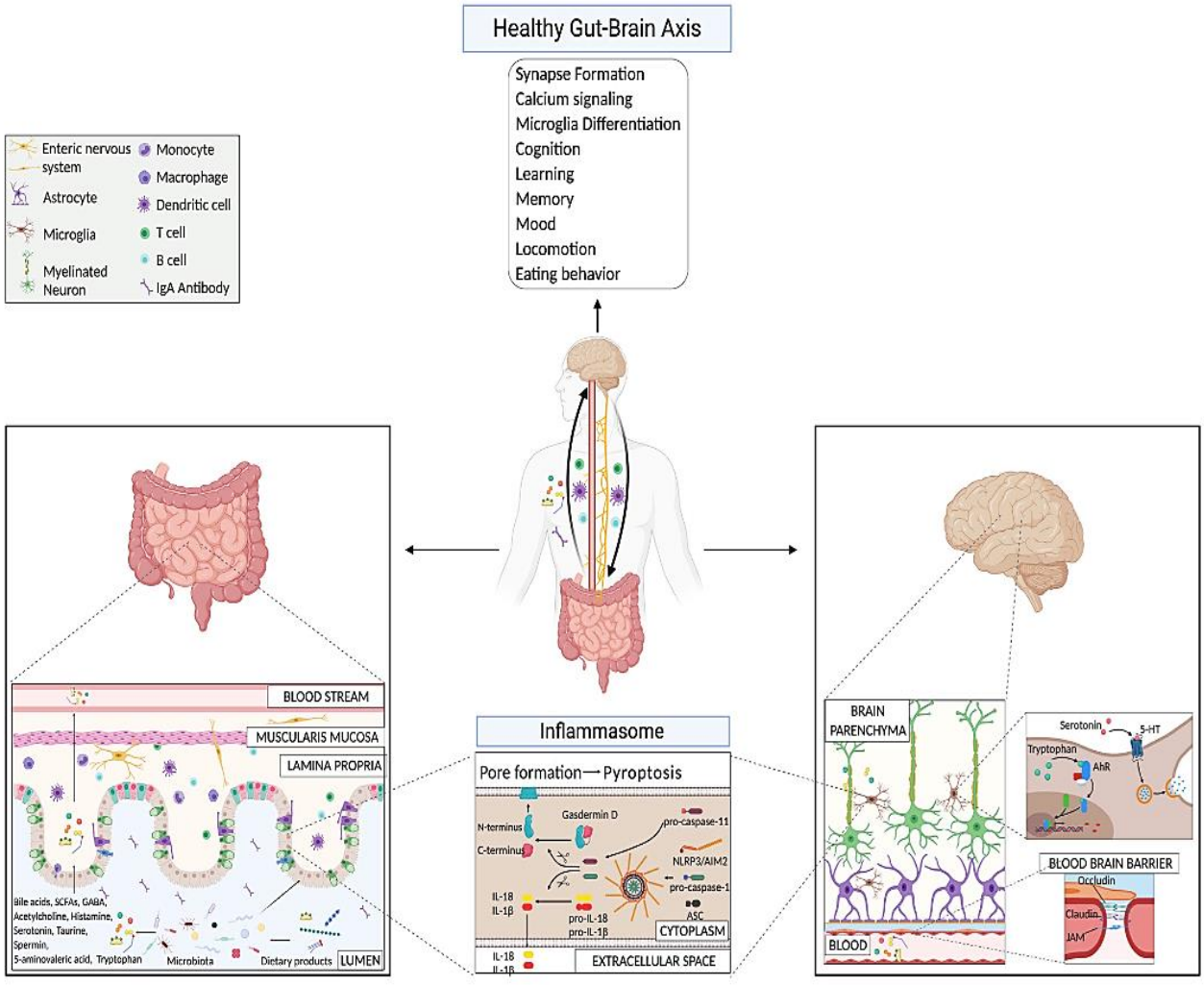

Figure 1: Gut-brain axis mechanisms under physiological conditions, highlighting microbial products and the inflammasome pathway [9].

Neural signalling: Bidirectional communication between the CNS and ENS is facilitated by the vagus nerve, which is the main pathway or connection that allows communication between the brain and the gut. Afferent fibres (about 80%) will transmit the signals from the gut to the brain regarding gut microbiota, immunological function, nutritional status, and mucosal health [10]. The efferent fibres (about 20%) will carry the signal from the brain to regulate immunological functions, enzyme secretion, and gastrointestinal (GI) motility [11]. Vagal activity serves as an important anti-inflammatory mechanism since it is directly linked to parasympathetic tone and shown to reduce gut inflammation [12]. Further, vagal stimulation triggers the release of

neurotransmitters such as serotonin, GABA, and dopamine, affecting emotional and cognitive processes [13]. Thus, high vagal activity is linked to increased stress adaptability and improved emotional regulation, while low vagal activity will lead to anxiety and depression [14]. The gut wall has a vast neuronal network called the ENS, sometimes referred to as the "second brain," which independently controls blood flow, secretion, and gut motility. It also plays an important role in the GBA by communicating with the central nervous system through the vagus nerve. It utilizes neurotransmitters like serotonin and GABA to send the signals, and recent research suggested that the gut microbiota can influence its development and functions [15].

Endocrine signalling: The endocrine system plays a significant role in GBA by releasing hormone that affects the activities of the CNS and the gut. One of the important systems that controls stress response is the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus releases Corticotropin-releasing hormone in responses to stress, which activates the pituitary gland to further release adrenocorticotropic hormone, which in turn triggers the adrenal glands to release cortisol. This hormonal cascade influences mood, cognition, and digestive functions [16]. Hyperactivation of the HPA axis will lead to abnormal increase in cortisol level, leading to anxiety, depression, and other mental illnesses [17]. The stomach produces hormones like ghrelin and leptin, which regulate appetite and energy balance and have neuromodulatory effects on the brain [18]. Psychiatric and GI conditions, like as depression and irritable bowel syndrome (IBS), have been linked to dysregulation of endocrine signalling [19, 20]. Recent studies have demonstrated that certain gut microbes can influence systemic hormone levels, highlighting a microbiome-endocrine interface with potential therapy implications for mood and stress-related diseases [21].

*Immune interactions***:** The gut is home to over 70% of the body's immune cells, which have intimate interactions with the gut bacteria there. Through pattern recognition receptors like Toll-like receptors (TLRs), this microbiota regulates immunological responses, causing the production of cytokines like interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which affect gut permeability and brain function [22-23]. Mood disorders such as anxiety and sadness are linked to chronic low-grade inflammation, which is frequently a result of dysbiosis [24]. These immunological signals can contribute to neuroinflammation and disruption of the HPA axis by acting through vagal pathways or by crossing the blood-brain barrier (BBB) [25].

Metabolic signalling: Through the fermentation of food fibres, the gut microbiota produces metabolites, especially short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, which have a significant impact on the GBA. These SCFAs function as neuroactive signalling molecules as well as colonocyte energy substrates [26]. By altering neurotransmission, microglial activity, and barrier integrity, SCFAs have the ability to traverse the blood-brain barrier [27]. The synthesis of important neurotransmitters and their precursors, such as glutamate (a precursor for GABA) and tryptophan (a precursor for serotonin), as well as the direct synthesis of serotonin and dopamine by particular microbial strains, is also facilitated by the microbiota [7]. These metabolites provide pathways for therapeutic interventions in neuropsychiatric illnesses since they are essential for brain development, affective modulation, and stress response [7, 14].

Table 1: Major signalling pathways in the gut-brain axis and their neurological effects [8-24].

Components	Key players	Mechanisms involved	Impact on brain
Neural	Vagus nerve, ENS	Neurotransmitters, afferent/efferent signals	Mood, cognition
Endocrine	HPA axis, ghrelin, leptin	Hormone release, stress response	Mood, appetite
Immune	Cytokines, TLRs, T cells	Inflammation, BBB signalling	Neuroinflammation
Metabolic	SCFAs, tryptophan, dopamine	Neurotransmitter synthesis	Behaviour, memory

*Role of the microbiota in maintaining GBA balance***:** Through its modulation of intestinal barrier integrity, neuroimmune signalling, and neurotransmitter synthesis, the gut microbiota plays a crucial role in preserving GBA homeostasis. Through vagal afferents, cytokines, and microbial metabolites such as SCFAs, commensal

bacteria communicate with immunological and epithelial cells to maintain mucosal balance and send signals to the central nervous system [8]. Digestion and metabolism, particularly the creation of SCFA and vitamins, are facilitated by a healthy microbiome. Synaptic plasticity, neurodevelopment, and emotional control. Regulatory T cells and cytokine signalling for immune regulation [1].

Impact of dysbiosis on brain function and behaviour: Several neuropsychiatric and developmental problems have been linked to dysbiosis, or microbial imbalance, which interferes with GBA signalling. The factors linked to depression, anxiety, autistic spectrum disorders, and neurodegeneration include increased BBB permeability, impaired neurotransmitter synthesis, and increased pro-inflammatory cytokines (IL-6, TNF-α) that promote neuroinflammation [22]. There is potential for reducing these negative effects and improving mental health by reestablishing microbial balance with probiotics, prebiotics, and dietary practices [2].

Psychobiotics: Psychobiotics are described as live organisms that interact with the GBA to improve mental health in the host when consumed in sufficient amounts [5]. From the early use of probiotics for gut health to their neuroactive potential in mood and behavioural problems, this idea was presented by Dinan et al. [28]. The phrase refers to microorganisms and microbial products that affect the activities of the CNS through a variety of processes: metabolic pathways, immunological signalling, and neurotransmitter regulation [6].

Classification of psychobiotics: Psychobiotics can be classified into several categories based on their composition and functional mechanisms in **Table 2**.

Table 2: Classification of psychobiotics with examples

Category	Definition	Examples	Mechanism of action
Probiotics [29]	Live microorganisms that, when taken in sufficient quantities, have positive effects on mental health.	*Lactobacillus rhamnosus GG*, *Bifidobacterium longum*, *L. helveticus*	Modulate GABA, serotonin; reduce inflammation; improve mood and cognition.
Prebiotics [30]	Food ingredients that are indigestible but encourage the formation of good gut bacteria.	Inulin, Fructooligosaccharides (FOS), Galactooligosaccharides (GOS)	Enhance probiotic growth; reduce stress-related behaviors via microbiota modulation.
Synbiotics [31]	Combination of probiotics and prebiotics that act synergistically.	*B. breve* + GOS, *L. rhamnosus* + inulin	Improve gut colonization and boost neurochemical output.
Postbiotics [32]	health-promoting metabolic byproducts or non-viable microbial products.	Short-chain fatty acids (SCFAs: acetate, butyrate), microbial enzymes, peptidoglycans	Anti-inflammatory effects, maintain gut barrier, cross BBB to influence brain activity.
Engineered Psychobiotics [33]	Synthetic or genetically altered strains intended to generate certain neuroactive substances.	Engineered *E. coli* producing GABA, synthetic *Bacteroides* delivering dopamine precursors.	Precision targeting of psychiatric symptoms; potential in neurodevelopmental and neurodegenerative disorders.

Mechanisms of psychobiotic action: Psychobiotics, defined as live bacteria that confer mental health benefits when consumed in sufficient quantities or strains that positively influence behaviour, intestinal permeability, neuroactivity, and reduce pro-inflammatory and stress responses. They are regarded as promising candidates for novel approaches in the management and therapy of mental disorders. Due to their high acceptability and significant potential, psychobiotics are increasingly viewed as a novel approach in addressing mental health conditions [34]. Their mechanisms involve several interconnected pathways, as explained in **Figure 2**.

Neurotransmitter modulation: Psychobiotics, mainly *lactobacillus, Bifidobacterium,* produce or stimulate host cells to increase the production of neurotransmitters such as serotonin, GABA, and dopamine [35]. These neurotransmitters act locally within the enteric nervous system to regulate digestion, gut motility, and enzyme secretion, or act on the brain by three main pathways. The vagus nerve acts as a direct communication channel between the gut and the brain. It detects the neurotransmitter changes in the gut and then transmits the signals

to brain regions involved in mood and behaviour, such as the amygdala and hippocampus [36]. Some neurotransmitter precursors, like tryptophan, and microbial metabolites, like short-chain fatty acids, can enter into bloodstream. Then these compounds may cross the blood-brain barrier and are converted to neurotransmitters like serotonin in the brain [37]. Psychobiotics can interact with immune cells in the gut or bloodstream to regulate the release of cytokines. By increasing the anti-inflammatory activity (e.g., IL-10) and reducing the pro-inflammatory mediators (e.g., IL-6, TNF-α), they will maintain immune balance [35].

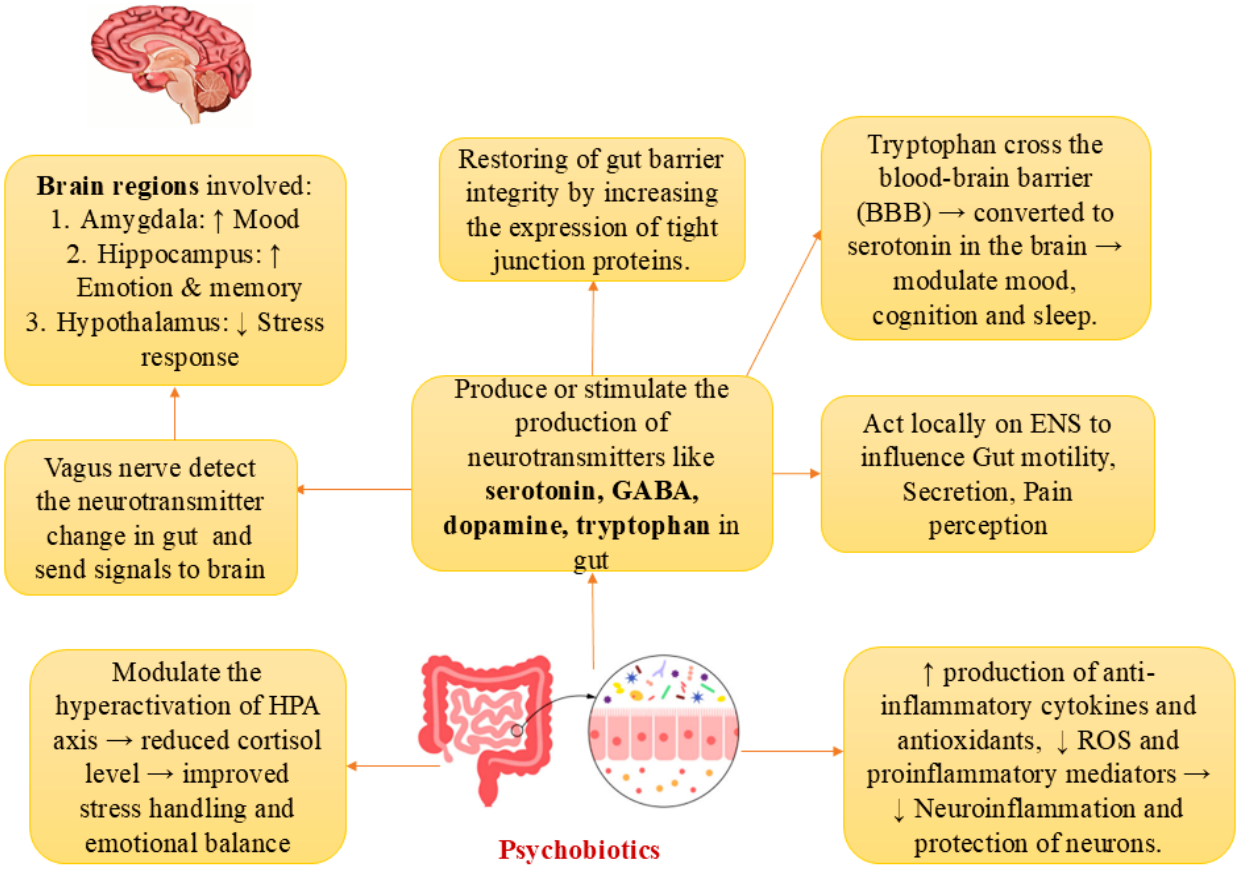

Figure 2: Mechanism of action of psychobiotics

HPA axis regulation: Certain psychobiotics will reduce the hyperactivity of the HPA axis leading, to the modulation of elevated cortisol levels. This modulation will contribute to better stress management, reduce anxiety, improve mood, and emotional stability [35].

Reduction of neuroinflammation and oxidative stress: Neuroinflammation and oxidative stress are responsible for the development and progression of several psychiatric and neurodevelopmental disorders. Oxidative stress can damage neurogenesis and synaptic plasticity. By increasing the anti-inflammatory activity, they inhibit the neuroinflammation. Additionally, psychobiotics increase the antioxidants like superoxide dismutase (SOD) and glutathione peroxidase in the body, which neutralize reactive oxygen species, lowering the oxidative stress and neuroinflammation. They will protect the neuron from oxidative damage [37].

Modulation of intestinal permeability: In conditions like stress, infection, and dysbiosis, the gut barrier will be compromised and leading to increased intestinal permeability, which is commonly known as 'leaky gut'. Hence, the harmful substances like lipopolysaccharides (component of the outer membrane of gram-negative bacteria), partially digested food particles, and microbial metabolites will enter to bloodstream and promote the release of proinflammatory mediators leading to neuroinflammation factors causing psychiatric conditions such as depression and anxiety [35, 36]. Psychobiotics, as Lactobacillus and Bifidobacterium strains will

restore gut barrier integrity by increasing the expression of tight junction proteins (occludin, claudins, and zonula occludens). These proteins will reduce gut permeability and prevent the translocation of toxins. Psychobiotics promote the mucous production and modulate the immune system to restore the integrity. Hence, by reinforcing the gut barrier, reducing intestinal permeability, increasing mucous production, and modulating immune function, will improve the cognitive function, mood, and emotional resilience [35, 37].

Production of neuroactive microbial metabolites: Psychobiotics will interact with dietary components and host cells and increase the production of several neuroactive metabolites like short-chain fatty acids (SCFAs) such as butyrate, acetate, and propionate. These SCFAs can cross blood brain barrier and also can on vagus nerve to reduce inflammation, support the integrity of the gut lining and to stimulate the release of brain-derived neurotrophic factor (BDNF), affecting brain function and mood [35, 37]. Psychobiotics will have significant impact in tryptophan metabolism, an amino acid that is the precursor for serotonin synthesis. Certain psychobiotics will increase the conversion of tryptophan to serotonin in the gut while decreasing its diversion to the kynurenine pathway, which when dysregulated leads to neuroinflammation and neuro-degeneration. Psychobiotics help sustain appropriate serotonin levels and lessen the synthesis of toxic kynurenine derivatives by controlling this metabolic balance, which eventually improves mental health, blood brain barrier integrity, emotional stability, and stress tolerance [35].

Vagal nerve activation: Psychobiotics will activate afferent vagal nerve fibres either by directly interacting with the gut lining or by releasing neurotransmitters (serotonin, GABA) and microbial metabolites like short-chain fatty acids (SCFAs). Afferent signals are then sent to brain regions like the amygdala, and hippocampus which regulate mood, stress response, and emotional behaviour [37].

Engineering the gut-brain connection using psychobiotics: GBA is a complex, bidirectional communication system connecting the gut and brain, involving neural, endocrine, immune, and metabolic pathways [1]. The psychobiotics therapy is now expanded through synthetic biology, gene editing, nanotechnology, and AI, offering more targeted, potent, and personalized interventions [38].

Role of synthetic biology in designing custom psychobiotics: Synthetic biology plays an important role in designing custom psychobiotics by modifying the functions of microbes that have positively impact on mental health. Through techniques like CRISPR-cas9 gene editing and metabolic engineering, synthetic biology produces tailored probiotics that can modulate the GBA, potentially decreasing the symptoms of various mental health conditions [38].

Engineered strains producing GABA, serotonin, and others: Psychobiotics will increase the production of neuroactive substances like GABA, serotonin, and dopamine to improve mental health. GABA is an inhibitory neurotransmitter plays an important role in regulating anxiety and improving sleep. *Lactobacillus plantarum* and *Bifidobacterium adolescentis* strains have genetically developed to increase the activity of glutamate decarboxylase, which converts glutamate to GABA [39]. Serotonin is possible to modify engineered *E. coli Nissle 1917* to produce more 5-HTP (serotonin precursor) from tryptophan. *Bacillus subtilis* strains have also been engineered to release serotonin directly in the gut [40]. Dopamine and others: Some experimental strains propose to improve catecholamine biosynthesis (dopamine, norepinephrine), although clinical applications are still in early stages [41]. Anti-inflammatory mediators: By reducing intestinal inflammation and indirectly improving brain function through the GBA, Lactococcus lactis has been modified to release IL-10, an anti-inflammatory cytokine [42].

Microbiome editing using CRISPR and phage therapy: Scientist have developed tools like CRISPR and phage therapy that modify the bacteria in the gut. CRISPR selectively removes the disease-causing bacteria and is involved in gene editing of the microbiome to increase the production of microbial metabolites. They also modify the bacterial gene to influence tryptophan-kynurenine pathways [33]. Phage therapy uses viruses,

which will target the specific bacterial strains in the gut and inhibit the disease-causing bacteria without in the gut disturbing the beneficial ones. They maintain gut balance and reduce neuroinflammatory mediators [43].

Encapsulation and delivery systems for targeting gut regions: Microencapsulation: Bacteria are enclosed in biopolymer coatings (alginate, chitosan), protect the bacteria against the stomach acid and bilem and allow sustained and delayed release of psychobiotics [44]. *Nanoparticles:* Use of lipid-based or polymeric nanoparticle formulation of psychobiotics or bacterial metabolites [45]. *Enteric-coated capsules:* enteric coated formulation of psychobiotics that releases its contents only in the alkaline environment of the intestine, not the acidic stomach [46]. *Targeted delivery:* Psychobiotic capsules tagged with biosensors can release contents in response to gut biomarkers or inflammation [47].

Use of AI and machine learning to personalize psychobiotic treatments: Artificial intelligence (AI) and machine learning are used to create personalized psychobiotic treatments. It will personalize the medication for individuals with depression, anxiety, autism, or PTSD by predicting how the individual will respond to specific psychobiotic strains [48, 49].

Challenges and ethical considerations: One of the major challenges in developing psychobiotics-based therapies is significant intersubject variability in gut microbiome composition. This means a treatment that works for one person may not work for another, making personalized solutions complicated. Regulatory and safety concerns are also major issues, since biotherapeutics must be proven to be safe before approval, and there is always a risk of unintended side effects or adverse events. Another concern is that altering the gut microbiota to influence mood or behaviour raises deep ethical questions about manipulating someone's personality or emotions through their gut bacteria. Lastly, public trust and acceptance of engineered psychobiotics is not guaranteed, as people may be uncomfortable with the idea of taking genetically modified microbes to influence their mental health. All of these points need careful scientific, ethical, and social discussion before psychobiotics can become mainstream therapies [49-54].

Future directions: Integration of psychobiotics with microbiome analysis, genetics, and AI leads to personalized treatment for the treatment of mental illness, including anxiety and depression. Microbiome analysis facilitates early detection and focused treatment. Long-term research and extensive clinical trials are necessary to prove the effectiveness and safety of psychobiotics. Research should be carried out to determine the effect of nutrition on the GBA axis and how the combination of psychobiotics with nutrients will enhance mental illness. Also, the discovery of new biomarkers like inflammatory signals and microbial metabolites may aid in tracking the effectiveness of treatment and the health of the gut-brain connection [53-55].

Conclusion: The gut-brain axis plays an important role in neuropsychiatric and gut disorders. The gut flora plays a significant role in mental health due to its effect on the gut-brain axis. Gut flora produces various neuroactive substances like serotonin, GABA, and short-chain fatty acids that affect behaviour, mood, and cognitive functions. Any imbalance or disruption in the natural composition of gut microorganisms (dysbiosis) may lead to mental illness. Hence, targeting the gut microbiota may provide novel strategies for treating psychiatric disorders. Psychobiotics target the gut-brain axis through a variety of mechanisms such as immunological regulation, gut barrier strengthening, and neurotransmitter modulation, providing a novel and promising approach to managing mental health. Advances in psychobiotics include engineered microbial strains, targeted delivery systems, personalized therapies, and combination therapies improving mental health. Despite these advances, challenges like individual differences, regulatory issues, and ethical concerns remain.

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