

Psychobiotics: Deciphering its role in neuropsychiatry

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Abstract

Psychobiotics, a novel group of probiotics and prebiotics, are a relatively recent discovery, found to modulate central nervous system (CNS)-related functions and behaviors via neuronal, immunological, and metabolic pathways, thus improving not only gastrointestinal (GI) functions, but also suggesting strong antidepressant and anxiolytic potential. Scientists are moving closer to the possibility of treating mental and behavioral illnesses with advanced and cost-effective approaches, targeting dietary modifications in the form of “psychobiotic” supplements consisting of brain-benefiting bacteria, as they uncover more and more about the gut-brain axis. This review examines the relevant scientific work that has been generated so far, analyzing the efficacy of psychobiotic treatment in improving mental health and neuropsychiatric disorders, providing a complete assessment of its potential as an alternative therapy for psychiatric disorders and its future prospects in this domain.

Keywords: Gut-brain axis; Mental health; Neuropsychiatric disorders; Prebiotics; Probiotics; Psychobiotics

1. Introduction

Gut microbial influence on human physiology has found great relevance in the scientific community, with the recent unveiling of its potential link with the brain, also referred to as the Gut-Brain Axis (GBA), sparking significant interest among researchers [1]. GBA may be thought of as a bidirectional communication pathway between the central and enteric nervous systems that connect the brain's emotional and cognitive centers with peripheral intestinal processes [2]. This gut-brain crosstalk has portrayed a rather sophisticated information exchange that not only supports adequate gastrointestinal (GI) homeostasis maintenance, but is also likely to have diverse consequences on emotion, motivation, and higher cognitive processes.

Neurotransmitters like gamma-amino-butyric acid (GABA), for example, modulate the inhibitory-excitatory balance, necessary for proper brain function in mature brains [3], while low levels of serotonin have been associated with mental health disorders like depression and anxiety [4]. An abnormally short supply of acetylcholine noted in Alzheimer's patients indicates a possible correlation between the development of this disease and acetylcholine expression [5].

According to a recent study, the overall prevalence of anti-inflammatory bacteria, including those of the genera *Blautia*, *Roseburia*, and *Coprococcus*, was found to be substantially lower in fecal samples from Parkinson's disease patients and children with Autism Spectrum Disorder (ASD) [6].

Lactobacillus fermentum, *Alkaliphilus oremlandii*, *Cronobacter sakazakii*, *Cronobacter turicensis*, and *Enterococcus faecium* were found in the intestines of ninety medication-free schizophrenia individuals, in contrast to the gut of normal

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persons [7]. These findings point to an increase in the number of bacteria belonging to the Proteobacteria phylum. *Succinivibrio*, *Megasphaera*, *Collinsella*, *Clostridium*, *Klebsiella*, and *Methanobrevibacter* were found to be significantly abundant. However, a decrease in *Coprococcus*, *Roseburia* and *Blautia* was observed even in this case [7].

Furthermore, the development of Attention Deficit Hyperactivity Disorder (ADHD) was observed to be more prevalent in individuals demonstrating gut microbial dysregulation [6].

Adversities centering around the dysbiosis of the gut microflora, as investigated through pivotal experiments conducted on animal models, revealed exaggerated biological responses in the germ-free ones (lacking indigenous microbiome) in contrast to those raised with normal microflora [5]. These aberrant responses were mitigated using probiotic-induced bacterial recolonization, which in turn shed light on a novel class of compounds - the 'psychobiotics', which includes both probiotics and prebiotics.

The impact of the gut microbiome may therefore be considered crucial for stable neurological functioning, and through this review, we aim to analyze the therapeutic effects of psychobiotic treatment against the gut microflora disbalance.

2. Psychobiotics

2.1. Basic Concepts

Probiotics and prebiotics can both be classified under the umbrella of psychobiotics. Probiotics are described as "live microorganisms that bestow health benefits on the host when supplied in suitable doses" [8] with *Bifidobacterium* and *Lactobacillus* being among the most accepted ones, while prebiotics, which was developed in conjunction with probiotics, are introduced as "non-digestible dietary elements that benefit the host by selectively promoting the development and/or activity of one or a restricted number of bacteria already present in the colon" [8]. It is a substrate that is preferentially utilized by host bacteria to provide health benefits since dietary ones cannot be destroyed by host enzymes [8]. Oligosaccharides (OS), polyunsaturated fatty acids (PUFAs), conjugated linoleic acid, plant polyphenols, and some fermentable fibers are examples of such prebiotic substrates. Among OS prebiotics, fructooligosaccharides (FOS), galactooligosaccharides (GOS), mannanoligosaccharides (MOS), xylooligosaccharides (XOS), human milk oligosaccharides (HMO), and inulin stand out, with FOS and GOS being the most studied and widely recognized for their neural effects are FOS and GOS, which favorably stimulate the growth of *Bifidobacterium* and *Lactobacillus* [8].

However, psychobiotics distinguish themselves from traditional probiotics by their capacity to promote the production of neurotransmitters, enteroendocrine hormones, short-chain fatty acids, and anti-inflammatory cytokines. Owing to this potential, psychobiotics provide a wide variety of applications, including mood and stress relief, as well as its usage as an adjuvant in the treatment of various neurodevelopmental and neurodegenerative ailments [9]. Current research reveals a robust bidirectional communication route shared by the neuroendocrine system and gut bacteria [10]. It has been established that the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis, which is the principal neuroendocrine response system in the human body to physiological and physical stress, can impact the composition of the gut flora and increase gastrointestinal permeability [10]. The early colonization of the stomach by bacteria demonstrates alterations in numerous elements of the brain and behavior, including the stress response. It is thus fair to suppose that variations in intestinal permeability and the immune system might contribute to neuroendocrine dysfunction.

2.2. Mechanism of action

The gut contains a meshwork of nearly 500 million neurons, running from the esophagus to the anus [9]. This meshwork constitutes the enteric nervous system (ENS), the key player in coordinating all the events related to digestion to the brain and central nervous system (CNS), via the vagus nerve. This vagus nerve-mediated pathway that connects the ENS to the CNS has been proven to be the possible channel for gut microbiota to regulate the brain, and *vice versa* [9].

A recent study was successful at providing evidence of germ-free mice having intestinal neural abnormalities in the jejunum and ileum, in comparison to the control [1]. Germ-free mice also showed reduced nerve density, fewer nerves per ganglion, and a greater number of myenteric nitrergic neurons [1]. This evidence indicates the critical role the microbiome plays in influencing one's neural functioning, behaviour, and response to various kinds of stress. This link was further established by the study which revealed that patients exhibiting signs of depression tend to display a microbiota composition that evidently digresses from the normal one. When the changed microbiota was transferred to germ-free rats by transplanting faecal matter (faecal microbiota transplantation, FMT) from depressed patients, the rats displayed a dysregulated microbiota, along with symptoms associated with anxiety [9]. Although the mechanism of

this function is yet to be clearly chalked out, certain key members in the regulation have been identified, as depicted in Fig. 1.

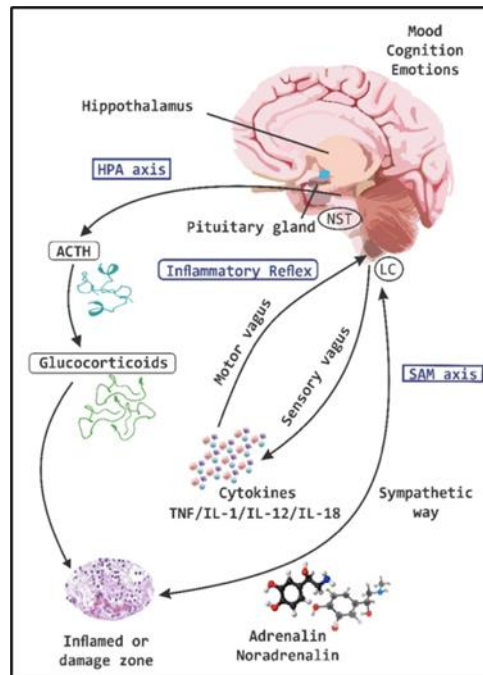


Figure 1 Regulatory pathways of the neuroimmune axes via the central nervous system (CNS), hypopituitary adrenal (HPA) axis, the sympatho-adrenal medullary (SAM)-axis, and the inflammatory reflex. (ACTH- adrenocorticotropic hormone; NST- Nucleus of solitary tract; LC- Locus coeruleus; TNF- Tumor necrosis factor; IL- Interleukin; photograph adapted from Bermúdez-Humarán et al., 2019 [8].

2.2.1. Short Chain Fatty Acids (SCFAs)

Probiotics or gut-friendly bacteria like *Lactobacillus* and *Bifidobacterium*, upon metabolizing prebiotic fibers such as plant polysaccharides, are responsible for increasing the production of short-chain fatty acids (SCFAs) in the gut, including acetate, butyrate, lactate, and propionate [1].

These SCFAs then enter the circulation, where the majority of the pool is directed to the liver [1]. A small portion of these SCFAs, however, migrate into the CNS but the extent to which such a small fraction would modulate neurotransmission remains unanswered. However, there does exist evidence to prove their psychotropic activity at pharmacologically determined concentrations. SCFA receptors are found in the CNS and peripheral nervous system (PNS) [1]. Free fatty acid receptor 3 (FFAR3) is found abundantly in rat brain tissue and in the sympathetic ganglia. FFAR3 signaling controls the propionate-induced intestinal gluconeogenesis via gut-brain neurocircuitry. Feeding of propionate also affects regions of the CNS that are involved in receiving signals from the portal areas via the vagal and spinal pathways [11]. These results demonstrate the influence the SCFAs have in controlling the CNS and PNS and may have a putative effect on psychological processes. In rats, chronic (28 days) and acute systemic sodium butyrate injections (0.6 g/kg) combined with fluoxetine (10 mg/kg) significantly reduce despair in rats, in comparison to when fluoxetine was administered independently [11]. An increase in brain-derived neurotrophic factor (BDNF) transcript levels was also observed, indicating its role in the observed behavior [11].

SCFAs interact with the gut mucosal enteroendocrine cells, which express FFARs, to catalyse the release of gut hormones such as cholecystokinin (CCK), peptide tyrosine tyrosine (PYY), and glucagon-like-peptide-1 (GLP-1) [12]. PYY and GLP-1 are capable of penetrating the brain and their administration in rodents has been proven to affect behavior [1].

However, SCFAs are more likely to influence the psychological processes as an epigenetic modifier, via histone deacetylases (HDACs). SCFAs tend to inhibit HDACs; HDAC inhibitors function as cognitive enhancers in fear, anxiety, and trauma-related processes and hence project potential as a therapeutic, combined with psychotherapy to promote long-term positive treatment outcomes, along with relapse prevention [11]. A study established the positive effect that chronic inhibition of HDACs by intraperitoneal injection of sodium butyrate (1.2 g/kg daily for 4 weeks) had in wild-type mice and in mice with brain atrophy, improving learning and memory in both [11].

2.2.2. Neurotransmitters

Psychobiotics also promote the production of neurotransmitters in the gut, allowing modulation of neurotransmission in the proximal synapses of the ENS. This includes hormones like dopamine, serotonin, noradrenaline, and GABA. Table 1 provides a comprehensive account of the various families of gut bacteria that produce different neurotransmitters. 16S rRNA sequencing along with functional magnetic resonance imaging (fMRI) in patients with major depressive disorder, indicated a negative correlation of relative abundance of fecal *Bacteroides* with brain patterns concurrent with depression [13].

Table 1 Summary of neurotransmitters produced by different gut bacteria [13] [14]

Sr. no.	Neurotransmitter	Gut microbiota families/genera	Examples of Bacterial Strains
1	Acetylcholine	<i>Lactobacillus</i>	<i>Lactobacillus plantarum</i>
2	Dopamine	<i>Bacillus</i> , <i>Escherichia</i>	<i>Escherichia coli</i> , <i>Bacillus subtilis</i>
3	GABA	<i>Bifidobacterium</i> , <i>Lactobacillus</i> , <i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Alistipes</i>	<i>Bifidobacterium adolescentis</i> , <i>Lactobacillus plantarum</i> (ATCC14917), <i>Alistipes putredinis</i>
4	Noradrenaline	<i>Bacillus</i> , <i>Escherichia</i>	<i>Escherichia coli</i> (K-12), <i>Bacillus mycoides</i>
5	Serotonin	<i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Escherichia</i>	<i>Lactobacillus plantarum</i> (F18595), <i>Streptococcus thermophilus</i> (NCFB2392)
6	Histamine	<i>Lactobacillus</i> , <i>Enterobacter</i>	<i>Lactobacillus plantarum</i> (F18595), <i>Lactococcus lactis</i> subsp. <i>cremoris</i> (MG 1363)

The altered levels of serotonin in the striatum and hippocampus of the brain of germ-free mice [15], increased levels of serotonin and dopamine in the prefrontal cortex of the brain of mice treated with *Lactobacillus plantarum* [6], and an increase in the levels of noradrenaline in rats supplemented with *Lactobacillus helveticus* NS8 [16], all demonstrate the prominent role probiotics have on the levels of neurotransmitters.

2.2.3. Stress Response

The HPA axis becomes dysfunctional during chronic stress or illness, which leads to a disruption in the production and function of stress-related hormones [14]. Like the stress hormone, cortisol, is often found elevated in patients with depression.

Studies have demonstrated the recruitment of corticotrophin-releasing hormone (CRF) receptors in the colon when stress is present [9]. This further induces changes at the level of gastrointestinal function, and an increase in the levels of ACTH and plasma corticosterone levels [9]. Glucocorticoids are responsible for dysregulating the gut barrier function, leading to reduced integrity of the epithelium and permitting outward movement of bacteria. This triggers an inflammatory immune response [1]. Pro-inflammatory cytokines released due to stress-induced by high levels of glucocorticoids are also known to reduce the integrity of the gut barrier [9]. Additionally, bacteria can regulate inflammation directly by increasing the concentration of certain cellular elements like lipopolysaccharide (LPS, pro-inflammatory), which is a process also associated with depression [17]. Psychobiotic supplements with *Lactobacillus* or *Bifidobacterium* are capable of restoring the gut barrier integrity and reducing stress-induced gut leakiness [1]. *Lactobacillus rhamnosus* GG has been found to amend gut barrier dysregulation by inhibiting pro-inflammatory signaling by the tumor necrosis factor (TNF)- α [1].

3. Studies in Animal Models to establish psychobiotic action

Multiple animal studies have successfully established the role played by psychobiotics on the neural responses of individuals. Synapsing of the vagus nerve on the enteric neurons enables gut-brain communication [9]. This has been established by studies wherein damaging the vagus nerve led to a lack of any physiological response to the psychobiotics [18].

Rodent models like BALB/c mice that were innately stressed, were administered *Lactobacillus rhamnus* JB-1 [14]. They exhibited reduced intensity of anxiety and depression, along with long-term changes in both their GABA_A and GABA_B

receptor expression in the CNS [14]. Additionally, a somewhat blunt corticosterone response to stress was observed, indicating that the probiotic might have downregulated HPA-axis activity [1]. In another set, where these BALB/c mice underwent a vagotomy, they failed to show any of the above-mentioned responses and no anxiolytic effect was observed [18].

In another recent study, *Mycobacterium vaccae* was administered to rats and a marked reduction in brain inflammation was observed. It also prevented stress caused by anxiety [19]. In BALB/c mice, administration of live *M. vaccae* before and after a maze learning task was associated with reduced anxiety and shorter maze completion duration, which demonstrated improved learning abilities in the same task [20].

Probiotics like *Lactobacillus helveticus* NS8 were shown to reduce levels of post-restraint anxiety and improved post-restraint object recognition memory in Sprague-Dawley rats that were exposed to chronic stress [1]. These rats expressed lower levels of corticosterone and adrenocorticotropic hormone (ACTH) [1]. They also displayed an increase in anti-inflammatory cytokine IL-10 production, BDNF mRNA, noradrenaline, and serotonin in the hippocampus [1].

Psychobiotics have also shown a potential in delaying amyotrophic lateral sclerosis (ALS). Mice models were administered with the prebiotic GOS and GOS-rich prebiotic yogurt daily, starting from the age of 8 weeks until death [21]. These mice displayed a delayed onset of ALS, along with a prolonged lifespan, less oxidative stress in skeletal muscles, improved muscular dystrophy, microglia activation, and apoptosis of the spinal cord [21]. The study credited this function of GOS to the attenuation of increased homocysteine levels in the blood, an amino acid associated with the pathogenesis of ALS. Additionally the prebiotic was thought to increase Vitamin B₁₂ and folate production, both of which are needed for homocysteine metabolism [21].

GOS has also been used to study disorders involving anxiety and neuroinflammation. 8-week old mice were supplemented with B-GOS (Bimuno formulation of GOS) for 3 weeks [8]. They showed reduced LPS-induced anxiety and decreased elevated cortical Interleukin (IL)-1 β and 5-hydroxy-tryptamine or serotonin 2A (5-HT_{2A}) receptor expression in the frontal cortex of the brain, induced by LPS, in the absence of altered 5-hydroxy-tryptamine (5-HT) metabolism [8]. Hence, they could establish that the prebiotic-induced anti-inflammatory response regulated the anxiolytic function [8].

4. Human Trials/Clinical Trials

The current evidence concerning the efficacy of psychobiotic intervention through probiotic and prebiotic-based therapies in the management of stress and anxiety, neurological abnormalities, and its impact on cognition in humans are examined, as well as recommendations for future intervention techniques and developments in this arena are made strongly.

4.1. In Mental Health Disorders

To investigate the ability of probiotics in the prevention of mental health ailments like depression in humans, researchers administered a multispecies probiotic formulation comprising *Bifidobacterium lactis* W, *B. bifidum* W2, *Lactobacillus brevis* W, *L. acidophilus* W37, *L. salivarius* W2, *L. casei* W5 and *Lactococcus lactis* (W19 and W58) to 20 healthy people, while the Control group received a placebo through 4 weeks [22]. By the end of 4 weeks, probiotic-users demonstrated a substantial overall decrease in cognitive response to depressed state [22].

A clinical trial on healthy subjects (of sample size 22) found that consuming strains of *Bifidobacterium longum* 1714 (1x10⁹ colony-forming units every stick) for four weeks enhanced cortisol production and hippocampal-dependent visuospatial memory, as well as lowered subjective anxiety and everyday stress [23]. Long-term consumption of *Lactobacillus gasseri* CP2305 tablets (1x10¹⁰ bacterial cells per 2 tablets) enhanced psychological state and sleep quality in young students (of sample size 60) subjected to chronic stress [24].

A further manner of how probiotics may influence mood is through their capacity to control discomfort in the stomach. *L. acidophilus* has been found to alleviate pain by activating opioid and cannabinoid receptors in intestinal epithelial cells. The opium and cannabinoid systems regulate mood, pain, reward, and addictive behavior [22].

4.2. In Neurodegenerative Disorders

The significant decline in Autism Diagnostic Observation Schedule - Calibrated Severity Score (ADOS-CSS) (both Total and Social-Affect scores) in the Non-Gastrointestinal Symptoms (NGI)-group treated with probiotics compared to the placebo group is a novel and promising finding of a 2020 study [25]. Although derived through a secondary study, this

result is extremely noteworthy from a clinical standpoint, particularly in light of the aforementioned psychometric features of the utilized tool. Over six months, a mean reduction of 0.81 in total ADOS-CSS and 1.14 in Social-Affect ADOS CSS demonstrates a clinically significant reduction in Autism Spectrum Disorder (ASD) symptoms [25].

A study published in 2020 by Den et al. shows probiotics that are affordable, widely available, and well-tolerated might be prospective alternatives for the treatment or prevention of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) [26].

They further discovered that either single-strain or multi-strain probiotics were useful for increasing cognitive performance, indicating that *Bifidobacterium* and *Lactobacillus* strains might be the best options [26].

Lactobacillus plantarum PS128 supplementation over 12 weeks, in conjunction with continuous anti-Parkinsonian therapy, enhanced the Unified Parkinson's Disease Rating Scale (UPDRS) motor score and quality of life in Parkinson's disease patients [27]. This result indicated that PS128 may be useful as a therapeutic adjuvant in the treatment of Parkinson's disease. To further establish the effectiveness of PS128 supplementation in the future, placebo-controlled trials are required to be conducted [27].

Schizophrenia (SCZ) patients were administered the probiotic *Bifidobacterium breve* A-1 for 4 weeks, and their anxiety, depression, and Positive and Negative Syndrome Scale (PANSS) ratings improved. Ghaderi et al. in 2019 evaluated probiotic supplement treatment in SCZ patients for 12 weeks by delivering a vitamin D and probiotic mixture including *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *L. fermentum*, and *L. reuteri* [28]. There was a substantial reduction in metabolic abnormalities and circulating C-reactive protein (CRP), indicating decreased inflammation, as well as improvements in general and total PANSS scores and plasma total antioxidant capacity [28].

5. Conclusion

Intestinal dysbiosis has repercussions that extend beyond the host's nervous system. The expanding body of studies on psychobiotics in domains as diverse as Health Sciences, Microbiology, Neurobiology, Biotechnology and Food Sciences supports the gut microbiome's influence on the GBA. Given its importance in the host's mental and physical balance, the gut-brain axis is considered to be a "virtual organ." Combating intestinal dysbiosis in an individual is becoming increasingly important in the treatment of neuropsychiatric illnesses, especially with the introduction of new treatments like "psychobiotic therapy," which have shown promising outcomes in animal and human trials. The key players in this respect have been established as being largely from the genera *Lactobacillus* and *Bifidobacterium*, while several additional ones have just been found that may prove even more effective in this therapy in the coming years.

Although our review demonstrates how psychobiotics may impact mood and behavior, it is conceivable that other neurotransmitter systems and/or neuropeptides may also play a part in the treatment of neuropsychiatric disorders, in addition to ones expressed through gut microbiota regulation.

So far there has been little translational research in this sector, and further studies on the efficacy of psychobiotics in the alleviation of neuropsychiatric disorders are required to validate these findings.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no potential conflict of interest.

Author Contributions

Souvik Roy and Lopamudra Choudhury were responsible for the paper's conceptualization. All authors have contributed to writing the final manuscript. Souvik Roy and Lopamudra Choudhury conducted the reviewing and editing. The work has been read by all authors and finalized.

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