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Research Article

Comprehensive Review on Psychobiotics: The Next-Generation Microbial Biomedicine and Biotherapeutics

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Abstract

Psychobiotics are a special novel class of probiotics that significantly affect treating neuropsychiatric, neurodevelopmental, and neurodegenerative disorders, leading researchers towards mining psychobiotics to evolve novel biomedicine and biotherapeutics in neuroscience. Psychobiotics also known as neurochemical-producing microbial biofactories, vary from conventional probiotics in their ability to produce or stimulate the production of every neurotransmitter, short-chain fatty acids, enteroendocrine hormones, anti-inflammatory cytokines, and chemokines. In current research, Psychobiotics are potential venues for improving the bidirectional communication between central nervous system and gastrointestinal tract defined as microbiota gut brain axis. The accumulating evidence elucidates consumption of pharmacological psychotropic drugs as treatment options for maintaining neurological health is often associated with life-threatening endocrine and metabolic side effects. Within this perspective the use of microorganisms with psychobiotic properties has gained attention in the scientific community in recent years. Through the evidence of clinical trials, the beneficial effects and efficacy of psychobiotics in treating neurological disorders are becoming clearer. The formulation of novel psychobiotic-based neuropsychiatric biotherapeutics is much anticipated which will open up a completely new avenue for tailored medication and healthcare in mental health. However, such clinical investigations remain challenging at present in terms of design and target populations. In this review work, we focused on the existing evidence supporting the role of psychobiotics in ameliorating neuropsychiatric, neurodegenerative, and neurodevelopmental disorders, scope and advancements made in the field, highlighting the challenges and knowledge gaps connected with conducting scientific investigations to answer unresolved key question in the field.

Keywords: Brain-derived Neurotrophic Factor; Gut-Brain Axis; Mental Illness; Prebiotics; Psychobiotics

Abbreviations

BDI: Beck Depression Inventory; BDNF: Brain-Derived Neurotrophic Factor; BID: ("bis in die") Twice a Day; CNS: Central Nervous System; IBS-QoL: Irritable Bowel Syndrome Quality of Life questionnaire; ELS: Early-Life Stress (ELS); ENS: Enteric Nervous System; GSH: Glutathione; PPAR-g: Peroxisome Proliferator-Activated Receptor Gamma; TGF-b: Transforming Growth Factor Beta; PBMCs: Peripheral Blood Mononuclear Cells; LDLR: Low-Density Lipoprotein Receptor; MADRS: Montgomery- Åsberg Depression Rating Scale; MDD: Major Depressive Disorder; MGB: Microbiota-Gut-Brain Axis; NMS-Quest: Non-motor Symptoms Questionnaire; OQ45: Outcome Questionnaire 45; PARP: Poly (ADP-ribose) polymerase-1; QIDS-SR16: Quick Inventory of Depressive Symptomatology 16-Item Self-Report; SHAPS: Snaith Hamilton Pleasure Scale; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; UPDRS: Unified Parkinson's Disease Rating Scale; VEGF: Vascular Endothelial Growth Factor

Introduction

People's mental health is impacted by the high amounts of stress, anxiety, and tension they endure in today's fast-paced society. According to the World Health Organisation (2018), over 300 million individuals worldwide suffer from neuropsychiatric, neurodevelopmental, and neurodegenerative illnesses, which lower productivity and quality of life while raising healthcare expenses. With a typical beginning around age 20, over 29.1% of persons will encounter at least one neurological disorder [1]. Due in large part to the gut-brain connection, research indicates that the gut microbiota is associated with mental health, impacting disorders such as multiple sclerosis, Alzheimer's, ADHD, Tourette syndrome, ALS, depression, and anxiety [2].

The relevance of the microbiome in neurological illnesses has been brought to light by developments in the study of the microbiota-gut-brain axis (MGB) [3]. Brain and gut microbiome development go hand in hand, and early-life disturbances can raise the risk of depression [4,5]. Conditions like Alzheimer's, Parkinson's, and schizophrenia show specific microbiota alterations, including changes in Firmicutes, Bifidobacterium, and Bacteroidetes levels [6]. Although it is important to maintain a healthy gut microbiota, neurodegenerative problems may result from the depletion of beneficial microbes caused by stress, food, pollution, antibiotics, and antibacterial agents [7]. Traditional psychiatric medications for these conditions frequently have endocrine and metabolic adverse effects that affect gut health [8]. With the ability to provide personalized psychobiotic therapy based on each patient's unique genetic makeup and microbiome composition, probiotics hold promise as adjunctive treatments for depression [9,10]. Through neurochemicals and metabolites, gut bacteria interact with the brain and influence signaling in the central nervous system (CNS) [11]. There is also research evidence that bacteria in the gut can produce metabolites that can circulate through the blood into the brain. Figure 1 illustrates the mode of action of psychobiotics. This review summarizes clinical studies and systematic reviews on psychobiotics for neurological disorders, examining their pathways, commercial status, and future research directions.

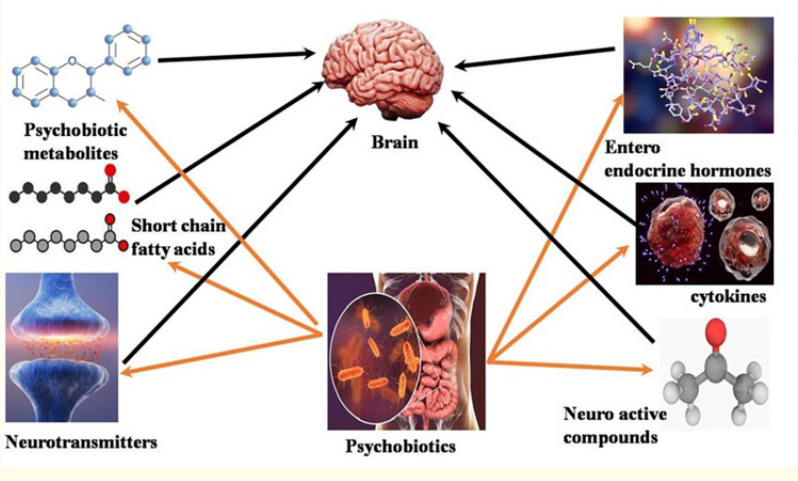

Figure 1: Illustration of the mode of action of psychobiotics.

Psychobiotics: The next generation neurochemical producing biofactories

Psychobiotics, often known as "mind-altering" probiotics, may work by promoting the production of physiologically active substances such as peptides, molecules, and mediators linked to neurotransmission [12]. Neuroactive substances such as serotonin, GABA, cytokines, short-chain fatty acids, psycho metabolites, catecholamines, and acetylcholine are known to be produced by psychobiotic bacteria in the human gut [13]. Bifidobacterium (e.g., *Bifidum, Bifidobacterium breve*), Lactobacillus (e.g., *Lactobacillus rhamnosus, Lactobacillus helveticus*), Saccharomyces, Streptococcus thermophilus, Enterococcus, and Clostridium are among the species that make up the psychotropic gut microbiota. Psychobiot-

ic-released neurotransmitters can cause epithelial cells to produce chemicals that impact neuronal signaling in the enteric nervous system, hence influencing behavior and brain function [14]. These microorganisms could therefore serve as delivery systems for neuroactive substances [15].

Since microbial neurochemical yields are typically too low for large-scale manufacturing, the concept of using psychobiotic bacteria as biofactories to produce neuro medicine is intriguing but difficult. It may be possible to create psychobiotic strains that overproduce useful neurochemicals thanks to developments in genetic engineering and selection [16]. Additionally, psychobiotics generate short-chain fatty acids, which may influence the brain through memory enhancement, blood-brain barrier integrity, neurotrophic factor levels, and neurotransmission modulation [11]. The psychobiotic bacteria that create short-chain fatty acids are listed in Table 1, along with their effects. The processes underlying these neuroactive effects require further investigation, and a useful biotechnological objective for the widespread use of psychobiotics may be to screen them for the generation of neurotransmitters.

Genus	Effect	References
Lactobacillus acidophilus,	Improves mental health and alleviates Neuronal damage	[17]
Lactobacillus casei,	Alleviates Depression and anxiety-like behaviour	[18]
Bifidobacterium breve	Decreases neurological deficit score, Facilitation of contextual fear extinction and increases spine density	[27]
Streptococcus	Improves cognitive function and alleviates brain damage	[19,20]
Bifidobacterium longum	Improves Sleep quality and lessens depression scores	[21]
Lactobacillus rhamnosus	Alleviates in Autism symptoms	[17]

Table 1: List of Psychobiotic gut microbiota producing Short-chain fatty acids and their effects.

Microbiota-gut-brain axis

The brain and gut communicate with each other in a bi-directional mode to form an axis called the MGB [21]. Figure 2 explains the possible communication routes in the gut-brain axis. The pathway through which the CNS/brain and gut signal with each other comprises the neuroimmune system, neuroendocrine system, autonomic nervous system (parasympathetic arm and sympathetic arm), enteric nervous system (ENS), and gut microbiota [22]. It is in recent times scientists noticed the significance of gut microbe's communication with the brain. The autonomic nervous system in the gut-brain signaling includes the parasympathetic and sympathetic nerves, which communicate both efferent and afferent neural signals between the ENS the gut, and the brain. The gut consists of a mesh network of approximately 500 million neurons comprising the ENS, a portion of the autonomic nervous system, covering the complete tract from the esophagus to the anus. The ENS controls the coordination of numerous functions of digestion which it executes with input and feedback from the brain and CNS, through the vagus nerve [23]. The CNS and ENS gets interlinked by the vagus nerve during differentiation and development of the two systems from a neural crest formed during initial embryogenesis. The brain communicates through neurons to the vagus nerve which controls the volume of signals and transmits the signal to the gut inter-neurons in a bi-directional manner, therefore maintaining the functions of the gut. It has been established as a potential route for the gut microbiota to influence the brain and vice versa. The link between ENS and gut microbiota has been scientifically confirmed many times [24]. Germ-free mice, i.e., mice with no commensal gut microbes, showed different patterns of behavior when compared to normal mice under conditions related to stress, supporting the concept that the gut microbiota and the brain's functions are interlinked. The role of gut microbiota is additionally demonstrated by the fact that they play a crucial part in the production of serotonin, which is a key neurotransmitter that influences appetite, motor emotional, autonomic, and cognitive behaviors [25].

The gut microbiota-ENS communication effects CNS signalling systems

CNS signaling systems are impacted by the gastrointestinal tract's ENS-bacteria interaction. ENS neurons interact with neu-

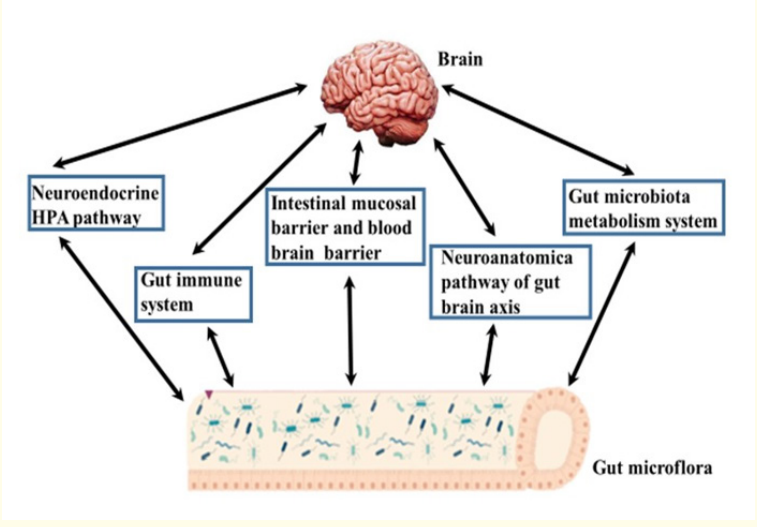

Figure 2: Explains the possible communication routes in the gut-brain axis.

rotransmitters and regulatory peptides made by enteroendocrine cells or resident bacteria after their dendrites terminate in the gut epithelium. The vagus nerve then transmits neurochemicals or hormones produced in the gut to the CNS, resulting in psychological advantages. Because vagotomy inhibits the body's natural reactions to psychobiotics, research on animals shows that the vagus nerve mediates the effects of these drugs [4]. Research on subdiaphragmatic vagotomy provides evidence for the involvement of the vagus nerve. In one study, healthy Balb/C mice treated with *L. rhamnosus* exhibited changed CNS GABA receptor expression and decreased anxiety and sadness, whereas vasectomized mice did not Christopher Lowry's team found that injecting rats with *Mycobacterium vaccae* reduced brain inflammation and stress-induced anxiety [26]. They further studied whether *M. vaccae* could mitigate postoperative cognitive dysfunction (POCD), characterized by inflammation, memory decline, and impaired focus, especially in elderly patients' post-surgery. In one study, aged rats were treated with *M. vaccae* or saline for three weeks before surgery. Results showed that immunized rats experienced reduced brain inflammation and avoided surgery-induced memory loss [27]. Such findings suggest that certain psychobiotic bacteria could support mental and cognitive health.

Microbiota-gut-brain axis in mental illness: Mode of action

The microbiota plays a significant role in modulating the host's immune response and maintaining overall internal balance. Changes in the composition of the gut microbiota have been observed in various immune-related illnesses. Metabolites produced by specific gut microorganisms, such as short-chain fatty acids (SCFAs), tryptophan (Trp), and bile acid (BA) metabolites, have far-reaching effects. These metabolites influence genetic and epigenetic regulation and have consequences on the metabolism of immune cells, affecting both immunosuppressive and inflammatory cell functions [28]. Moreover, the bacteria also confer several other neuroprotective tasks comprising antioxidant properties and suppression of beta-amyloid fibril formation through the same pathways. Psychobiotics act through the vagus nerve and the action of various metabolites including enteroendocrine hormones, SCFAs, neurotransmitters, and cytokines. They cause a rise in the level of short-chain fatty acids like lactate, acetate, propionate, and butyrate which upon contact with the endocrine cells of the mucosal lining catalyze the synthesis of hormones peptide tyrosine tyrosine (PYY), glucagon-like peptide-1 (GLP-1) and cholecystokinin (CCK). The hormones and (SCFAs) then circulate in the body to influence the nervous system. The vagus nerve linking the CNS and ENS is activated by several bacterial products such as peptides, endotoxins, and inflammatory cytokines, recognized by the neuropeptide sensors linked with dendritic cells in the gut which then transmit signals to the brain [4]. Figure 3 illustrates the possible mechanisms of action of psychobiotics in mental illness.

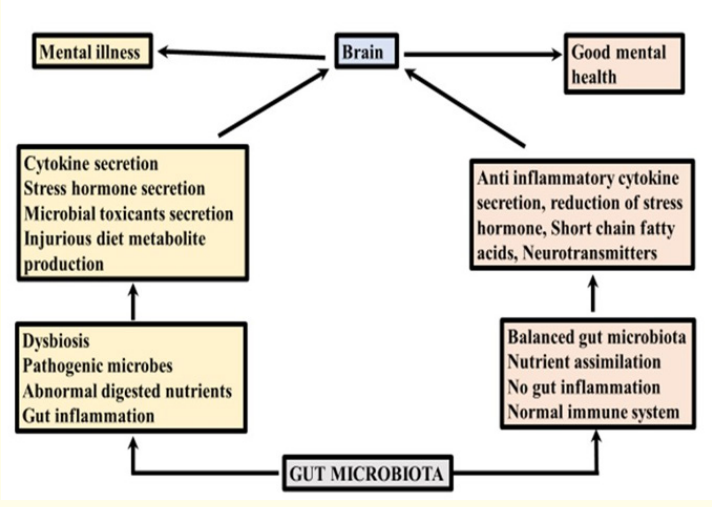

Figure 3: Illustrates the possible mechanisms of action of psychobiotics in mental illness.

The enteric nervous system is an extremely multifaceted network.

That uses several neurotransmitters and therefore a misbalance in the levels may influence the functioning of the enteric nervous system causing altered signals to reach the brain. Moreover, psychobiotics and the overall profile of the gut microbiota can affect tissue levels of mood-regulating minerals such as zinc and magnesium. Further than direct glycemic and nutritional effects there are additional interesting ways in which psychobiotics and the gut microbiota are associated with the brain. It proved that supplementation with Bifidobacterium also delivers systemic defense against lipid peroxidation and reduces brain monoamine oxidase activity, thus significantly increasing inter-synaptic neurotransmitter levels [7]. A dosage of probiotics with psychobitics properties will not only re-establish the function of the gut barrier, making it unaffected by harmful microorganisms but will additionally reduce circulating concentrations of pro-inflammatory cytokines and glucocorticoids. Some peripheral inflammatory events trigger the vagus nerve to cause a significant decline in the release of proinflammatory cytokines from intestinal macrophages which is intermediated by α7nAchR [29]. Certain probiotics with psychobitics property have the potential to initiate the mediation of anti-inflammatory responses by suppressing the levels of the pro-inflammatory cytokines TNF-α and IL-6. Both pro-inflammatory cytokines, along with IL-1β and IL-2, are key contributors to activating anxiety, depressive moods, and many affective disorders [30]. In a research study, a psychobiotic *L. helveticus* NS8-fed group also displayed increased levels in the anti-inflammatory cytokine interleukin-10 [4]. The level of anti-inflammatory cytokines is significantly increased, henceforth, enhancing the integrity of the gut barrier, blood-brain barrier and assisting towards the reduction of total inflammation.

Therapeutic effects of psychobitics in neuropsychiatric disorders

Neuropsychiatric disorders seriously compromise the well-being of affected individuals, with their undesirable effects on mental health and on the capability of offspring to learn and of adults to work. These disorders have a significantly high occurrence, can have a premature onset (for instance, schizophrenia in early adulthood and autism in infantile) or relapsing-remitting course (as in obsessive-compulsive disorder and mood and anxiety disorders), and frequently have disabling symptoms. For these causes, neuropsychiatric disorders show, in comprehensive, an upsetting impact on the families involved and on the human capital of the entire globe. The relationship between an individual's emotional resilience in stressful situations and their gut microbiota composition is significant. The widespread adoption of psychobiotic probiotics could potentially lead to a decrease in the reliance on pharmaceutical antidepressants, which are associated with a range of potentially harmful side effects [31].

Psychobiotics and early-life stress (ELS) in animal models

Mood disorders such as major depressive disorder, anxiety, bipolar disorder, and PTSD, along with ELS, are significant risk factors for later neuropsychiatric disorders (NPDs) and substance misuse. Studies link early depression onset with childhood adversity, while ELS impacts CNS structures like the prefrontal cortex, amygdala, and hippocampus, creating distinct neuroinflammatory and neuroanatomical changes [32]. MS, used to study depression sensitivity, also models gut-brain axis dysfunction, influencing GI processes as seen in conditions like IBS [33]. ELS changes microbiota across species, including piglets and rodents.

Lacidofil® reduced MS-induced colonic dysbiosis, restoring Lactobacilli, lowering corticosterone levels, and enhancing gut barrier integrity. Early Lacidofil® treatment during ELS reduced middle-aged stress dysregulation and improved water avoidance stress response. Given to dams from PND2–PND14, Lacidofil® transferred to pups via lactation, blocking MS-induced emotional development acceleration and adult-like memory formation, although no effects on anxiety were noted in PND17 EPM tests [2].

L. rhamnosus GG combined with a prebiotic reduced MS-triggered anxiety and improved memory but didn't lower corticosterone. Alone, *L. rhamnosus* GG mitigated MS's impact on glucocorticoid receptor mRNA in the hippocampus and on GABA receptor subunit expression only with prebiotic support [44]. *B. bifidum* G9-1 reduced MS-induced corticosterone levels, intestinal dysbiosis, and fecal frequency [35]. Both live and heat-killed *L. paracasei* PS23 decreased MS-induced depression and anxiety behaviors, linked to higher IL-10 levels [36,37]. Lacidofil® also blocked MS's generational transmission of stress effects through paternal line supplementation and normalized pubertal timing in MS-affected rats [46]. In humans, a small study reported decreased depressive symptoms in stressed medical students after Lacidofil® intake, warranting further investigation. Specific strains, including *B. infantis* 35624 and *L. plantarum* PS128, improved stress and depression measures in MS models, adjusting cytokine and neurotransmitter levels. *B. pseudocatenulatum* CECT 7765 regulated stress response and HPA activity in MS pups, stabilizing neurotransmitters and reducing inflammation *L. fermentum* CECT 5716 prevented stress-induced intestinal barrier dysfunction and corticosterone increases [38].

Clinical trials on psychobiotics for major depressive disorder (MDD)

Depression has a complex etiology involving genetic, physiological, and environmental factors. A major neurophysiological change in major depressive disorder (MDD) is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, seen in 40–60% of individuals with depression [39]. HPA axis dysfunction includes elevated cortisol and corticotropin-releasing hormone, increased neuronal activity, and abnormal feedback loops related to glucocorticoid resistance [40]. Research on psychobiotics for MDD is advancing, with clinical studies showing promising antidepressant effects despite some inconsistencies in evaluation methods [41]. The variability in symptomatology and evaluation tools must be considered, as not all psychobiotics impact the same aspects of depression [42].

Scientists found that MDD patients taking *Lactiplantibacillus plantarum* 299v for 8 weeks showed improvements in cognitive functions, despite no changes in depression scores [43]. This was associated with an increased 3-hydroxykynurenine to kynurenine ratio. In healthy young adults, L. plantarum 299v reduced cortisol levels under stress and improved IBS symptoms [44], enhancing intestinal barrier integrity in animal models [45]. Researchers reported that combining *Bifidobacterium longum* Rosell®-175 and *L. helveticus* Rosell®-52 improved Beck Depression Inventory scores in MDD patients on SSRIs, with indications of better tryptophan availability for serotonin production. This formulation increased appetite and BDNF levels in MDD patients [46]. In self-referred patients, there was no overall effect on depression symptoms, but those with higher vitamin D levels showed better mood improvement.

Psychobiotics: A potential substitute to conventional anxiolytics

Anxiety and depression commonly go together, and many investigations of the MGB in anxiety comprise measures of depression and vice versa. Much of the proof for a connection between anxiety and the MGB comes from preclinical studies, whereby anxious-like characteristics may be inferred from the animal's behavior in definite conditions, such as the elevated plus maze test, open-field test, light/dark box, or in reaction to particular stressors. Germ-free mice showed decreased anxiety-like behavior when compared with conventionally reared animals along with exaggerated corticoste-

rone reactions to stress demonstrating altered HPAaxis function, although germ-free rats showed exaggerated anxiety responses. It is significant to note that variations in anxiety due to psychobiotic treatment are species and strain reliant [49]. Improvements in definite anxiety measures have been reported in a few numbers of probiotic intervention investigations of healthy control participants and chronic fatigue syndrome. Moreover, a multi-strain probiotic [*S. thermophilus (2 different strains), L. bulgaricus, L. lactis subsp. lactis, B. lactis L. acidophilus, L. reuteri L. plantarum*] was in recent times proved to have anxiolytic effects in a minor study of healthy controls. Fascinatingly, B-GOS considerably reduced anxiety levels in individuals with IBS. One more recent work has recognized *Lactobacillus plantarum* DR7 as a potential psychobiotic, where it lessened anxiety- and stress-linked symptoms in a randomized, double-blind, placebo-controlled study [50]. On the other hand, there is a strong necessity for additional translational investigations for in-depth inspection of the effects of psychobiotics on anxiety.

Psychobiotic therapeutics in Schizophrenia

Schizophrenia is a complex and challenging neural disorder characterized by negative and positive neurobehavioral dysfunctions, including psychosis, delusion, cognitive dysfunction, apathy, and social withdrawal. A trial by Dickerson., *et al*. assessed psychobiotic supplementation in a 14-week placebo-controlled study with resistant schizophrenia patients, finding no significant changes in symptom severity between the psychobiotic and placebo groups. Tomasik., *et al*. observed the immunomodulatory effects of psychobiotics alongside conventional antipsychotics through cytokine variations unaffected by other antipsychotics [49].

Psychobiotic therapeutics in bipolar disorder

Bipolar disorder is marked by recurring episodes of both depression and mania or hypomania. Typically, bipolar disorder manifests between the ages of 15 and 25, with depression often being the most common initial symptom. It causes severe disease burden and results in important impairments in social and cognitive functions. In clinical practice, however, the diagnosis of BD is still not yet developed and missing objective or specific biomarkers. Postponed or missed diagnosis of BD negatively affects the management and prognosis of this disease. As a result, further understanding the pathogenesis of BD and recognizing biomarkers with effective diagnostic or prognostic efficiency is of great urgency. In euthymic patients with bipolar disorder, an 8-week successive everyday intake of psychobiotic mixture supplement, a mixed combination of 9 human bacterial strains belonging to genus Bifidobacterium and Lactobacillus, as an instruction suggested dose, improved gastrointestinal quality of life, and reduced bad cognitive reactions [50]. Furthermore, the same research group further demonstrated that a 12-week supplement with this psychobiotic mixture supplement could enhance psychomotor processing speed and performance concerning attention and executive action in euthymic patients with bipolar disorder. Another scientific investigation proposed that adjunctive probiotic supplements (*Bifidobacterium lactis* strain and *Lactobacillus GG* strain) decreased the rehospitalization percentage in patients freshly discharged for mania. Even though the particular mechanisms by which psychobiotic microorganisms benefit mental health remain unidentified, it is possible that they re-establish the gut microbiota and control host immune reactions in reaction to several antigens. Though these research investigations are preliminary, they demonstrated crucial evidence that manipulating the gut microbiome, either supplemented with psychobiotic bacteria or eradicating detrimental microorganisms, thus has the efficiency as a therapeutic approach in the treatment or prevention of bipolar disorder. The key task for developing microbiome-targeted therapy is to recognize particular gut bacteria or their metabolites linking to mental health in bipolar disorder patients [50].

Therapeutic effects of psychobitics in neurodegenerative disorders

Psychobiotic therapeutics in Parkinson's disease (PD)

Parkinson's disease (PD), primarily a neurodegenerative disorder marked by motor dysfunction, is largely influenced by aging. In a 3-month randomized, double-blind, placebo-controlled trial, PD patients received a psychobiotic supplement containing *Lactobacillus reuteri*, *L. acidophilus*, *B. bifidum*, and *L. fermentum*. The psychobiotic group showed reduced scores on the Unified Parkinson's Disease Rating Scale (UPDRS), lower MDA and hs-CRP levels, increased glutathione (GSH), and improved insulin function compared to controls. In another trial, psychobiotic supplements downregulated IL-8, IL-1, and TNF-a and upregulated peroxisome proliferator-activated receptor gamma (PPAR-g) and transforming growth factor beta (TGF-b) in peripheral blood mononuclear cells (PBMCs), though no effect was observed on low-density lipoprotein receptor (LDLR), vascular endothelial growth factor (VEGF),

or other oxidative stress markers. The scientific investigations revealed that recipients with PD who were using psychobiotic supplements showed better gastrointestinal functions. Patients with PD who consumed fermented milk comprising various strains of psychobiotic bacteria demonstrated a betterment of constipation. Treatment with a psychobiotic mixture of *B. infantis* and *L. acidophilus strains considerably* lowered bloating and abdominal pain [47]. The clinical studies with psychobiotics in Parkinson's disease and their outcomes are illustrated in Table 2.

Table 2: The clinical studies with psychobiotics in Parkinson's disease and their outcome.

Study model	Duration of Psychobiotics administration	Psychobiotics, dosage and route of administration	Test	Outcome	Reference
Patients with PD (Mean age: 76.05 years) Male = 17 Female = 23	3 months	*L. acidophilus* and *B. infantis* tablet/twice/day	Hoehn and Yahr scale, NMS-Quest	Abdominal pain ↓ Bloating ↓	[48]
Subjects with PD Psychobiotics: N = 25 Placebo: N = 25	12 weeks	Psychobiotic supplements: 8109 CFU/day	Randomized, double-blind, placebocontrolled clinical trial, PBMC	IL-1, IL-8 and TNF-a levels ↓ TGF-b and PPAR-g levels ↑ LDLR and VEGF levels: NA	[19]

Psychobiotic therapeutics in Alzheimer's disease (AD)

Alzheimer's disease is a serious neurodegenerative disorder with memory and cognitive disablement. The proofs of the effects of psychobiotics on ameliorating cognitive disorders are inadequate. Agahi., *et al*. explored the effect of psychobiotic supplementation on patients with severe AD. The results showed that severe AD patients were unresponsive to psychobiotic supplementation. In one of the explorative intervention studies using many strains, *L. plantarum* W62, *B. lactis* W52, *L. casei* W56, *L. acidophilus* W22, *Lactococcus lactis* W19, *B. lactis* W51, *B. bifidum* W23, *L. salivarius* W24 and *L. paracasei* W20 on patients with AD. The tryptophan metabolism in serum and gut bacteria composition was affected by psychobiotic intervention. Bonfili and coworkers reported that intake of psychobiotic formulation (SLAB51) on transgenic AD mice considerably decreased oxidative stress by initiating SIRT-1-dependent mechanisms [20]. Two investigations examined the influence of many psychobiotic strains, *Lactobacillus fermentum*, *L. acidophilus*, *B. longum* and *B. lactis* on an animal model of AD. The total counts of *Lactobacillus* spp. and *Bifidobacterium* spp. were improved, and Coliform was reduced in the stool after the psychobiotic intervention. Moreover, psychobiotic intake improves memory deficits and learning in AD rats compared with control rats. The decline in inflammation and oxidative stress and the number of amyloid plaques were detected in the Alzheimer- psychobiotic group [47].

Therapeutic effects of psychobitics in neurodevelopmental disorders in Tourette syndrome (TS)

Tourette syndrome is a neurological disorder that is normally initially noticed in infancy. The clinical treatments of TS comprise deep brain stimulation (DBS), antipsychotics, α2-adrenergic agonists, and behavioral treatments. As per one of the recent case reports, fecal microbiota transplantation (FMT) intensely ameliorates Tourette syndrome after 8 weeks of treatment. Another placebo-controlled, double-blind, randomized clinical trial enrolled patients to clarify the effect of PS128 on Tourette syndrome. The main results were assessed through the Yale Global Tic Severity Scale (YGTSS) after 8 weeks of intervention [50].

Required investigations to overcome technical and conceptual knowledge gaps in the development of psychobiotics

Monitoring gut microbes in fecal samples should be a part of studies on long-term (months) psychobiotic usage. Psychobiotics and prebiotics should be researched independently because they may have diverse effects on the microbiota. It is necessary to compare young and old subjects methodically and assess the behavioral and biological impacts across time. To predict both advantages and potential disadvantages, studies should also monitor altera-

tions' functional effects, such as glutamate and GABA variations. Although unpredictable, adverse effects, individual differences, and modifiers of psychobiotic outcomes should all be closely watched. Psychobiotics should be evaluated in clinical studies as supplements to antidepressants and anxiolytics, and strain-specific effects should be examined to validate initial results [8]. The development of a theoretical explanation for why and how specific strains and species exhibit varying effects would enable precise estimations of which strains have which effects in what situations. Currently, there is no such framework.

Conclusion

In conclusion, the novel class of probiotics known as "psychobiotics," which can help with neurodevelopmental, neurodegenerative, and neuropsychiatric disorders as well as anxiety and stress reduction, has promise for treating mental health concerns. By altering the gut microbiota, lowering inflammation, and affecting insulin and oxidative processes, psychobiotics have shown advantages. In relation to several neurological illnesses, they may also help stimulate the vagus nerve and regulate the accumulation of α-synuclein in enteroendocrine cells. Numerous clinical studies have demonstrated the safety and benefits of psychobiotics, which has resulted in the global distribution of a variety of medicines based on them. For them to be regarded as a routine treatment for certain illnesses, more investigation is required to validate their mechanisms and effectiveness.

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