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Review Article
Therapeutic Potential and Recent Development of Psychobiotics for the Management of Brain Disorders

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Abstract

Translational studies indicate that probiotics may have an impact on depression, stress responses, anxiety, behavior and cognitive functions. Psychobiotics are the type of probiotic substances having potential mental health benefits when ingested through interactions with gut-microbiota. Psychobiotics exert these health benefits through Microbiota-brain communication by producing neurotransmitters such as serotonin and gamma-aminobutyric acid, which act through the gut-brain axis. Psychobiotics have been reported for beneficial use as anti-Alzheimer's, anti-depressant and anxiolytic effects characterized by systemic, cognitive and emotional changes. Development of psychobiotics as a therapeutic candidate may open up the possibility for manipulation of gut-microbiota for effective management of various psychological disorders and co-morbidities. The objective of this article was to conduct the systemic literature review and analysis of reported study related to psychobiotics and to understand the possible mechanism of psychobiotics involved in the communication between brain and gut-microbiome. During last decade, researchers have compiled convincing evidence that suggests the gut-microbiome influence mental health and cognition. Therefore, it is important for the researchers to explore more about the gut-microbiota-brain connections. In this review, it was revealed that use of psychobiotics formulations might be a safe and effectual therapeutic strategy to treat psychotropic disorders including depression, anxiety, Alzheimer's disease as well as dementia. However, exhaustive and mechanistic researches are warranted to investigate the potential of psychobiotics on microbiome-gut-brain axis in humans and therapeutic candidate as clinical uses for brain disorders.

Key words: Psychobiotics, gut-microbiome, gut-brain axis, psychological disorders, neurotransmitter

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INTRODUCTION

A psychotic disorder or Psychosis is a mental disorder characterized by abnormal thoughts, behaviors, feelings and cognition. The lifetime prevalence of at least one mental disorder is 29.1% and two disorders is 12.6%. The median age-of-onset for any mental disorder is 20 and morbidity risk from 20-70 years[1] of age is 37.1%. It is well understood that diet is a key modulator of intestinal health and gut-microbiome and gut-microbiota can be manipulated by taking prebiotics and probiotic supplements[2]. From recent research, it is becoming evident that gut microbiomes have a significant influence on brain function and psychological behavior. Evidences are accumulating to support the hypothesis that gut-microbiota affects central neurochemistry and psychological behavior[3,4]. Gut-microbes can produce and metabolize a wide range of neurotransmitters and neuroactive substances found in the human brain such as melatonin, serotonin, catecholamine's, gamma-aminobutyric acid (GABA), acetylcholine and histamine which affects gut-brain axis[5,6]. Therefore, the novel approach for altering the brain function and treating psychological disorders is to manipulate gut-microbiota with psychobiotics[4,7].

Psychobiotics can be defined as a live organism which on ingestion produces health benefits in patients suffering from psychological disorders. Ingestion of specific psychobiotics produces beneficial psychological effects. Moreover, it affects the hypothalamic-pituitary-adrenal (HPA) axis and neuroactive substances in the brain[8]. Translational studies indicate that psychobiotics may have an impact on depression, stress responses, behavior, anxiety and cognitive functions (Fig. 1). Results from pre-clinical and initial phases of clinical setup during recent decades suggest that psychobiotics may be helpful in reducing anxiety, depressive symptoms and stress-related psychiatric disorders[8,9]. However, more studies evaluating the therapeutic potential of psychobiotics in neuropsychological disorders are still warranted. The purpose of this review article was directed on the species of micro-organisms as psychobiotics, recent finding on therapeutic role and development of psychobiotics for the management of brain disorders and to explore the possible mechanism involved in the communication between gut-microbiome and brain.

PSYCHOBIOTICS AND HISTORICAL DEVELOPMENT

A decade ago, a notion that the bacteria in gut could guide behavior and mental health was seen as strange. But today, it is well established that the trillions of micro-organisms in the gastrointestinal tract, collectively

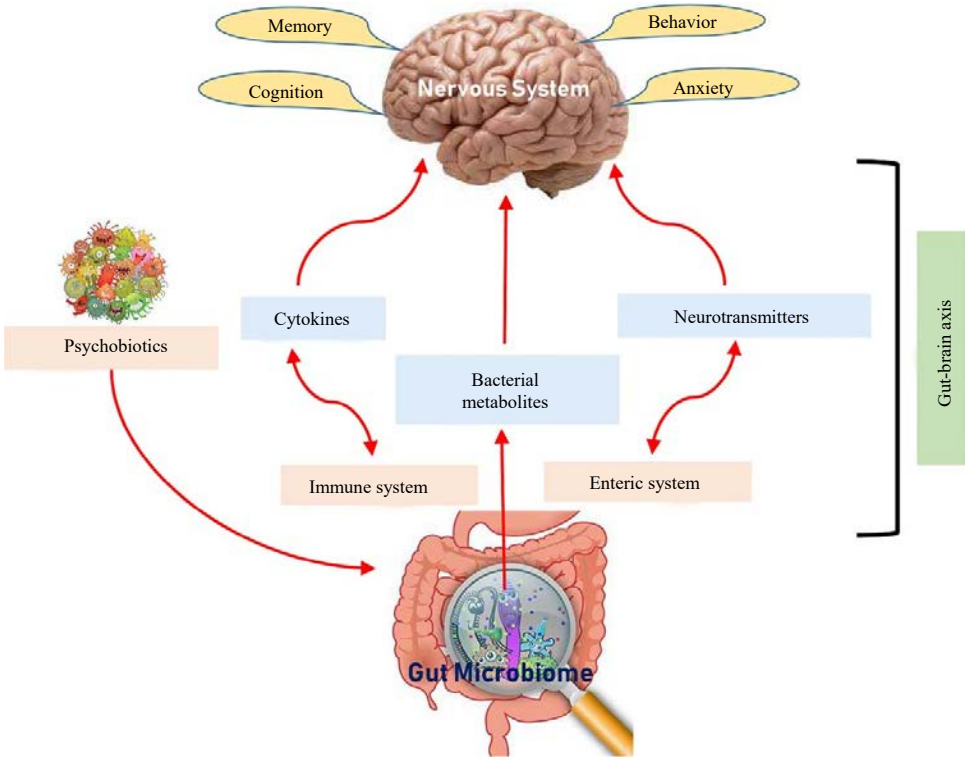

Fig. 1: Translational studies with psychobiotics and an impact of psychobiotics on behavior, anxiety and cognitive functions

known as the microbiome influence health in countless ways[10]. Inside the gut, microbiome helps us in developing the immune system, making nutrients, defense against infection and produce neurochemicals important for brain function[11].

In early 19th century, "Pliny the Elder" the Roman naturalist revealed the benefits of probiotics when it used fermented milk to treat intestinal problems. In late 19th century Elie Metchnikoff, of the Pasteur Institute in Paris discovered the health benefits of probiotics[12]. In 1907, Metchnikoff observed that the people living in rural areas of Bulgaria, in spite of harsh climates and extreme poverty had large average life spans than those in wealthy European populations[13]. It was also discovered that these villagers were drinking fermented yoghurt drink every day during his study he found that *Lactobacillus bulgaricus*, a probiotic improved the health of these villagers and may have helped the longevity of their lives[13,14].

Metchnikoff's pioneering research related to probiotics prompted him and leading researchers to discover many types of probiotics such as *Saccharomyces boulardii*, *Lactobacillus acidophilus* and *Bifidobacterium infantis*, all of these can have different effects on the body[13]. Professor Ted Dinan of University College Cork in Ireland, in 2012 first introduced the term "Psychobiotics" to describe the specific microbes that when consumed result in beneficial effects on mood, cognition and motivation. During last decades, several probiotics are used for the development of therapeutic formulations with psychobiotics[3]. Some potential strain of micro-organism used for the development of psychobiotics are described below:

***Bifidobacterium longum*:** *Bifidobacterium longum* is a Gram-positive, catalase-negative, rod-shaped bacterium present in the human gastrointestinal tract. A number of strains belonging to the genus *Bifidobacterium* have been proposed as beneficial supplements for a wide range of health conditions and treating stress-induced visceral through the regulation of the neural function and normalize the HPA-axis functions[15]. Probiotic preparations containing *Bifidobacterium* strains, alone or in combination with other bacteria[15] have been tested in human clinical studies and demonstrating the efficacy of probiotics in the prevention, alleviation or treatment of different pathologies[16].

***Bifidobacterium infantis*:** *Bifidobacterium infantis* is a Gram-positive, anaerobic, branched rod-shaped bacterium. It is a member of the *Bifidobacteria* family, a strain of bacteria that is normally found in the human intestines and have a symbiotic bacteria-host relationship with humans. It is non-infectious and is commonly used in probiotic supplements[17].

***Clostridium butyricum*:** *Clostridium butyricumis* an anaerobic, endospore forming, butyric acid producing, Gram- positive bacillus that commonly resides in the intestine of healthy animals and humans and is a probiotic that has been characterized for its beneficial effects in gastrointestinal disease via modulating gut-microbiota and their metabolic short chain fatty acids (SCFAs) including propionate, acetate and butyrate[18].

***Escherichia coli*:** *Escherichia coli* is a Gram-negative bacteria found normally in gut. It is the most intensively studied bacteria for probiotic properties[19,20]. The species of *Escherichia coli* is probably the furthermost studied species of all known bacteria and as a consequence an impressive amount of information is available about it Beimfohr [21]. Over the last few decades, novel probiotic properties have been discovered and it is well established that *Escherichia coli* has a positive effect in various psychological disorders such as stress[20]. The future of probiotic *E. coli* may lay in what Alfred Nissle originally discovered to treat gastrointestinal infections, which nowadays are often caused by antibiotic-resistant pathogens[22].

***Lactobacillus rhamnosus*:** *Lactobacillus rhamnosus* is a Gram-positive, heterofermentative, facultative anaerobic bacteria. It was firstly isolated from fecal samples of humans. It was identified as a potential probiotic strain due to its good growth characteristics, resistance to acid and bile and good adhesion capacity to the intestinal epithelial layer. It is a very widely used probiotic strain and is present in variety of commercially available probiotic products[23].

***Lactobacillus helveticus*:** *Lactobacillus helveticus* is a rod-shaped, lactic-acid producing bacterium of the genus *Lactobacillus*. It is an important industrial thermophilic starter that is mainly employed in the fermentation of milk for the manufacture of cheese. *In vitro* studies showed that *L. helveticus* possesses many common probiotic properties, such as the ability to survive gastrointestinal transit, adhere to epithelial cells, antagonize pathogens. Moreover, it can also treat stress-induced visceral pain[15,24].

***Lactobacillus plantarum*:** *Lactobacillus plantarum* is a Gram- positive, aero-tolerant, rod shaped bacteria, commonly

found in meat, dairy products and fermented food products. It colonizes in the human gastrointestinal-tract and produces variety of physiological and psychological health benefits[25].

PSYCHOBIOTICS AND NERVOUS SYSTEM

Co-morbidity with central nervous system (CNS) disorders and stress related clinical consequences has been perceived in severe and mild types of intestinal dysbiosis give emphasis to the role of brain-gut signals such as immune factors and neurotransmitters[26-28]. Functional upregulation of the CNS by gut-microbiota is based on neural, metabolic, endocrine and immunological mechanisms. Enteric nervous system which controls the neural pathway is the main division of autonomic nervous system that governs the gastro intestinal (GI) functions and vagal afferent nerves that convey sensory information from viscera to the CNS. It is evident from current research that gut neuro-motor functions are influenced by modulating gut microbiome by psychobiotics[29]. Emerging evidences showed that the effects of psychobiotics might be mediated by the spinal cord, vagus nerve or by neuroendocrine systems. Therefore, the relationship between microbiota, stress and mood is an important area of research. Robust pre-clinical evaluation in rodents suggested that many psychobiotics possess anxiolytic or antidepressant activity and psychobiotics as a therapeutic agent in psychological disorders seems reasonable suggestion[8,30]. The mechanisms by which gut-microbiome can influence CNS function are mediated directly via microbe-host interaction or indirect effect mediated by microbial metabolites. In a study, stressed mice over an extended period showed increased growth of bacterial groups (genus *Alistipes*) and stressed mice showed depression through inflammatory pathways. In an independent study, reduced level of Oscillibacter in the gut was observed, which is related to psychological depressive state. Valeric acid, which structurally resembles GABA is the primary metabolic end product of Oscillibacter[30,31].

In some pre-clinical studies, it was found that certain probiotics or live micro-organisms have potential mental health benefits such as *Lactobacillus rhamnosus* has been found to reduce the corticosterone release and stress-related behavior in anxious mouse strain. It has been also found that *Lactobacillus rhamnosus* can alter central expression of GABA receptors[32]. Therefore, the gut-microbiota can influence CNS functions and might be useful target for development of psychobiotics for brain disorders described in below section through neural, metabolic, endocrine and immunological mechanisms.

PSYCHOBIOTICS AND STRESS

From a study it is found that *Bifidobacterium longum* R0175 and *Lactobacillus helveticus* R0052 reduce stress-induced gastrointestinal discomfort. *Bifidobacterium longum* R0175 and *Lactobacillus helveticus* R0052 could also contribute to psychological wellbeing of subjects with reduced anxiety and stress and could render a prophylactic approach against stress-related diseases[33]. There is huge number of evidences which support commensal organisms within the gastro-intestinal tract which play an important role in early programming and later responsivity of the stress system. Dinan and Cryan[34] found that gut pathogens such as *Escherichia coli*, if taken or if they enter the gut can activate the HPA. However, during *in-vivo* studies, animals raised in a germ-free environment with psychological stress show increased HPA-axis responses, which normalize with mono colonisation by certain bacterial species such as *Bifidobacterium infantis*[34,35].

PSYCHOBIOTICS AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disorder which occurs due to accumulation of neurofibrillary tangles and amyloid plaques along with disruption of cholinergic neurons in the basal part of forebrain and is associated with memory deficits and cognitive defects[36]. Major treatment objectives of AD are to increase the Acetylcholine level in the CNS and prevent the degeneration of cholinergic neurons of the brain. In addition, several studies revealed that due to impairment of mitochondrial function with age, there is a reduction in cellular energy production and elevation in levels of Reactive Oxygen Species (ROS) and increased level of ROS produces a pattern of cumulative damage of cellular macromolecules which is associated with the aetiology of AD[37,38].

The AD is one of the most common forms of senile dementia[39]. It is characterized with short-term memory loss which at later stages ends up with the complete loss of self-sense in patients. It is the serious social problem as it poses a great threat to older individuals and their families. The AD is characterized by two main pathological markers in the brain, one if "Senile plaques" (SPs) and the other "Neurofibrillary tangles" (NFTs). "Senile plaques" are the extracellular aggregates composed of amyloid β (Aβ) peptides, while the "Neurofibrillary tangles" are intracellular aggregates composed of hyperphosphorylated Tau protein[40]. The degree of cognitive impairment and the prevalence rate of the disease is influenced by older age, early onset of the

disease and several poor health conditions[41]. The gut microbiome is a dynamic ecosystem which is affected by several factors including metabolism, genetics, antibiotic treatment, geography, diet, age and stress[42]. From recent studies, it is found that there is relationship between cognitive behaviors and alterations in the gut micro-biome. Recently, it has been reported that the administration of probiotics or bacterial infection with an enteric pathogen can modulate cognitive behaviors including learning and memory in germ free animals (containing no microbiota) with intestinal dysbiosis[43]. Some complications such as oxidative stress, cognitive disorders, insulin resistance, neuro-inflammation and altered lipid metabolism, which can be observed in AD are identified to be influenced by the gut-microbiota as well as probiotics. Akbari *et al.*[44] conducted a clinical trial to assess if reinforcement of the intestinal microbiome with the probiotic supplementation helps to improve metabolic and cognitive disorders in the AD patients.

Glutamate is metabolized by microbes of *Lactobacillus* species which leads to the production of GABA, which is the major inhibitory neurotransmitter in the CNS and dysfunctions on GABA signalling pathway are linked to depression, anxiety, defects in synaptogenesis and cognitive impairment including AD[3,10,45-47].

In an another example, brain-derived neurotrophic factor (BDNF) has pleiotropic effects on differentiation, synaptogenesis, neuronal development and the synaptic plasticity that controls cognitive function and has been found that it is reduced in serum and brains of patients suffering with anxiety, schizophrenia and AD[46,48,49]. Experimental infectious model was developed with altered micro-biota profile and it was found that BDNF expression is reduced in the cortex and hippocampus of "germ free" mice and this decrease in the BDNF expression was found to be associated with progressive cognitive dysfunction and increased anxiety behaviour[48-50].

Kumar *et al.*[51] developed the experimental animal model of neurodegeneration, memory impairment and oxidative damage in mice with the supplementation of D-Galactose. D-Galactose supplementation also results in a decrease in the expression of nerve growth factors and other proteins related to it, which results in the degeneration of neurons and finally reduce the levels of acetylcholine in brain regions[52,53].

Recent studies have demonstrated that the *Lactobacillus plantarum* have the protective effects against D-Galactose and scopolamine induced memory deficit in mice[54,55]. In another study, it was demonstrated that *Lactobacillus plantarum* NDC75017 ameliorates the learning and memory capability in aging rats[56]. In addition, MTCC1325 strain of *Lactobacillus plantarum* also have the antioxidant activity and ability to produce acetylcholine neurotransmitter in both *in vitro* and *in vivo*[57]. *Lactobacillus plantarum* MTCC 1325 also results in enhanced organ index and body weight gain, improved learning skills and the behavioral activity through elevation in the cholinergic neurotransmitter in cerebral cortex and hippocampus regions of brain and restored histopathological abnormalities back to the normal conditions etc. Thus all these findings suggested that the *Lactobacillus plantarum* MTCC 1325 may have anti-Alzheimer properties against D-Galactose induced AD[58].

PSYCHOBIOTICS AND DEPRESSION

Probiotics are essential for healthy humans or host. Adverse effects are seen in gut in the absence of probiotic bacteria, these are not seen only locally in the gut but also affects central HPA and monoaminergic activity, these features are implicated in the aetiology of depression[59]. Anti and pro-inflammatory cytokines balance remarks in the pathophysiology of depression on the basis of hypothesis it seems that probiotics may possess antidepressant activity[60].

According to the cytokine hypothesis of depression when there is impairment in the function of immune system it leads to symptoms of depressive illness due to this there is increased activation of pro-inflammatory mediators[60-62]. This data is collected from both animal studies[61,63,64] and clinical reports[65-67] which clearly shows that there is increases in pro-inflammatory cytokines like, TNF-α, IL-1b and IFN-a which are mainly responsible of depression-like symptoms. Furthermore, increased plasma concentrations of pro-inflammatory cytokines are balanced with many antidepressant drugs, like the selective serotonin re-uptake inhibitors (SSRIs), the tricyclic antidepressants (TCAs) and which is observed in patients suffering from depression[67,68].

Pathological abnormalities of depressive illness predominantly originate in the brain which is treated by probiotic bifidobacteria and potential antidepressant effects of this treatment may be mediated via three major interacting pathways that comprise the neuroendocrine, neuronal and immune systems. Therefore, the expression of corticotrophin-releasing factor (CRF) and vasopressin (AVP) in the hypothalamus and also the basal plasma corticosterone concentrations were quantified to assess the effects of chronic probiotic treatment on the neuroendocrine system. Affected immune parameters by probiotics were analyzed by

peripheral blood cytokines. Finally, alteration in monoamine concentrations, neurotransmitter activity and levels of tryptophan and its metabolites were measured in various brain regions to establish the effect of bifidobacteria treatment[59].

The release of the pro-inflammatory cytokines TNF-α, IL-6 and IFN-c by bifidobacteria in response to immune disorder suggested that this probiotic treatment may be beneficial in depression. The central transcription inhibitory property of bifidobacteria is also reported to mediate the inflammatory response[69]. Decrease in the production of the anti-inflammatory cytokine IL-10 is observed in contrast to the many reports that suggested an increase in IL-10 release in response to probiotics[19,70].

PSYCHOBIOTICS AND ANXIETY

In the last decade there are considerable evidences which support the role of gut-brain signalling to psychological disorders. It was found that chronic stress is always associated with increased susceptibility to functional gastrointestinal disorders, inflammation and there is strong evidence for co-morbidity between psychological disorders and gastrointestinal symptoms[71,72]. It is well established that physiological functions including immunity is regulated by gut microbial community[26,73] and there are growing evidences of its impact on the CNS. The administration of specific microbial strains reduces depression and anxiety-like behaviours[74,75]. The emergent corollary demonstrated the inextricable relationship between the immune, nervous systems and microbiome and their roles in regulating neural function and behaviour[76]. In a study, *Lactobacillus rhamnosus* JB-1TM (JB-1) was given orally to mice as test organism to demonstrate anxiolytic effect of this strain. It was demonstrated that *Lactobacillus rhamnosus* led to changes in neurotransmitter levels in the brains of mice[77] and also had antidepressant and anxiolytic activity on baseline behaviours[75].

To investigate the impact of the brain-gut axis on emotional behaviors, *Lactobacillus plantarum* PS128 was administrated to a germ-free (GF) mouse. On administration of live PS128, elevated plus maze test was performed and significant increase was found in the total distance travelled in the open field test and reduction in the time spent in the closed arm, however in case GF mice there was no significant effects in the depression-like behaviors. Also, the administration of chronic live PS128 significantly increased the levels of dopamine and serotonin and in the striatum but not in the hippocampus or prefrontal cortex. It was also found that there are no adverse effects on physical health on chronic administration of PS128. Thus chronic administration of live PS128 is safe and could induce beneficial changes in emotional behaviors. The behavioral changes are due to the increase in the monoamine neurotransmitters in the striatum. Therefore, daily intake of the *Lactobacillus plantarum* strain PS128 could elevate mood and improve anxiety-like behaviors. It may be beneficial in ameliorating psychological disorders as well[78].

PSYCHOBIOTICS AND VASCULAR DEMENTIA

Vascular dementia (VaD) is the second most common type of dementia after Alzheimer's disease, results from a reduction in the supply of blood to cerebral part of brain by a blocked or diseased vascular system and results in a progressive decline in learning, memory and cognitive function[79]. Clinical evidence suggested that chronic cerebral hypo-perfusion is responsible for cognitive decline and hippocampal neuronal injury in neurodegenerative diseases[80,81]. The possible mechanisms leading to vascular dementia are mainly oxidative stress and apoptosis[82].

These recent studies demonstrated that VaD is associated with gut-microbiota. These studies supported the use of *C. butyricum* as a safe and effective therapeutic option against VaD, it acts through the gut microbiome-butyrate-brain axis to prevent and treat VaD in mice. The dietary *C. butyricum* can influence gut microbiome and lead to changes in the fecal butyrate content that raise butyrate in the brain and modulate CNS functions including brain development and behavior[83]. A recent study suggests that butyrate, as an inhibitor of his tone deacetylase (HDAC), improves spatial learning and memory ability and can provide anti-apoptotic and neuroprotective effects against ischemic stroke[84]. Therefore, the administration of live *C. butyricum* may become an adjuvant therapy for VaD patients[78].

CONCLUSION

It was concluded that use of psychobiotics formulations might be safe and effective therapeutic strategy for the treatment of psychotropic disorders like, depression, anxiety, Alzheimer's disease and dementia. In addition, it can also enhance the learning, memory and cognitive function. However, comprehensive and mechanistic studies are still warranted to explore the beneficial role of psychobiotics in microbiome-gut-brain axis interactions in humans.

SIGNIFICANCE STATEMENT

This study discovered the safe use of psychobiotics formulations to treat certain devastating disorders regarding brain functioning. This review will help the researchers to understand the extensive scope of psychobiotics for the treatment and management of patient suffering from brain disorders.

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