Review Article

Psychobiotics, Novel Therapeutic Agents for the Psychiatric Disorders

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Abstract | Various neurological disorders such as Parkinson's disease, Alzheimer's disease, autism spectrum disorder in young children, stress, anxiety etc., are afflicting the people all over the world. The pathophysiology of some of these disorders is not fully understood. Furthermore, the conventional therapies are not effective for all patients with psychiatric disorders. Hence, alternative therapeutic strategies/agents are much needed. Clinical researchers suggest that certain microorganisms (beneficial microorganisms/probiotics) could be substituted for conventional therapies and/ or can be used in combination with current drugs. Such beneficial microorganisms which can influence the central nervous system and cure the neurological complications are referred to as psychobiotics. In fact, the psychobiotics are the probiotic/ prebiotic agents which when present in the human gut region will not only improve the gut health but also influence the central nervous system *via* gut-brain axis, and counteract the symptoms of various neurological disorders. Till date, numerous probiotic bacteria and prebiotic compounds were identified and the majority of them are able to influence the nervous system. In various clinical trials on animal models and humans, it was proved that psychobiotics are effective in ameliorating the clinical symptoms of neurological disorders. Some of the researchers are employing psychobiotics in combination with traditional drugs for treatment of the psychiatric disorders. The aim of the current review is to investigate the concept of psychobiotics, detailing their mechanisms of action and discussing their potential applications in the treatment of certain psychiatric disorders. Subsequently, this study delineated the characteristics of psychobiotics and highlighted their impacts on the nervous system. Additionally, various psychobiotics utilized in the management of specific psychiatric conditions have been examined based on numerous clinical trials and experiments conducted on both animal models and human subjects.

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Introduction

Currently, mental disorders, including Parkinsons's disease, anorexia nervosa, Alzheimer's disease, autism in children, clinical depression, anxiety, stress, insomnia, and schizophrenia are prevalent worldwide (Oroojzadeh *et al.*, 2022). Especially, clinical depression is the most common global psychological

issue. Around 3.8% of people worldwide are suffering from depression that is affecting their abilities and quality of life. The depression is a severe sociomedical issue and individuals suffering from it are at a high suicidal risk. The patients suffering from clinical depression are being treated by conventional antidepressant therapy; however, only around 70 % of the patients are responding to this conventional antidepressant treatment. Hence, for treatment of the remaining 30 % patients (who are not responding to the antidepressant therapy), it is mandatory to identify/ discover alternative and safe methods of therapy (Dziedzic *et al*., 2024). Similarly, several other psychiatric disorders are also not cured effectively by the current traditional drugs and even some patients are completely resistant to the traditional therapeutic agents. Current research studies and various clinical trials revealed that psychobiotics (probiotics or prebiotics or both) when administered orally, serve as an alternative and effective agents for the treatment of the various psychiatric disorders. The objectives of this study are to make an emphasis on the concept of psychobiotics, their modes of action, and significant therapeutic uses of psychobitocs (*i.e*., probiotics and prebiotics) in counteracting the manifestations of the mental disorders.

Microbiota-gut-brain axis

The two-way communication between the central nervous system and the gut microbiota constitutes the Microbiota-gut-brain axis. The gut microbiota includes the various microorganisms residing in the gut and their genomes. The microbiota-gut-brain axis is a network through which both gut microbiome and brain jointly regulate the health. The microbiota-gut-brain axis is a system consisting of enteric nervous system, central nervous system, and endocrine system, including immunological, neuro-related, and metabolic regulatory compounds. Though the brain and gut are located at different regions in the human body, there are several theories that proposed various pathways by which the gut microorganisms coordinate with the central nervous system. The gut microorganisms produce or induce the secretion of certain neurotransmitters such as serotonin, gamma-aminobutyric acid, and dopamine (Magalhaes-Guedes, 2022).

The enteric nervous system is equipped with millions of nerve cells, which are located in the mucosa of gut, and regulate the various functions of the gut region. The direct interaction between intestinal tract and central nervous system occurs through a vagus nerve (De Lartigue *et al*., 2011). The vague nerve originates from the brain stem, and stimulates the gut region and enteric nervous system. The entire gut region is stimulated by a vague nerve that includes 80 % afferent and 20 % efferent fibers. The afferent fiber terminals of a vague nerve respond to the inflammatory chemicals, dietary ingredients, metabolic products released by bacteria (beneficial/ probiotic) and gastrointestinal regulatory peptides, and transfer signals to the brain. (Waise *et al*., 2018).

The non-clinical studies conducted on human beings revealed that gut microorganisms regulate public behavior, anxious behavior, and bodily performance (Oroojzadeh *et al*., 2022). The human gut microflora plays a key role in maintenance of health. The decreased *Lactobacillus* and *Bifidobacterium* population in the gut region results in major depressive disorder (depression). In the gut region of patients suffering from Alzheimer's disease, the *Bifidobacterium* species number is very low. In autism patients, a lower bacterial biodiversity has been reported. Disturbance in the gut microflora may lead to the occurrence of attention deficit hyperactivity disorder (Cheng *et al*., 2019).

Probiotics, prebiotics and psychobiotics

Probiotics: Probiotics are defined as microorganisms that when consumed in enough quantities improve health conditions of the host (Reid *et al*., 2019). The term, probiotics was first used by Lilly and Stilwell (1965), which means "for life" in Greek. Probiotics are regarded as functional foods, resembling traditional foods, but exhibit physiological functions, increase nutritional quality, and regulate gut health (Ailioaie and Litscher, 2021).

Prebiotics: The prebiotic is an ingredient associated with our dietary components that is not utilized (digested) by the human body, and is resistant to the action of gastric and enteric enzymes. Prebiotics are selectively used by certain gut bacteria that ferment them to produce various metabolites, which in turn improve the human health. Thus, prebiotics enhance growth of the beneficial bacteria that maintain the overall health of the host (You *et al*., 2022).

Psychobiotics: The concept of psychobiotics was first used in 2012, and were described as microorganisms

that when consumed in enough quantity, confer relief to the individuals suffering from the psychological disorders. The psychobiotics include probiotics and prebiotics that can enhance the mirobiota-gut-brain axis signals and improve neurological related actions such as behavior, thinking and reasoning, and nervousness (Evernel *et al.*, 2019). In the gut, psychobiotics express antidepressant and anxiolytic effects through the gut-brain axis. Thus, they exert positive influence on the cognitive health and the emotional behavior (Oroojzadeh *et al.* 2022). Furthermore, psychobiotics can be defined as beneficial bacteria (probiotics) or ingredients (prebiotics) that support such beneficial bacteria, which enhance the gut bacteria and brain coordination (Sarkar *et al.*, 2016). Moreover, the psychobiotics can be considered as future probiotics for the central nervous system, and could be regarded also as unique class of probiotics that exert positive influence on functions of the nervous system and may be employed for treatment of the various psychological disorders (Kwak *et al.*, 2023).

Mechanisms of action of psychobiotics

The mechanisms of action of psychobiotics basically involve three modes, mainly (i) influencing the hypothalamic-pituitary-adrenal axis stress response and lowering systemic inflammation, (ii) exerting direct influence on the immune system, and (iii) releasing of neurologically active molecules such as proteins, short chain fatty acids, and neurotransmitters (Table 1 and Figure 1) (Kimse *et al.*, 2024).

Psychobiotics in the gut region produce extracellular vesicles that contain the cellular components of the bacteria. The blood absorbs these extracellular vesicles from the gut and through blood circulation, they reach the brain. Thus, the extracellular vesicles release various neurologically active molecules and influence the functions of the central nervous system (Bleibel *et al.*, 2023).

Potential psychobiotic microbial strains

Some of the potent bacterial strains that can be developed and used as psychobiotics include:

Lactobacillus helveticus: *Lactobacillus helveticus* is a Gram-positive bacillus that produces lactic acid. It is usually used as starter culture during milk fermentation for the production of cheese. It possesses usual probiotic features such as surviving in gut, attaching to epithelial cells, and controlling intestinal pathogens. Above all, it can be employed for the treatment of stress induced visceral complications (Ait-Belgnaoui *et al.*, 2018).

Escherichia coli: The *Escherichia coli* is a Gram-negative, rod-shaped bacterium living in the gut region. Till date, extensive researches have been conducted on the probiotic characteristics of *E. coli.* Several experimental studies revealed that *E. coli* can be used for treatment of several psychological issues, especially stress (Beimfohr, 2016).

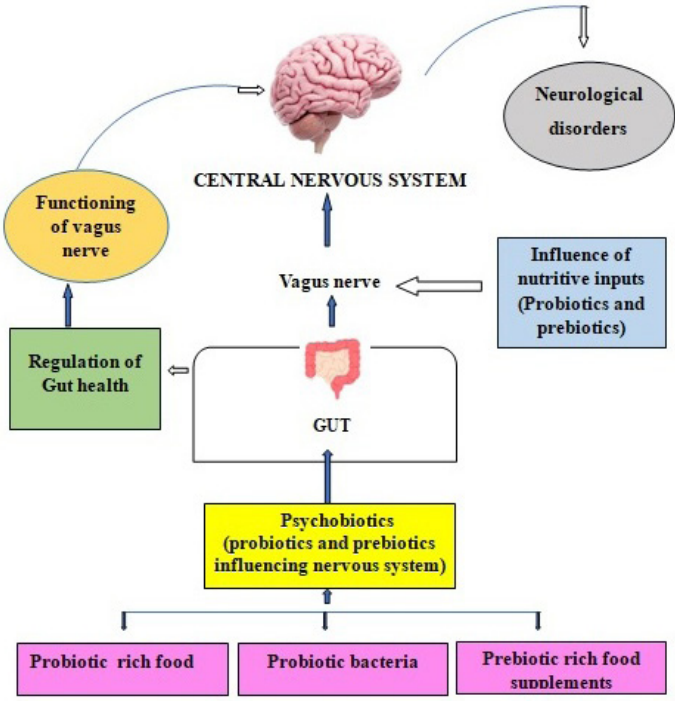

Figure 1: *Influence of psychobiotics on the gut and the central nervous system depicted by Del Toro-Barbosa et al. (2020).*

Table 1: *List of neurologically active substances produced by psychobiotics in the gut region.*

Psychobiotics in the gut region	Neurological metabolites released	References
Lactobacillus plantarum	Acetyl choline	(Chen *et al.*, 2021)
Enterococcus faecium BS5	Gamma amino butyric acid	(Bs *et al.*, 2021)
Bifidobacterium infantis	Tryptophan and serotonin precursor	(Desbonnet *et al.*, 2008)
Escherichia coli	Norepinephrine, serotnin, and dopamine	(Chen *et al.*, 2021)
Bacillus amyloliquifaciens SB-9	5-hydroxy tryptophan, Melatonin, and serotonin	(Jiao *et al.*, 2016)

Bifidobacterium longum: *Bifidobacterium longum* is a Gram-positive, rod shaped bacterium occurring in the intestine of humans. The *Bifidobacterium* species are known for their potent probiotic effects. *Bifidobacterium* species are used for treatment of stress induced visceral problems *via* modulating the nervous functions and optimizing the hypothalamic-pituitary-adrenal axis activities. The human clinical studies revealed that *Bifidobacterium* species, solely or combined with other probiotic bacterial strains, have cured and/ or prevented various complications (Ait-Belgnaoui *et al*., 2018).

Bifidobacterium infantis: *Bifidobacterium infantis* is a symbiotic bacterium existing in the human gut. It has a unique ability of selectively utilizing the oligosaccharides present in the human milk. Hence, researchers assumed that *B. infantis* can be specifically used for health benefits of premature infants (Batta *et al*., 2023).

Clostridium butyricum: The *Clostridium butyricum* is a Gram-positive, rod shaped, strictly anaerobic, and endospore forming bacterium. It produces butyric acid and lives in the gut region of humans and animals. *C. butyricum* is a bacterium with potent probiotic properties, which can be used for treatment of gastrointestinal infections. It exerts positive effects by secreting several metabolites such as short chain fatty acids, propionic acid, acetic and butyric acids (Seki *et al*., 2003).

Lactobacillus rhamnosus: *Lactobacillus rhamnosus* is a Gram-positive, rod shaped, and facultative anaerobe. It is heterofermentative lactic acid bacterium. Several studies proved *L. rhamnosus* as a potent probiotic bacterial species due to its unique growth features, mainly resistance to acids and bile juice, and adequate adhering ability to the epithelial layer of the intestine. It is the most widely employed probiotic bacterial species, and is currently available in the markets as a commercial probiotic product (Segers and Lebeer, 2014).

Lactobacillus plantarum: The *L. plantarum* is a Gram-positive, rod shaped, and aerotolerant bacterium. It widely exists in meat and meat products, milk and milk products, and fermented products. It lives in the gastro-intestinal tract of human beings and confers several health benefits (De Vries *et al*., 2006). The following Table 2 presents some of bacterial species that experimentally act as effective psychobiotics.

Table 2: *Psychobiotic bacterial strains used in clinical trials and proved to be effective in the treatment of psychiatric disorder***s** *(Cichonska et al., 2023).*

Psychobiotic bacterial Strains	Clinical trial/experiment model	Beneficial effects observed
Lactiplantibacillus plantarum C29	Human volunteers with slight cognitive disorder	Improvement of cognitive behavior
Lactiplantibacillus plantarum DR7	Humans suffering from stress	Improvement of cognitive functions and memory and increased serotonin production
Lactibplantibacillus plantarum P8	Stressed humans	Reduction of anxiety symptoms and improvement of memory and cognitive behavior
Lactobacillus helveticus NS8	Rats with chronic stress	Reduced symptoms of anxiety and depression and improvement of cognitive functions
Lacticaseibacillus rhamnosus JB-1	Mice	Reduction of corticosterone associated with stress and improvement of anxiety and symptoms
Lacticaseibacillus rhamnosus GG	Older and middle aged adult volunteers	Improvement of cognitive abilities
Lactobacillus gasseri CP2305	Younger adults induced with chronic stress	Reduction of anxiety and sleeplessness.
Bifidobacterium breve A1	Patients suffering from Schizophrenia	Improvement of anxiety and depression symptoms
Bifidobacterium bifidum ATCCVR 29521	Wistar rats	Reduction of dead cell number and enhanced release of acetylcholine in the brain of rats suffering from Alzheimer's disease
Bacillus coagulans MTCC 5856	Patients suffering from major depressive disorder and intestinal bowel syndrome	Reduced symptoms of depression and intestinal bowel syndrome

Therapeutic applications of psychobiotics

Alzheimer's disease: The Alzheimer's disease (AD) is linked to various factors like increase of age, genetics, head damage, vascular complications, microbial infections, and environmental pollutants. Up to date, the exact causes for the Alzheimer's disease are not known. Various theories have been proposed for the cause of Alzheimer's disease, out of which two have been considered. The first one is abnormality in cholinergic activity, while the other is variation in amyloid beta protein secretion. However, no hypothesis is accepted for the cause of Alzheimer's disease (Breijyeh and Karamn, 2020). In the Alzheimer's patients, accumulation of neurofibrillary tangles and amyloid plaques is observed with interrupted functioning of cholinergic nerves in the base portion of forebrain. These patients suffer from memory issues and cognitive disorders (Kumar *et al*., 2015). The treatment of Alzheimer's disease aims to enhance the acetylcholine concentration and control the degeneration of cholinergic nerve cells in the brain region. Research studies reported that the malfunctioning of mitochondrion with increased age, leads to a low cellular energy production and increase of reactive oxygen species (ROS). High concentrations of ROS may cause damage to the cellular macromolecules, which can be linked to the Alzheimer's disease (Mufson *et al*., 2008).

A previous studys conducted on amyloid beta induced AD mice model by Kobayashi *et al*. (2017) revealed that the cognitive abnormalities can be treated by employing a probiotic bacterial strain, named *B. breve* strain A1. Upon administration of *B. breve* strain A1into AD mice, there was a decreased state of the altered behavior in the treated mice. The mode of action of this probiotic strain was assumed to be control of the amyloid beta induced immune response and neuroinflammation (Kobayashi *et al*., 2017). The mixture of probiotic lactic acid bacteria and Bifidobacteria prevented the damage of brain and amyloid beta aggregations in AD mice during the initial stages of the disease (Bonfili *et al*., 2017). When a mixture of probiotic *B. longum, L. acidophilu, B. lactis,* and *L. ferment* was administered into the mice injected with amyloid beta1-42 (intra hippocampal), an improvement of the clinical features was observed, including place memory, stress due to oxidation, and learning deficiencies. Various previous studies conducted by Zhang *et al*. (2017), Nagpal *et al*. (2019), Yue *et al*. (2021) on animal models reported that probiotics can be used for the treatment/prevention of Alzheimer's disease. Although studies on human beings are ongoing, but still much evidence is required to prove the role of probiotics in combating the Alzheimer's disease.

Parkinson's disease

The Parkinson's disease is a neurological (neurodegenerative) complication occurs when the brain is devoid of dopamine. Dopamine acts as a neurotransmitter and regulates various functions such as memory, cognitive abilities, movement, sleep, and other functions. The dopamine deficiency in the brain of Parkinson's disease patients is responsible for motor deficiency and may be the cause of cognitive disabilities (Emamzadeh and Surguchov, 2018). Zhu *et al*. (2012) reported that during the catecholamine synthesis in the brain, the enzyme, tyrosine hydroxylase catalyzes the rate-limiting reaction step in catecholamine biosynthetic pathway. Decreased synthesis of tyrosine hydroxylase results in the low production of dopamine and thus leads to Parkinson's disease.

Based on their *in vitro* and *in vivo* experiments on Parkinson's disease patients, Castelli *et al*. (2020) reported that upon consumption of SLAB51 (*i.e*., a nine probiotic living bacteria formulation, which contains *Streptococcus thermophilus, B. longum, B. breve, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii* subsp. *bulgaricus* and *L. brevis*) an enhanced tyrosine hydroxylase immune reactivity and protected dopaminergic neurons in the brain region (mainly, striatum and substantia nigra) was observed. Clinical studies conducted by Tamtaji *et al*. (2019) reported that administration of a probiotic mixture of *L. reuteri, L. acidophilus, B. bifidum,* and *L. fermentum* into patients suffering from Parkinson's disease resulted in an improvement of the patient's condition. Numerous probiotic bacteria release tyrosine decarboxylase in the gastrointestinal tract that synthesizes dopamine from levodopa. In the intestine of Parkinson's disease patients, the concentration of levodopa becomes decreased when the patients are administered with probiotics (Van Kessel *et al*., 2019). Perez *et al*., (2015) reported that tyrosine decarboxylase gene was identified in many bacterial strains, more particularly in the species of *Enterococcus* and *Lactobacillus.*

Depression

The major depressive disorder (MDD) is a serious

mental disorder, its symptoms include sleeplessness, anhedonia, fatigue, suicidal tendency, guilty feeling, loss of appetite, and depressed mood (Ferrari *et al.*, 2013). Depression ranks fourth among the global human health disorders. According to the World Health Organization (WHO), globally around 35,00,000 people are affected by depression and more than 8,00,000 are committing suicide annually. It is estimated that by 2030, the depression stands as first human health issue in the world. The pandemic situation due to COVID-19 has greatly increased the number of depression cases, where 27.6 % more cases have been reported compared to pre-pandemic conditions (Salari *et al.*, 2020). Various antidepressant drugs are used to cure depression, including mirtazapine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, non-selective serotonin and norepinephrine reuptake inhibitors, selective norepinephrine reuptake inhibitors, and other agents (Cryan and Dinan, 2015). The current drugs are ineffective on about 30 % of the MDD patients. Thus, new antidepressants and novel approaches are urgently needed (Miyanishi and Nitta, 2021). The recent studies reported by Bibbo *et al.* (2022); Radjabzadeh *et al.* (2022); Kumar *et al.* (2023) on the use of microbiota have presented a key connection between depression and gut microflora. Miyoka *et al.* (2018) reported that combination of traditional antidepressant drugs and probiotics proved to be effective for the treatment of patients who were resistant to conventional drugs. Various preclinical studies and clinical trials revealed that altering the gut microflora by administration of probiotic bacteria has proved to be effective in the treatment of depression and other health issues of humans (Gao *et al.*, 2023).

The psychobiotics enhance absorption of nutrients, production of short chain fatty acids and gamma-aminobutyric acid (GABA), anti-oxidant properties, and counteract the cognitive disorders (Nosrani *et al.*, 2021). All these activities/ products are associated, either directly or indirectly, with the control/ treatment of depression. Various probiotic bacterial strains (single strain/ mixture/ formulations) and fermented foods (*i.e.*, rich with probiotics) have been tested for their effectiveness on treatment of depression (*i.e.*, anti-depressive properties). In many previous studies, *Bifidobacterium* and *Lactobacillus* strains have been widely used (Gao *et al.*, 2023; Merkouris *et al.*, 2024; Rahmannia *et al.*, 2024). In a recent study, a Gram negative bacterium; *Akkermansia mucinipila*, has displayed psychobiotic properties when used on a rodent model (Ding *et al.*, 2021).

Anxiety disorders

The disorders associated with anxiety are quite common among humans (Thibaut, 2017). The most widely observed anxiety disorder is specific phobia, where the rate of prevalence is 12.1 % in a year, while the agoraphobia is the anxiety disorder with the least prevalence rate of 2.5 in a year. The females are more susceptible to anxiety compared to males; the anxiety ratio in males and females is approximately 1:2 (Remes *et al.*, 2018). In the central nervous system, the key compounds that mediate the anxiety are assumed to be serotonin, gamma-aminobutyric acid (GABA), dopamine, and norepinephrine. A previous study revealed that autonomic nervous system; specifically sympathetic nervous system, is associated with the major anxiety symptoms (Martin *et al.*, 2009).

In a previous study, Steenbergen *et al.* (2015) applied *L. lactis* W19, *L. brevis* W63, *B. bifidum* W23, *L. casei* W56, *B. lactis* W52, *L. salivarius* W24, and *L. lactis* W58 on twenty volunteers suffering from anxiety disorders for a period of four weeks. Interestingly, the obtained results showed that the participants displayed reduced sad mood associated with negative thoughts. It was assumed that the bacteria might have shown impact on serotonin. Luang-In *et al.* (2020) administered 6 probiotic bacterial strains (*i.e. B. adolescentis* TBRC 7154, *Pediococcus pentosaceus* WS11, *L. lactis* subsp. *lactis* TBRC 375, *B. adolescentis* TBRC 7154, *L. plantarum* SK321, and *L. fermentum* SK324); isolated from Thai fermented foods, on male Wistar mice for two weeks to study the effect of probiotic bacteria on the behavior of these mice. The trials results revealed that the treated mice had shown significantly decreased symptoms of anxiety. Moreover, Lee *et al.* (2021) tested the psychobiotic effect of *B. adolescentis* NK98 and *L. reuteri* NK33 (*i.e.*, probiotic NVP-1704) on reducing the sleeplessness, stress, anxiety, and depression in healthy adults exhibiting sub-clinical symptoms. Results revealed that the probiotic NVP-1704 was effective in treatment of psychiatric disorders and insomnia.

Autism disorders

The autism spectrum disorders are serious neurological complications which occur in neonates and young children (Li and Zhou, 2016), and are manifested by abnormal social behavior. A previous

report issued by the Global Burden of Diseases, Injuries, and Risk Factors (2016) revealed that 62.2 million children worldwide were affected by autism spectrum disorders. Various health issues such as depression, epilepsy, Tourette syndrome and anxiety, and gut related issues are also associated with autism spectrum disorders (Feng *et al*., 2023). Furthermore, the prevalence of these disorders may increase in due course, thus further studies on treatment of autism are required (Vos *et al*., 2023). Various factors are responsible for autism spectrum disorders including genetic and environment-related factors. Several recent studies provided enough evidence that the gut microorganism's imbalance may induce the development of autism spectrum disorder symptoms, proving that gut bran-axis link is invalid (Ahmed *et al*., 2020). In the gut region of children suffering from autism spectrum with constipation, several deleterious pathogenic bacteria such as *E. coli, Shigella* spp., and *Clostridium* spp. have been detected in relatively high numbers (Straiti *et al*., 2017). In a recent study, the toxin producing *C. histolyticum* has been isolated from the fecal matter of autism children (Feng *et al*., 2023). In the urine of autism children, high levels of *p*-cresol and *p*-cresyl sulphate have been reported, where *Clostridium* spp. and *Pseudomonas stutzeri* are assumed to be the cause (Altieri *et al*., 2011).

Various clinical studies reported that psychobiotics (*i.e*., probiotics and prebiotics) can reduce the clinical features of autism and maintain the gut microbe balance (Shaaban *et al*., 2018; Meguid *et al*., 2022). Experiments on mice revealed that there is a considerable improvement in the emotional and social behavior in those mice upon administration of probiotics (Sunand *et al*., 2020). The prebiotic compounds occurring in wheat fiber control the harmful bacteria (*i.e., Clostridium* spp.) and enhance the growth of beneficial bacteria (*i.e. Bifidobacterium* spp.) (Lefranc-Millot *et al*., 2012). Muhammad *et al*. (2022) reported that probiotics (*i.e*., beneficial bacteria) in the gut region produce neurologically active compounds. *L. brevis* and *B. denticola* synthesize gamma-aminobutyric acid, while *E. coli* and *Staphylococcus aureus* produce dopamine. Recently, many researchers/clinicians use De Simone Formulation (DSF) supplement made up of 8 probiotic bacterial strains, mainly *B. longum, L. paracasei, L. acidophilus, B. breve, L. delbrueckii* subsp. *bulgaricus, L. plantarum, B. infantis,* and *Streptococcus thermophiles* for clinical treatment of autism children. This DSF formulation must be administered orally to the autism children for a period of six months (Santocchi *et al*., 2020).

Psychobiotic rich foods

Several previous studies conducted by Porras-Garcia *et al*. (2023); Shah *et al*. (2023); Balasubramanian *et al*. (2024) on human beings revealed that the intake of natural fermented foods, foods fermented by starter cultures/ individual microorganisms, and certain plant products reduced the manifestations of psychiatric disorders and cognitive issues. Kim and Shin (2019) study reported that in women, there were no noticeable effects of probiotic-rich food on the depression symptoms. On the other hand, in men, the clinical symptoms of depression have been reduced by the probiotic-diet. Oshawa *et al*. (2017) conducted a controlled, randomized, and double blind study on the middle aged adult healthy volunteers, who consumed 190 grams of milk fermented by *L. helveticus* every day for a period of eight weeks. In these volunteers, there were improvements in the cognitive behavior and memory. Many other studies also revealed that consumption of foods rich with psychobiotics (*i.e*., probiotics/prebiotics) has improved the complications associated with the neurological disorders (Karbownik *et al*., 2022; Dahiya and Nigam, 2022; Freijy *et al*., 2023). Table 3 demonstrates some of the foods rich with psychobiotics.

Table 3: *Foods containing psychobiotics (Cichonska et al., 2023).*

Psychobiotic food	**Psychobiotic microbial strain(s) associated**
Cheese and yoghurt	*L. plantarum* 299v
Ice cream	*L. plantarum* ATCC 8014
Skimmed milk with milk protein concentrate	*Bacillus coagulans* MTCC5856
Milk based dessert sauce	*L. casei* Shirota
Apple and watermelon juice	*L. plantarum* ATCC 8014
Whole soy beans	*L. plantarum* P8
Coconut milk and tomato juice	*L. reuteri* DSM 17938

Conclusions and Recommendations

The psychobiotics include both probiotics and prebiotics which when administered orally improve the microbiota-gut-brain axis interaction and counteract the neurological disorders. Various clinical trials and research studies have confirmed that the

administration of psychobiotics (*i.e.*, prebiotics and probiotics) can effectively prevent or treat the psychological disorders. Further, the foods, especially the fermented foods/ dairy foods containing probiotics/prebiotics, can improve the mental health when consumed regularly. In many studies, it has been revealed that patients who consume foods rich in psychobiotics exhibit reduced symptoms of psychiatric disorders compared to those who consume food devoid of psychobiotics. The administration of psychobiotics as therapeutic agents is still under study. Currently, researchers are using psychobiotics in combination with traditional drugs to treat those patients suffering from various psychiatric disorders. To improve the reliability of the current findings, it is recommended that future research studies must consider more rigorous and high standard approaches such as enhanced randomization and blinding methods. Furthermore, it is proposed these future researches should investigate the variety of treatment strategies to comprehend how the different psychobiotic strains and their combinations can enhance the therapeutic outcomes for the different ailments. In the future, psychobiotic formulations may become the sole potent drugs for treating the various neurological disorders.

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Novelty Statement

The current review provides a comprehensive analysis of the emerging field of psychobiotics, highlighting their potential as novel therapeutic agents for psychiatric disorders by modulating the gut-brain axis. Additionally, the review consolidates the latest research and clinical trials on psychobiotics, offering insights into their efficacy in treating various psychiatric conditions, including depression, anxiety and related complications.

Author's Contribution

Praveen Reddy P: Conceptualization and formal analysis.
Praveen Reddy P, K. Sandhya and Aparna Srikantam: Investigation.
Praveen Reddy P. and K. Sandhya: Data curation and writing original drafts.
Praveen Reddy P and Aparna Srikantam: Reviewing, editing the manuscript and scientific corrections.

Conflict of interests
The authors have declared no conflict of interests.

References

Ahmed, S.A.S., Elhefnawy, A.M., Azouz, H.G., Roshdy Y.S., Ashry, M.H., Ibrahim A.E., Ibrahim A.E. and Mehessein, M.A., 2020. Study of the gut microbiome profile in children with autism spectrum disorder: A single teretiary hospital experience. J. Mol. Neurosci., 70(6): 887-896. https://doi.org/10.1007/s12031-020-01500-3

Ailioaie, L.M. and Litscher, G., 2021. Probiotics, photobiomodulation, and disease management: Controversies and challenges. Int. J. Mol. Sci., 22(9): 4942. https://doi.org/10.3390/ijms22094942

Ait-Belgnaoui, A., Payard, I., Rolland, C., Harkat, V., Braniste, V., Theodorou, V. and Tompkins, T.A., 2018. *Bifidobacterium longum* and *Lactobacillus helveticus* synergistically suppress stress-related visceral hypersensitivity through hypothalamic-pituitary-adrenal axis modulation. J. Neurogastroenterol. Motil., 24(1): 138-146. https://doi.org/10.5056/jnm16167

Altieri, L., Neri, C., Sacco, R., Curatolo, P., Benvnuto, A., Muratori, F., Santocchi, E., Bravaccio, C., Lenti, C., Saccani, M., Rigerdetto, R., Gandione, M., Urbani, A. and Persico, A.M., 2011. Urinary p-cresol is elevated in small children with severe autism spectrum disorder. Biomarkers, 16(3): 252-260. https://doi.org/10.3109/1354750X.2010.548010

Balasubramanian, R., Schneider, E., Gunnigle, E., Cotter, P.D. and Cryan, J.F., 2024. Fermented foods: Harnessing their potential to modulate the microbiota-gut-brain axis for mental health. Neurosci. Biohehav. Rev., 158: 105562. https://doi.org/10.1016/j.neubiorev.2024.105562

Batta, V.K., Rao, S.C. and Patole, S.K., 2023. *Bifidobacterium infantis* as a probiotic in preterm

infants: A systemic review and meta-analysis. Pediat. Res., 94(6): 1887-1905. https://doi.org/10.1038/s41390-023-02716-w

Beimfohr, C., 2016. A review of research conducted with probiotic *E. coli* marketed as symbioflor. Int. J. Bacteriol., 2016: 3535621. https://doi.org/10.1155/2016/3535621

Bibbo, S., Fusco, S., Ianiro, G., Settanni, C.R., Ferrarese, D., Grassi, C., Cammarota, G. and Gasbarrini, A., 2022. Gut microbiota in anxiety and depression: Pathogenesis and therapeutics. Front. Gastroenterol., 1: 1019578.

Bleibel, L., Dziomba, S., Waleron, K.F., Kowalczyk, E. and Karbownik, M.S., 2023. Deciphering psychobiotics mechanism of action: Bacterial extracellular vesicles in the spotlight. Front. Microbiol., 14: 1211447. https://doi.org/10.3389/fmicb.2023.1211447

Bonfili, L., Cecarnini, V., Berardi, S., Scarpona, S., Suchodolski, J.S., Nasuti, C., Fiorini, D., Boarelli, M.C., Rossi, G. and Eleuteri, A.M., 2017. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. Sci. Rep., 7(1): 2426. https://doi.org/10.1038/s41598-017-02587-2

Breijyeh, Z. and Karamn, R., 2020. Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules, 25(24): 5789. https://doi.org/10.3390/molecules25245789

Bs, S., Thankappan, B., Mahendran, R., Muthusamy, G., Femil Selta, D.R. and Angayarkanni, J., 2021. Evaluation of GABA production and probiotic activities of *Enteric faecium* BS5. Probiot. Antimicrob. Prot., 13(4): 993-1004. https://doi.org/10.1007/s12602-021-09759-7

Castelli, V., Angelo, M., Lombardi, F., Alfonsetti, M., Antonosante, A., Cantanesi, M., Beneditti, E., Palumbo, P., Cifone, M.G., Giordana, A., Desideri, G. and Cimini, A., 2020. Effects of the probiotic formulation SLAB51 *in vitro* and *in vivo* Parkinson's disease models. Aging (Albany NY), 12(5): 4641-4659. https://doi.org/10.18632/aging.102927

Chen, Y., Xu, J. and Chen, Y., 2021. Regulation of neurotransmitters by the gut microbiota and effects on cognition in neurological disorders. Nutrients, 13(6): 2099. https://doi.org/10.3390/nu13062099

Cheng, L.H., Liu, Y.W., Wu, C.C., Wang, S. and Tsai, Y.C., 2019. Psychobiotics in mental health, neurodegenerative and neurodevelopmental disorders. J. Food Drug Anal., 27(3): 632-648. https://doi.org/10.1016/j.jfda.2019.01.002

Cichonska, P., Kowalska, E. and Ziarno, M., 2023. The survival of psychobiotics in fermenented food and the gastrointestinal tract: A r https://doi.org/10.3390/microorganisms11040996 eview. Microorganisms, 11(4): 996.

Cryan, J.F. and Dinan, T.G., 2015. More than a gut feeling: The microbiota regulates neurodevelopment and behaviour. Neuropsychopharmacology, 40(1): 241-242. https://doi.org/10.1038/npp.2014.224

Dahiya, D. and Nigam, P.S., 2022. Probiotics, prebiotics, synbiotics, and fermented foods as potential biotics in nutrition improving health via microbiome-gut-brain axis. Fermentation, 8(7): 303. https://doi.org/10.3390/fermentation8070303

De Lartigue, G., de La Sarre, C.B. and Raybould, H.E., 2011. Vagal afferent neurons in high fat diet-induced obesity; intestinal microflora, gut inflammation and cholecystokinin. Physiol. Behav., 105(1): 100-105. https://doi.org/10.1016/j.physbeh.2011.02.040

De Vries, M.C., Vaughan, E.E., Kleerebezem, M. and de Vos, W.M., 2006. *Lactobacillus plantarum*-survival, functional and potential probiotic properties in the human intestinal tract. Int. Dairy J., 16(9): 1018-1028. https://doi.org/10.1016/j.idairyj.2005.09.003

Del Toro-Barbosa, M., Hurtado-Romero, A., Garcia-Amezquita, L.E. and Garcia-Cayuela, T., 2020. Psychobiotics: Mechanisms of action, evaluation methods and effectiveness in applications with food products. Nutrients, 12(12): 3896. https://doi.org/10.3390/nu12123896

Desbonnet, L., Garrett, L., Clarke, G., Bienenstock, J. and Dinan, T.G., 2008. The probiotic *Bifidobacteria infantis*: An assessment of potential antidepressant properties in the rat. J. Psych. Res., 43(2): 164-174. https://doi.org/10.1016/j.jpsychires.2008.03.009

Ding, Y., Bu, F., Chen, T., Shi, G., Yuan, X., Feng, Z., Duan, Z., Wang, R., Zhang, S., Wang, Q., Zhou, J. and Chen, Y., 2021. A next-generation probiotic: *Akkermansia muciniphila* ameliorates chronic stress-induced depressive-like behavior in mice by regulating gut microbiota and metabolites. Appl. Microbiol.

Biotechnol., 105(21-22): 8411-8426. https://doi.org/10.1007/s00253-021-11622-2

Dziedzic, A., Maciak, K., Blizniewska-Kowalska, K., Gatecka, M., Kobierecka, W. and Saluk, J., 2024. The power of psychobionts in depression: A modern approach through the Microbiota-Gut-Brain Axis: A literature review. Nutrients, 16: 1054. https://doi.org/10.3390/nu16071054

Emamzadeh, F.N. and Surguchov, A., 2018. Parkinson's disease: Biomarkers, treatment and risk factors. Front. Neurosci., 12: 612. https://doi.org/10.3389/fnins.2018.00612

Evernel, A., Unsalver, B.O. and Ceylan, M.E., 2019. Psychobiotics. Adv. Exp. Med. Biol., 1192: 565-581. https://doi.org/10.1007/978-981-32-9721-0_28

Feng, P., Zhao, S., Zhang, Y. and Li, E., 2023. A review of probiotics in the treatment of autism spectrum disorders: Perspectives from the gut-brain axis. Front. Microbiol., 14: 1123462. https://doi.org/10.3389/fmicb.2023.1123462

Ferrari, A.J., Charlson, F.J., Norman, R.E., Pattern, S.B., Freedman, G., Murray, C.J., Vos T. and Whiteford, H.A., 2013. Burden of depressive disorders by country, sex, age and year: Findings from the global burden of disease study 2010. PLoS Med., 10(11): e1001547. https://doi.org/10.1371/journal.pmed.1001547

Freijy, T.M., Cribb, L., Oliver, G., Metri, N.J., Opie, R.S., Jacka, F.N., Hawrelak, J., Rucklidge, J.J., Ng, C.H. and Sarris, J., 2023. Effects of a high-prebiotic diet versus probiotic supplements versus synbiotics on adult mental health: The "Gut Feeling" randomized controlled trial. Front. Neurosci., 16: 1097278. https://doi.org/10.3389/fgstr.2022.1019578

Gao, J., Zhao, L., Cheng, Y., Lei, W., Wang, Y., Liu, X., Zheng, N., Shao, L., Chen, X., Sun, Y., Ling, Z. and Xu, W., 2023. Probiotics for the treatment of depression and its comorbidities: A systemic review. Front. Cell. Infect. Microbiol., 13: 1167116. https://doi.org/10.3389/fcimb.2023.1167116

Jiao, J., Ma, Y., Liu, C., Song, Y., Qin, Y., Yuan, C., and Liu, Y., 2016. Melatonin-producing endophytic bacteria from grapevine roots promote the abiotic stress-induced production of endogenous melatonin in their hosts. Front. Plant Sci., 7: 1387. https://doi.org/10.3389/fpls.2016.01387

Karbownik, M.S., Mokros, L., Dobielska, M., Kowalczyk, M. and Kowalczyk, K., 2022. Association between consumption of fermented food and food-derived prebiotics with cognitive performance, depressive, and anxiety symptoms in psychiatrically healthy medical students under psychological stress: A prospective cohort study. Front. Nutr., 9: 850249. https://doi.org/10.3389/fnut.2022.850249

Kim, C.S. and Shin, D.M., 2019. Probiotic food consumption is associated with lower severity and prevalence of depression: A nationwide cross-sectional study. Nutrition, 63-64: 169-174. https://doi.org/10.1016/j.nut.2019.02.007

Kimse, L., Reinis, A., Mikelsone-Jansone, L., Gintere, S. and Kruminina, A., 2024. A narrative review of psychobiotics: Probiotics that influence the gut-brain axis. Medicina, 60: 601. https://doi.org/10.3390/medicina60040601

Kobayashi, Y., Sugahara, H., Shimada, K., Mitsuyama, E., Kuhara, T., Yasuoka, A., Kondo, T., Abe, K. and Xiao, J.Z., 2017. Therapeutic potential of Biofidobacterium breve strain A1 for preventing cognitive impairment in Alzheimers disease. Sci. Rep., 7(1): 13510. https://doi.org/10.1038/s41598-017-13368-2

Kumar, A., Pramanik, J., Goyal, N., Chauhan, D., Sivamaruthi, B.S., Prajapati, B.G., Prajapati, B.G. and Chaiyasut, C., 2023. Gut microbiota in anxiety and depression: Unveiling the relationships and management options. Pharmaceuticals (Basel). 16(4): 565. https://doi.org/10.3390/ph16040565

Kumar, A., Singh, A. and Ekavali. 2015. A review on Alzheimer's disease pathophysiology and its management: An update. Pharmacol. Rep., 67(2): 195-203. https://doi.org/10.1016/j.pharep.2014.09.004

Kwak, M.J., Kim, S.H., Tanpure, R., Kim, J.I., Jeon, B.H., and Park, H.K., 2023. Psychobiotics and fecal microbial transplantation for autism and attention deficit/hyperactivity disorder: Microbiome modulation and therapeutic mechanisms. Front. Cell. Infect. Microbiol., 13: 1238005. https://doi.org/10.3389/fcimb.2023.1238005

Lee, H.J., Hong, J.K., Kim, J.K., Kim, D.H., Jand, S.K., Han, S.W., Han, S.W. and Yoon, I.Y., 2021. Effects of probiotic nvp-1704 on mental health and sleep in healthy adults: an 8-week randomized, double-blind, pacebocontrolled trial. Nutrients, 13(8): 2660. https://doi.

org/10.3390/nu13082660

Lefranc-Millot, C., Guerin-Deremaux, C., Wils, D., Neut, C., Miller, L.E. and Saniez-Degrave, M.H., 2012. Impact of a resistant dextrin on intestinal ecology: How altering the digestive ecosystem with nutriose, a soluble fibre with prebiotic properties, may be beneficial for health. J. Int. Med. Res., 40(1): 211-224. https://doi.org/10.1177/147323001204000122

Li, Q. and Zhou, J.M., 2016. The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder. Neuroscience, 32: 131-139. https://doi.org/10.1016/j.neuroscience.2016.03.013

Lilly, D.M. and Stillwell, R.H., 1965. Probiotics: Growth-promoting factors produced by microorganisms. Science, 147(3659): 747-748. https://doi.org/10.1126/science.147.3659.747

Luang-In, V., Katisart, T., Konsue, A., Nudmamud-Thanoi, S., Narbad, A., Saengha, W., Wangkahart, E., Pumriw, S., Samapitto, S. and Ma, M.L., 2020. Psychobiotic effects of multi-strain probiotics originated from Thai fermented food in a rat model. Food Sci. Anim. Resour., 40(6): 1014-1032. https://doi.org/10.5851/kosfa.2020.e72

Magalhaes-Guedes, K.T., 2022. Psychobiotic therapy: Method to reinforce the immune system. Clin. Psychopharmacol. Neurosci., 20(1): 17-25. https://doi.org/10.9758/cpn.2022.20.1.17

Martin, E.I., Ressler, K.J., Binder, E. and Nemeroff, C.B., 2009. The neurobiology of anxiety disorders: brain imaging, genetics, and psychoneuroendocrinology. Psychiat. Clin. North Am., 32(3): 549-575. https://doi.org/10.1016/j.psc.2009.05.004

Meguid, N.A., Mawgoud, Y.I.A., Bjorklund, G., Mehanne, N.S., Anwar, M., Effat, B.A.E., Chirumbolo, S. and Elrahman, M.M.A., 2022. Molecular characterization of probiotics and their influence on children with autism spectrum disorder. Mol. Neurobiol., 59(11): 6896-6902. https://doi.org/10.1007/s12035-022-02963-8

Merkouris, E., Mavroudi, T., Miliotas, D., Tsiptsios, D., Serdari, A., Christidi, F., Doskas, T.K., Mueller, C. and Tsamakis, K., 2024. Effects in the treatment of anxiety and depression. A comprehensive review of 2014-2023. Clin. Trials Microorgan., 12(2): 411. https://doi.org/10.3390/microorganisms12020411

Miyanishi, H. and Nitta, A., 2021. A role of BDNF in the depression pathogenesis and a potential target as antidepressant: The modulator of stress sensitivity 'Shati/Nat81-BNDF system" in the dorsal striatum. Pharmaceuticals (Basel), 14(9): 889. https://doi.org/10.3390/ph14090889

Miyaoka, T., Kanayama, M., Wake, R., Hashioka, S., Hayashida, M., Nagahama, M., Shihoh, O., Satoko, Y., Shoko, M., Hiroyuki, M., Hiroyuki, M., Masahiro, K., Muneto, I., Tomoko, A., Keiko, T., Abdul, A, I., Ryosuke, A., Arianna, A, R., Arata, O.N. and Jun, H., 2018. *Clostridium butyricum* MIYAIRI 588 as adjunctive therapy for treatment resistant major depressive disorder: A prospective open-label trial. Clin. Neuropharmacol., 41(5): 151-155. https://doi.org/10.1097/WNF.0000000000000299

Mufson, E.J., Counts, S.E., Perez, S.E. and Ginsberg, S.D., 2008. Cholinergic system during the progression of Alzheimer's disease: Therapeutic implications. Expert Rev. Neurotherapeut., 8(11): 1703-1718. https://doi.org/10.1586/14737175.8.11.1703

Muhammad, F., Fan, B., Wang, R., Ren, J., Jia, S., Wang, L., Chen, Z. and Liu, X.A., 2022. The molecular gut-brain axis in early brain development. Int. J. Mol. Sci., 23(23): 15389. https://doi.org/10.3390/ijms232315389

Nagpal, R., Neth, B.J., Wang, S., Craft, S. and Yadav, V., 2019. Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. eBioMedicine, 47: 529-542. https://doi.org/10.1016/j.ebiom.2019.08.032

Nosrani, E.A., Tamtaji, O.R., Aliolandi, Z., Sarkar, P., Ghazanfari, M., Tameh, A.A., Taghizadeh, M., Banikazemi, Z., Hadavi, R. and Taheri, M.N., 2021. Neuroprotective effects of probiotics bacteria on animal model of Parkinson's disease induced by 6-hydroxydopamine: A behavioral, biochemical, and histological study. J. Immunoassay Immunochem., 42(2): 106-120. https://doi.org/10.1080/15321819.2020.1833917

Ohsawa, K., Nakamura, F., Uchida, N., Mizuno, S. and Yokogoshi, H., 2017. *Lactobacillus helveticus*-fermented milk containing lactononadecapeptide (NIPPLTQTPVVVPPFLQPE) improves

cognitive function in health middle-aged adults: A randomized, double-blind, placebo-controlled trial. Int. J. Food Sci. Nutr., 69(3): 369-376. https://doi.org/10.1080/09637486.2017.1365824

Oroojzadeh, P., Bostanabad, S.Y. and Lotfi, H., 2022. The influence of gut microbiota on the gut-brain axis in neurological disorders. J. Mol. Neurosci., 72: 1952-1964. https://doi.org/10.1007/s12031-022-02053-3

Perez, M., Calles-Enriques, M., Nes, I., Martin, M.C., Fernandez, M., Ladero, V. and Alvarez, M.A., 2015. Tryamine biosynthesis is transcriptionally induced at low pH and improves fitness of *Enterococcus faecalils* in acidic environments. Appl. Microbiol. Biotechnol., 99(8): 3547-3558. https://doi.org/10.1007/s00253-014-6301-7

Porras-Garcia, E., Fernandez-Espada Calderon, I., Gavala-Gonalez, J. and Fernandez-Garcia, J.C., 2023. Potential neuroprotective effects of fermented foods and beverages in old age: A systematic review. Front. Nutr., 10: 1170841. https://doi.org/10.3389/fnut.2023.1170841

Radjabzadeh, D., Bosch, J.A., Uitterlinden, A.G., Zwinderman, A.H., Ikram, I.M., van Meurs, J.B.J., Luik, A. K., Niewdorp, M., Lok, A., van Duijn, C.M., Kraaji, R. and Amin, N., 2022. Gut microbiome-wide association study of depressive symptoms. Nat. Commun., 13: 7128. https://doi.org/10.1038/s41467-022-34502-3

Rahmannia, M., Poudineh, M., Mirzaei, R., Aalipour, M.A., Bonjar, A.H.S., Goudarzi, M., Kheradmand, A., Aslani, H. R., Sadeghian, M., Nasiri, M. J. and Sechi, L.A., 2024. Strain-Specific effects of probiotics on depression and anxiety: A meta-analysis. Gut Pathog., 16: 46. https://doi.org/10.1186/s13099-024-00634-8

Reid, G., Gadir, A.A. and Dhir, R., 2019. Probiotics: Reiterating what they are and what they are not. Front. Microbiol., 10: 424. https://doi.org/10.3389/fmicb.2019.00424

Remes, O., Wainwright, N., Surtees, P., Lafortune, L., Khaw, K.T. and Brayne, C., 2018. Generalized anxiety disorder and hospital admissions: findings from a large, population cohort study. BMJ Open, 8(10): e018539. https://doi.org/10.1136/bmjopen-2017-018539

Salari, N., Hosseinian-Far, A., Jalali, R., Vaisi-Raygani, A., Rasoulpoor S., Mohammadi, M., Rasoulpoor S. and Khaledi-Paveh., 2020. Prevalence of stress, anxiety, depression among the general population during the COVID-19 pandemic: A systematic review and meta analysis. Glob. Health, 16: 57. https://doi.org/10.1186/s12992-020-00589-w

Santocchi, E., Guiducci, L., Prosperi, M., Calderoni, S., Gaggini, M., Apicella, F., Tancredi, R., Billeci, L., Mastromarino, P., Grossi, E., Gastaldelli, A., Morales, M.A. and Muratori, F., 2020. Effects of probiotic supplementation on gastrointestinal, sensory and core symptoms in autism spectrum disorders: A randomized controlled trial. Front. Psych., 11: 550593. https://doi.org/10.3389/fpsyt.2020.550593

Sarkar, A., Lehto, S.M., Dinan, T.G., Cryan, J.G. and Burnet, P.W.R., 2016. Psychobiotics and the manipulation of bacteria-gut-brain signals. Trends Neurosci., 39(11): 763-781. https://doi.org/10.1016/j.tins.2016.09.002

Segers, M.E. and Lebeer, S., 2014. Towards a better understanding of *Lactobacillus rhamnosus* CG-host interactions. Microbial Cell Factories, 13: S7. https://doi.org/10.1186/1475-2859-13-S1-S7

Seki, H., Shiohara, M., Matsumura, T., Miyagawa, N., Tanaka, M., Komiyama, A. and Kurata, S., 2003. Prevention of antibiotic associated diarrhea in children by *Clostridium butyricum* MIYAIRI. Pediat. Int., 45(1): 86-90. https://doi.org/10.1046/j.1442-200X.2003.01671.x

Shaaban, S.Y., El-Gendy, Y.G., Mehanna, N.S., El-Senousy, W.M., El-Feki, H.S.A, Saad, K. and Al-Asheer, O.M., 2018. The role of probiotics in children with autism spectrum disorder: A prospective, open-label study. Nutr. Neurosci., 21(9): 676-681. https://doi.org/10.1080/1028415X.2017.1347746

Shah, A.M., Tarfeen, N., Mohamed, H. and Song, Y., 2023. Fermented foods: Their healh-promoting components and potential effects on gut microbiota. Fermentation, 9: 118. https://doi.org/10.3390/fermentation9020118

Steenbergen, L., Sellaro, R., van Hemert, S., Bosch, J.A. and Colzato, L.S., 2015. A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood. Brain, Behav. Immun., 8(10): e018539. https://doi.org/10.1016/j.bbi.2015.04.003

Strati, F., Cavalieri, D., Albanese, D., De Felice, C., Donati, C., Hayek, J., Jousson, O., Leoncini, S., Renzi, D., Calabro, A. and De Filippo, C., 2017.

New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome, 5: 1-11. https://doi.org/10.1186/s40168-017-0242-1

Sunand, K., Mohan, G.K. and Bakshi, V., 2020. Supplementation of lactobacillus probiotic strains supports gut-brain-axis and defends autistic deficits occurred by valproic acid-induced prenatal model of autism. Pharmacogn. J., 12(6s): 1658-1669. https://doi.org/10.5530/pj.2020.12.226

Tamtaji, O.R., Taghizadeh, M., Kakhaki, R.D., Kouchaki, E., Bahmani, F., Borzabadi, S., Oryan, S., Mafi, A. and Asemi, Z., 2019. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: A randomized, double-blind, placebo-controlled trial. Clin. Nutr., 38(3): 1031-1035. https://doi.org/10.1016/j.clnu.2018.05.018

Thibaut, F., 2017. Gender does matter in clinical research. Eur. Arch. Psych. Clin. Neurosci., 267(4): 283-284. https://doi.org/10.1007/s00406-017-0797-7

Van Kessel, S.P., Frye, A.K., El-Gendy, A.O., Castenjon, M., Keshavarjan, A., van Dijk, G., and El-Aidy, S., 2019. Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. Nat. Commun., 10(1): 310. https://doi.org/10.1038/s41467-019-08294-y

Vos, T., Abajobir, A.A., Abate, K.H., Abbafati, C., Abbase, K.M., Abd-Allah, F. and Murray, C.J.L., 2023. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries 1990-2016; a systematic analysis for the global burden of disease study 2016. Lancet, 390: 1211-1259.

Waise, T.M.Z., Dranse, H.J. and Lam, T.K.T., 2018. The metabolic role of vagal afferent innervations. Nat. Rev. Gastroenterol. Hepatol., 15(10): 625-636.

You, S., Ma, Y., Yan, B., Pei, W., Wu, Q., Ding, C., Wu, Q., Ding, C. and Huang, C., 2022. The promotion mechanism of prebiotics: A review. Front. Nutr., 9: 1000517. https://doi.org/10.3389/fnut.2022.1000517

Yue, X., Zhou, Y., Qiao, M., Zhao, X., Huang, X., Zhao, T., Cheng, X., Fan, M., Zhao, Y., Chen, R. and Zhu, L., 2021. Intermittent hypoxia treatment alleviates memory impairment in the 6-month-old APPswe/PS1De9 mice and reduces amyloid beta accumulation and inflammation in the brain. Alzheimer's Res. Therapy, 13: 194. https://doi.org/10.1186/s13195-021-00935-z

Zhang, L., Wang, Y., Xiayu, X., Shi, C., Chen, W., Song, N., Fu, X., Zhou, R., Xu, Y.F., Huang, L., Zhu, H., Han, Y. and Qin, C., 2017. Altered gut microbiota in a mouse model of Alzhiemer's disease. J. Alzheimer's Dis., 60(4): 1241-1257. https://doi.org/10.3233/JAD-170020

Zhu, Y., Zhang, Y. and Zeng, Y., 2012. Overview of tyrosine hydroxylase in Parkinsons's disease. CNS Neurol. Disord. Drug Target., 3(1): 350-358. https://doi.org/10.2174/187152712800792901