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REVIEW ARTICLE

A Review on Probiotic and Microbiota Modulation: A Promising Nutraceutical in the Management of Neurodegenerative and Psychiatric Conditions

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Abstract

Microbes as probiotics were found to provide the host with health benefits when given in proper doses. Researches are going on to analyze the positive relation of probiotics on digestive health including the changes in the microbial populations in the gut. The immune, nervous, and endocrine system are some of the locations outside of the gut that is affected by probiotics. The study focussed on the potential impact of the "microbiota-gut-brain axis" on CNS-related functions. The role of probiotics is highlighted in our study for the control of a number of CNS illnesses, including Alzheimer's disease, anxiety, obsessive-compulsive disorder, etc. This review also provides an overview of some clinically proven commercial probiotics and clinical studies reporting the impact of probiotics augmentation in cognition and symptoms in individuals with severe neurological and psychiatric illnesses.

Keywords: Microbiota, Neurodegenerative Disease, Pharmacology, Probiotics, Psychiatric Disease

1. Introduction

Understanding the two-way communication between the Central Nervous System (CNS) and the gastrointestinal tract depends on the Enteric Nervous System (ENS), usually described as the second brain of the body[1]. Enteric neurons interact well with the CNS via the endocrine system, vagus nerve, and immune system to keep the gut healthy[2]. Despite predictions that neurological and mental health diseases will become more common in the general population around the world, the response rate to traditional psychiatric and pharmacological treatment is still insufficient. Clinical, pharmaceutical, pharmacokinetic, and pharmacodynamic factors can all contribute to drug resistance to psychoactive substances. Recent animal research suggests that among these elements, the microbiota may have an underappreciated impact on the behaviour of its host and on drug metabolism, which may account for the ineffectiveness or heightened adverse effects of psychiatric drugs[3]. Elie Metchnikoff and colleagues first suggested the connection between gut bacteria and neurological illnesses in the 1900s, and it is now accepted by numerous research organizations. Although microbes in the gut have the ability to create and regulate a variety of immunological, metabolic, and neurochemical variables known to have a direct influence on the neurological system, it was often believed that Neurodegenerative Disorders (NDDs) were brought on by deficiencies in the nervous system[4]. Despite the gut microbiota's role in the pathology of neurodegenerative disease, it should come as no surprise that the microbiota can also protect the brain from harm. This can be accomplished in one of two ways: either by releasing the metabolites they create when host components like steroid hormones and bile acids are

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broken down, or by using probiotics to alter their makeup in the gut[5]. Surprisingly, the microbial makeup of the gut changes as the body's metabolism shifts from a healthy state to a diseased state[6,7]. Neurologic diseases that present at different ages, such as psychiatric disorders at a young age and AD and Parkinson's PD in the elderly, have been linked to changes in gut microbiota over the course of a person's lifespan. More indication of the connection between the gut microflora and its impact on brain function and health may be found in these age-related microbial alterations[8]. This demonstrates how the gut microbiota and the brain axis are interconnected and how this has a morbid relationship with many neurological and psychological illnesses. Probiotics are becoming more well recognized as having a possible function in treating different neurological illnesses and psychiatric disorders since neuroinflammation and gut-dysbiosis are frequent factors in the pathophysiology of these diseases.

2. Materials and Methods

A large database of various online resources is explored, and various reviews and research papers are studied using different keywords like probiotics, microflora, neurodegeneration, and psychiatric disorders. This study considers probiotic modulation and its benefits in the treatment of brain disorders. A large number of publications from different websites Google Scholar, Springer, Taylor and Francis, Elsevier, and Bentham are reviewed for the literature survey.

3. Micro-Biota Relation to the Nervous System

The fact that gut microbiota influences nervous system development serves as the main support for the hypothesis that it acts as a brain peacekeeper. The gut flora in rats and mice regulates the neonatal and adult maturation of the ENS[9,10]. The CNS receives signals from the ENS, which also regulates intestinal motility. Germ-Free (GF) mice have much more abnormal myenteric plexus in the jejunum and ileum than do Specific Pathogen-Free (SPF) mice. On postnatal day 3, the anomaly is accompanied by a decrease in nerve density, a rise in nitrergic neurons, and a reduction in the number of neuronal cell bodies per ganglion[11]. Additionally, enteric glial cells may be impacted by gut bacteria. The ENS must have enteric glial cells because they connect the gut to the brain[12]. Glial cell initial colonization and homeostatic flow in mice intestinal mucosa can be controlled by the intestinal microflora in the ileum[13]. When compared to normal mice, GF mice have considerably fewer mucosal enteric glial cells overall and in terms of density. This finding raises the possibility that enteric glial cells, along with the microbiota and microbial products, could influence gastrointestinal homeostasis. Additionally, the gut microbiota can control gastrointestinal motility and enteric neuron survival, possibly by being recognized by Toll-like receptors. A reduction in intestinal capacity by antibiotics' effects on the microbiota causes ENS abnormalities, especially when antibiotics reduce glial cell line-derived protein expression at the same time as neurotrophic substances[14]. A different study found that TLR4-deficient mice, GF mice, and wild-type mice with reduced gut microbes all had impaired gastrointestinal growth and lowered nitrergic neuronal numbers and motility[15]. It is important to note that the gut microbiome controls mouse blood-brain barrier permeability as well. The frontal brain, striatum, and hippocampus regions of GF mice express occludin and claudin-5 at lower levels than those of SPF mice[16]. The functionality of tight junctions is necessary for the blood-brain barrier to function. Administration of mice with *Clostridium tyrobutyricum* and sodium butyrate reduces blood-brain barrier permeability by raising tight junction proteins in comparison to control GF animals[16]. In a rat model exposed to a long-term water avoidance test, a rifaximin regimen boosts the production of the tight junction protein occludin and lowers the levels of the inflammatory interleukins, and tumour necrosis factor mRNA in the distal ileum, which lessens visceral hyperalgesia[17]. The effects of rifaximin are related to a greater level of *Lactobacillus* in the ileum. Certain *Lactobacillus* species, such as *Lacticaseibacillus casei*, reduce inflammation in the gut mucosa[18]. A recent study found that the bacteria that create spores in the human and mouse gut microflora stimulate the synthesis of colonic serotonin, which regulates platelet and intestine motility[19]. These studies point to a potential mechanism for how the brain's serotonergic system is regulated by the microbiome. Phytoestrogens are one example of additional microbial metabolites that may link gut and brain functioning. Equol is an estrogen created when certain mammalian components of the gut microbiota break down dietary daizén, a type of soy isoflavone[20]. Porcine faeces have been used to isolate equol-producing *Eubacterium bacteria*[21]. Equol treatment

reduces brain histological damage and inhibits phospho-Src to protect rats against reperfusion injury or cerebral ischemia[22]. It has been discovered that eating isoflavones enhances memory function and cognitive activity[23], albeit the processes are unknown. These results thus suggest the fascinating hypothesis that gut-derived equol may influence nervous system function.

4. Microbiome-Gut-Brain Axis

The bidirectional connection between the brain and the gut involves a variety of pathways, including the vagal nerve, the Hypothalamic-Pituitary-Adrenal (HPA) axis, Short-Chain Fatty Acid (SCFA) synthesis by bacteria, immunological mediators, and enteroendocrine signalling[24]. The fastest and most effective link between the brain and the gut is provided by the vagal nerve, sometimes referred to as the 10th cranial nerve and colloquially as the "wandering nerve". Vagal nerve ablation, formerly used to heal peptic ulcers, was connected to an increase in the prevalence of mental conditions in research studies in 1953 and 1961[25]. It's interesting to note that this method has recently proved to lower the prevalence of Parkinson's disease[26]. In a transgenic mouse model of autism (Shank3B/mouse), vagotomy was found to negate the impact of *Lactobacillus reuteri* on social group interactions[27]. SCFAs can affect behavior because they have the capacity to communicate with the brain indirectly through nerve activity[28]. Acetate, propionate, and butyrate make about 95% of SCFA molecules. The fact that SCFA levels are low in germ-free animals and those who have had antibiotic treatment supports the theory that the gut microbial fermentation of dietary fibers is the main source of SCFAs[24]. Neurotransmission can be modulated by SCFAs. As an illustration, propionic acid raises the production of the enzyme tryptophan hydroxylase, which can lower the amount of indoleamine serotonin and thus affect serotonergic neurotransmission[29]. Only a small number of studies have looked into the connections between neuropsychiatric diseases and SCFAs so far (Figure 1). According to the study, depressive women had higher levels of isocaproic acid than healthy women did, and their median acetate content was lower[30]. Immune mediators form significant connections between the brain and the gut microbiome. Circumventricular organs or the vagal nerve are two possible routes for cytokines

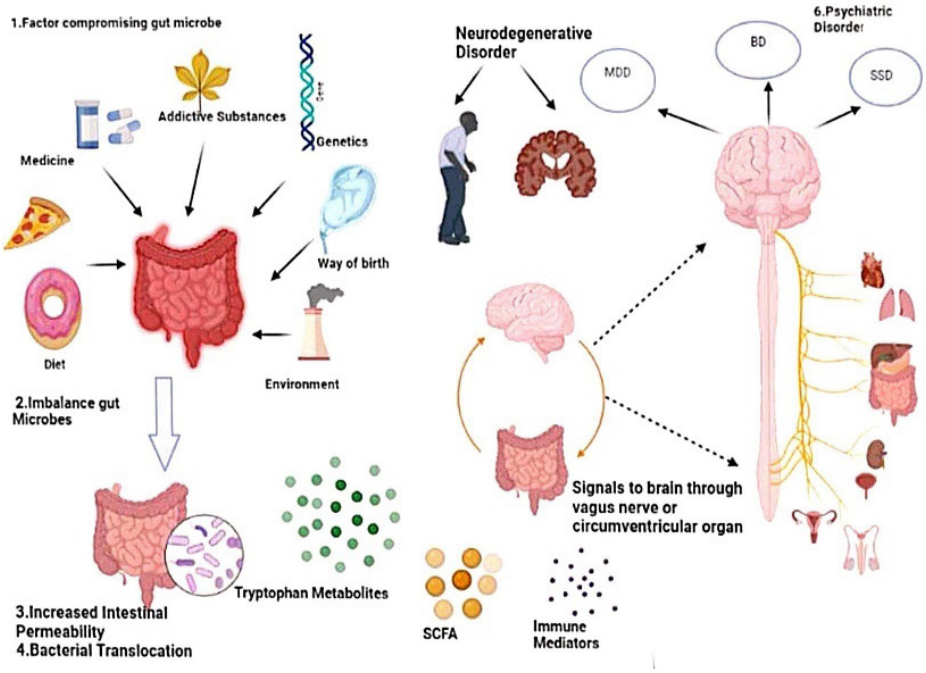

Figure 1. Schematic representation of factors affecting gut microbes and bidirectional communication between gut and brain through mediators such as tryptophan metabolites, SCFA, immune mediators by the vagus nerve, and its relationship to neurodegenerative and psychiatric disorders.

to communicate with the brain from the periphery[31]. Lipopolysaccharide-binding protein (LBP) is a blood protein that may bind bacteria or bacterium fragments. TLR-4, which is present on monocytes, macrophages, and microglia, is coupled to LBP by an easily dispersible cluster of differentiation 14 (sCD14)[32]. As a result, the nuclear factor kappa-light-chain promoter of activated B cells (NF-B) may activate, which might cause the production of cytokines that encourage inflammation[33]. Small amounts of bacteria or their presence can cause the immune system to get activated, which has an impact on the brain. LBP, sCD14, and NF-B blood levels are indicators of this route's activity. Researchers discovered that concentrations were higher in people who also had somatic symptom disorder and bipolar illness concurrently with gastrointestinal problems[34]. In addition, a recent analysis of the connection between the immune system and the gut flora in major depressive disorder emphasizes the importance of the immune system as a crucial role in the neurobiology of the gut microbiome and immune system in subtypes of depression[35]. Gut bacteria affect the metabolism of tryptophan in contrast to other metabolites[36].

Tryptophan is a crucial amino acid that is metabolized mostly through the kynurenine pathway and the serotonin (5-HT) pathway. In MDD, BD, and SSD, tryptophan, and kynurenine levels are decreased, as shown by a meta-analysis of 101 research[37]. The therapeutic impact of traditional antidepressants is achieved by raising central serotonin levels. Tryptophan-2,3-dioxygenase in the liver converts the majority of tryptophan into kynurenine for energy production or indoleamine-2,3-dioxygenase in response to inflammatory stimulation. Gut bacteria like *Clostridium perfringens* can modulate the gut's ability to produce 5-HT[38]. In one study, probiotic medication (*Lactobacillus helveticus* and *Bifidobacterium longum*) led to reductions in the kynurenine/tryptophan ratio in MDD patients[39]. Blood kynurenine levels and the kynurenine/tryptophan ratio were considerably lower after treatment, in accordance with a meta-analysis assessing the effects of probiotic supplements on the tryptophan-kynurenine pathway. According to the initial results, probiotics may be able to alter the tryptophan-kynurenine pathway[40].

5. Probiotics as Neuroprotective

As was previously mentioned, the vagus nerve, which has recently drawn a significant amount of attention, can link gut microbes to the brain. The vagus nerve handles efferent and afferent tasks. It is the primary nerve of the ANS's parasympathetic division, which controls a number of physiological processes such as heart rate, gastric motility, and bronchial constriction. Given the systemic and local actions of probiotic strains, it is conceivable that the vagus nerve is involved in the bulk of their physiological functions. In addition, it has been shown that the stimulation of the vagus nerve is a prerequisite for a number of impacts of gut bacteria or prospective probiotics on mental functioning[41]. Now, the neuroprotective properties of probiotics are acknowledged. In general, the nervous system, its cells, structure, and function are protected, recovered, or rebuilt by the neuroprotective impact. Probiotics' effects on the CNS in models of stress have been documented in a number of research studies. Male BALB/c mice were given *Lactobacillus rhamnosus (JB-1)* orally in order to study the probiotic's direct effects on the GABAergic system. The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is important in the regulation of a variety of physiological and psychological functions. Stressed mice's behaviour was improved by psychobiotic treatment with *L. rhamnosus*, significantly GABA mRNA and corticosterone concentrations were lowered[41]. Rats that were administered *Bifidobacterium infantis* and subjected to the forced swim test likewise demonstrated the antidepressant effects of the bacteria. This was done by considerably raising plasma levels of tryptophan and kynurenic acid while lowering the level of cytokines[42]. Although the precise processes underlying probiotics' ability to protect against neurodegenerative disorders are still unclear, they might be explained by circumstances that arise during the fermentation process. In the CNS, glutamate decarboxylase (GAD) is known to be converted into GABA by *LAB* (lactic acid bacteria)[43]. In an in vitro environment, PC12 cells' ability to proliferate was boosted by a culture extract of the GABA-producing *Lactobacillus buchneri* MS obtained from fermented kimchi. Due to its ability to manufacture GABA, *L. buchneri* has an improved ability to protect neurons against a variety of cell-killing substances, such as H2O2, paraquat, MnCl2, and dieldrin[44]. Given that epilepsy, Huntington's, and Parkinson's disease have been linked to considerable reductions in GABA expression levels, probiotics may offer an alternate method for slowing the advancement of these neurological conditions or preventing their emergence.

Probiotics may also help to decrease inflammation in the central nervous system, according to growing research: *LAB* significantly decreases the astrocyte response in the brain[45]. The production of anti-inflammatory cytokines was enhanced by *Lactobacillus sp*[46]. Increased antioxidant activities have been linked to the neuroprotective effects of *L. acidophilus* in other studies[47]. Additionally, *Hwangryunhaedoktang*, a traditional herb with soothing properties, was fermented with *L. acidophilus* KFRI 128 in comparison to its nonfermented counterpart, increasing HT22 cell survival against glutamate-induced neurotoxicity[48]. During the fermentation process, *LAB* in *Hwangryunhaedoktang* also produced a number of other substances, such as berberine, an alkaloid that has considerable antibacterial action against a number of diseases. Berberine was already demonstrated to have neuroprotection in ischemic conditions via lowering the activity of the N-methyl-D-aspartate (NMDA) receptor-1. Therefore, increasing the neuroprotective action of probiotics may be achieved by administering probiotic strains through fermented foods[49].

6. Probiotics in Neurodegenerative Disorder

6.1 Alzheimer Disease(AD)

Selective memory loss and dementia caused by aging are the main clinical signs. These are related to neuronal loss, the buildup of neurofibrillary tangles and threads in the grey matter, and extracellular senile plaques that resemble silk. Tau protein and amyloid beta-peptide (AβP) play critical roles in the development of brain cell destruction in the early stages of AD[50]. Alzheimer's is a long-term neurological condition that causes cognitive and memory deficits[51]. An investigation by a team of researchers looked at how probiotic therapy affected people with severe AD. Patients with severe AD were shown to be insensitive to probiotic treatment, according to the findings[52]. The gut bacteria's composition and the way tryptophan is processed in the serum were both affected by the probiotics' intervention. Recent studies showed that probiotic preparation (SLAB51) effectively lowers oxidative stress through SIRT-1-dependent pathways when administered to mutant AD mice[53].

Two investigations investigated the effects of several strains on experimental animals of AD, including *L. acidophilus, Lactobacillus fermentum, B. lactis,* and *B. longum*. The overall population of *Bifidobacterium* sp. and *Lactobacillus* sp. in the feces increased after the probiotic intervention, but Coliform levels decreased. In addition, supplementing with probiotics helps AD rats learn and remember better than control rats do. In the Alzheimer-probiotics group, there were decreased levels of amyloid plaques, inflammation, and oxidative stress[54]. Intriguingly, researchers in a study reported that changes in the gut bacteria precede the deposition of cerebral Aβ in an AD model and were accompanied by a weakened intestinal epithelial barrier, Aβ deposition along gut vessels, as well as an initial systemic inflammation that subsided after the onset of symptoms. This finding raises the possibility of a pre-symptomatic phase in which dysbiosis and peripheral inflammation may cause Aβ aggregation in the CNS[55]. Given the abundance of data regarding dysbiosis in AD, it would be reasonable to investigate whether microbiota-focused therapies could influence disease development. Probiotics based upon *Bifidobacteria* and *lactobacilli* or other beneficial commensals have been proven in several studies to reduce neuroinflammation, Aβ plaque burden, and cognitive issues in AD animal models[56,57]. Fermented milk from *L. helveticus* IDCC3801 may be used to treat memory-impaired mice, and rats' blood levels of AβP could be lowered[58]. It is commonly acknowledged that milk that has undergone *LAB* culture can include bioactive peptides which have numerous positive effects on human health. By lowering AβP synthesis, these drugs may significantly contribute to the suppression of amyloidogenic pathways. Comparatively speaking to other bacterial and yeast species, *Saccharomyces cerevisiae* showed the highest β-site APP-cleaving enzyme (BACE1) inhibiting activity[59]. Probiotics may also lower the risk of AD by increasing the levels of the proteins cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor, according to research (BDNF). For instance, *Lactobacillus pentosus var. plantarum C29* may boost the synthesis of both of these proteins in a scopolamine-induced animal model[60].

Intriguingly, the hippocampus, cerebral cortex, and amygdaloid complex are among the regions where BDNF is most concentrated. It may be highly susceptible to AD-related neuronal damage because of neuronal loss, plaque-associated neuritic dystrophy, and down-regulated BDNF expression in AD patients[61].

6.2 Parkinson's Disease (PD)

A characteristic of the condition is the gradual death in the substantia nigra of dopaminergic brain cells. Lewy bodies, which are eosinophilic intracytoplasmic globular deposits in the nuclei of neurons, are the key identifying feature[62]. More research has revealed that the aggregated, insoluble form of α-synuclein that comprises these entities is toxic. This cytosolic protein is widely expressed in presynaptic membranes and is present in large amounts in the brain[63]. It can bind to membrane phospholipids and is involved in presynaptic terminal membrane-related processes[64]. The two missense variants in α-synuclein that cause early-onset Parkinson's disease are A53T and A30P[65]. As the disease progresses, dementia becomes more prevalent, and more than one-third of persons with Parkinson's disease experience anxiety and depression[66]. Since 2015, almost 20 research have been released emphasizing the existence of particular microbial fingerprints linked to the disease. According to two meta-analyses, PD patients had higher concentrations of the families *Verrucomicrobiaceae* and *Lactobacillaceae*, as well as the genera *Akkermansia, Lactobacillus,* and *Bifidobacterium*, compared to controls. SCFA-producing bacteria, on the other hand, included the families *Lachnospiraceae* and *Prevotellaceae*, as well as the genera *Faecalibacterium, Roseburia, Blautia*[67,68]. In studies, utilising a probiotic blend of *L. acidophilus* and *B. infantis* dramatically reduced bloating and stomach pain[69]. Patients with Parkinson's disease also showed changes in their bowel movements and stool consistency after undergoing therapy with fermented milk including *L. casei Shirota* for 5 weeks[70]. Increased urine indoxyl sulphate levels are reported in Parkinsonian patients, which may indicate constipation or bacterial overgrowth in the small intestine[71]. Through the brain's deteriorating dopaminergic neurons, *H. pylori* infection may have a role in the onset of Parkinsonian symptoms[72]. Interestingly, it has been demonstrated that eliminating *H. pylori* improves tremor, rigidity, and walking capacity as well as the onset time of levodopa, the first-line pharmaceutical treatment for Parkinson's disease symptoms[73,74]. Probiotics are described by FAO/WHO as "live bacteria that, when fed or eaten in certain ratios, confer a benefit to the host. *Bifidobacteria* and *lactobacilli* found in probiotics have been shown to relieve PD-like symptoms[75]. When DOPA decarboxylase is present, a beneficial bacteria called *Bacillus* sp. may convert L-tyrosine to L-DOPA, which is subsequently converted to dopamine[76].

7. Probiotics in Psychiatric Disorders

7.1 Schizophrenia Disorder (SCZ)

Schizophrenia is predominantly an inherited condition, although several studies suggest that the gut flora may have a causative effect via epigenetic regulation (e.g., dietary factors and exposure to infectious agents), impact on the immune system, and neuroinflammation[77,78]. The relationship between the brain's microbiome and the immune system is crucial. There are signs of immune system disorders in schizophrenia. NMDA dysfunction in schizophrenia may result from a change in the microbiota's makeup. It's possible that endotoxin-related neuroinflammation contributes to the etiopathogenesis of schizophrenia[79]. In a recent study, researchers found evidence of the possible efficacy of *Bifidobacterium breve strain A1* in lowering symptoms of depression and anxiety among 29 SCZ patients. Although a placebo effect cannot be ruled out, they discovered this possible impact in open-label, single-arm research[80]. In a separate pilot investigation, the team of scientists found that giving probiotics to SCZ patients significantly normalized their levels of anti-*Candidiasis albicans* antibodies and the gastrointestinal discomfort caused by *C. Albicans* among 22 male volunteers[81]. Following probiotic therapy, 47 immune-related blood proteins were analyzed in 57 chronic SCZ patients. They found that probiotics significantly reduced von Willebrand factor levels and increased BDNF and monocyte chemotactic protein-1 levels, which may imply reduced intestinal permeability[82]. According to a study, patients with mild to moderate symptoms of schizophrenia were shown to have a lower probability of developing serious gastrointestinal issues after taking the probiotic supplement[83]. Minocycline, a tetracycline antibiotic, has been demonstrated to have an antipsychotic-like effect in a number of clinical and preclinical trials[84,85]. By altering gut microbiome data, minocycline may be demonstrating this influence (Figure 2).

7.2 Bipolar Disorder

The main objectives of treatment for bipolar disorders are to prevent subsequent episodes (recurrences) and to effectively manage acute manic and depressive episodes[86]. However, the findings of an increasing number of longitudinal outcome studies reveal that even intensive

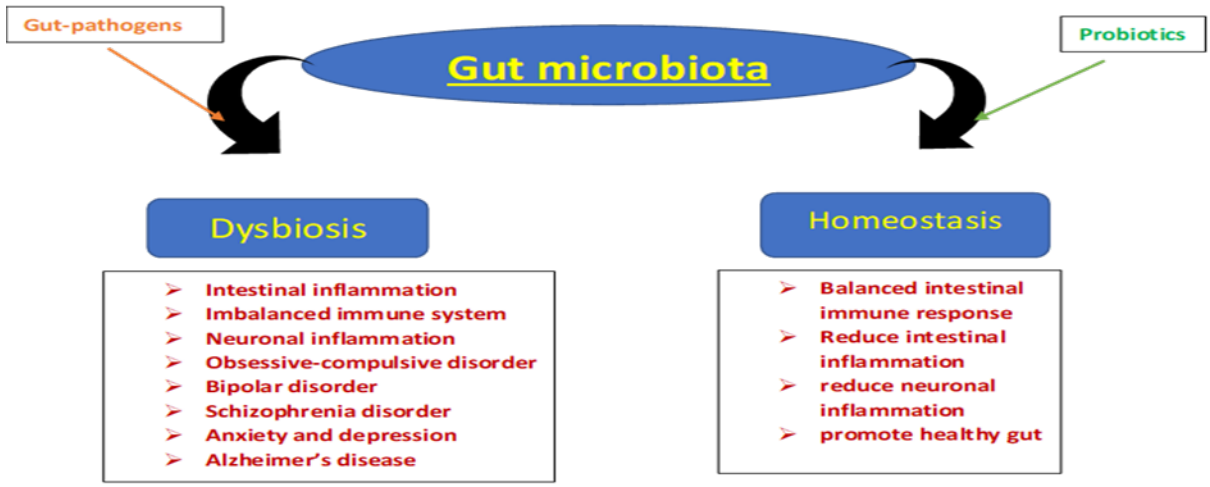

Figure 2. Precise representation between gut- microbiota and other diseases including the effect of the gut pathogen and probiotic in maintaining homeostasis.

medication therapy frequently has far fewer favourable benefits. Bipolar disorder is one of the major causes of impairment since full recovery between episodes is not seen among all patients[87,88]. Clinical studies employing probiotic supplements in bipolar illness have shown that probiotics are associated with a decreased risk of rehospitalization in 66 individuals who have just been released from the hospital after being treated for mania[89]. Another recent study identified significant improvements in 20 patients' attention and psychomotor processing speed, leading to the hypothesis that probiotic supplementation aids people with bipolar disorder in enhancing cognitive functioning. Since only one arm of the trial was used, the possibility of a placebo effect cannot be completely ruled out[90]. Contrarily, bipolar disorder is linked to satiety and diarrhea, a gastrointestinal ailment for which probiotics are known to be effective[91]. Probiotics may potentially be a helpful supplementary therapy for bipolar illness, especially in people with high intestinal permeability. More research supporting these findings will be useful as these trials suggest that probiotic treatment reduces gastrointestinal pain. The results that are currently available tend to suggest that bipolar disorder and maybe SCZ have had cognitive improvements. Future research might benefit from considering cognitive functioning, subjective well-being, and immunological/inflammatory biomarkers (Figure 2).

7.3 Anxiety Disorder

Anxiety disorders are a frequent form of mental health issue linked to excessive contemplation, thinking, unease, anxiety, and worry over future uncertainty based on real or imagined events. These conditions can have an effect on one's physical and mental health. Low GABA levels that reduce CNS nerve signaling are one of the many reasons that might cause anxiety condition. Reduced GABA levels and GABA-receptor binding are symptoms of a dysfunctional GABA system, as seen in neuroimaging investigations of anxiety patients[92]. Additionally, throughout the etiology of this specific disorder, changes have been found in a central GABA receptor[93]. As significant pharmacological targets for clinically useful anti-anxiety medications, the GABA receptors have already been identified (e.g., benzodiazepines)[94]. Probiotics have been shown to be effective in treating anxiety disorders. Exposure to *Lactobacillus* in vivo For instance, rats raised on *R. rhamnosus (JB-1)* for 28 days had lesser levels of stress-induced corticosterone, fewer depressive behaviours, and a less anxious phenotype[93]. Numerous studies have looked at how probiotics affect the symptoms of anxiety in conditions like IBS, but the outcomes are frequently inconsistent[95]. In trials on animals, probiotic supplementation had an impact on stress, the HPA axis response, and anxiety-related behaviour[96,97]. There is one article that presents RCT evidence on the use of a probiotic to treat individuals

with a generalized anxiety disorder (according to DSM-V criteria)[98]. However, no additional interventional research has been done on individuals with clinically significant anxiety disorders. This small but promising trial and the growing body of evidence presenting positive preclinical outcomes necessitate more studies in this field (Figure 2).

8. Conclusion

The association between microbes in the gut and neurons has propelled neuroscience research forward in new ways. In order to understand how gut microbes and their populations affect gut-brain communication pathways, scientists must pay close attention to the gut microbiome's scale and complexity. The bulk of studies that have been discovered so far has something to do with gut bacterial neurology. To fully comprehend how gut microbiota regulates gut-brain communication during neurodegeneration and mental illnesses, more study is needed. New theories on the pathophysiology and prognosis of the disease could be made possible by the findings of this research.

The necessity to research specific probiotics for the treatment of particular brain ailments is prompted by the absence of empirical data for commercial probiotic strains, even if innovative therapeutic approaches like fecal microbial translocation and probiotics have helped to some extent to enhance brain health. Thorough knowledge of how microbial modulator molecules contributes to neurotoxicity and neuroprotection will also be aided by the rising capability of in-silico techniques, but sadly, there are not many researchers in this field. Gut microbial metabolites continue to play neuroprotective and neurodegenerative roles, opening up possibilities for the development of innovative treatment methods. Our understanding of bacterial species in a large population with neurological and psychiatric diseases, including the impact of medication and dietary practices, has to be expanded. The use of probiotics designed for specific diseases could result from knowledge about variations in particular bacterial strains. Due to their favourable effects on various aspects of neurological illnesses, including the relevant metabolic pathways, probiotics seem to be helpful as adjuvant therapy. These products' tolerability and safety also appear to be advantages. Although there is some solid clinical evidence that probiotics can treat mental and neurodegenerative illnesses, it is currently relatively limited in human patients.

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10. List of Abbreviations

- ENS - Enteric Nervous System
- CNS - Central Nervous System
- NDDs - Neurodegenerative Disorders
- AD - Alzheimer's disease
- PD - Parkinson's disease
- GF - Germ-Free
- SPF - Specific Pathogen-Free
- TLR4 - toll-like receptor 4 gene
- HPA - Hypothalamic-Pituitary-Adrenal
- SCFA - Short-Chain Fatty Acid
- LBP - Lipopolysaccharide-Binding Protein
- sCD14 - Soluble Cluster of Differentiation 14
- 5-HT - 5-hydroxy tryptophan
- MDD - major depressive disorder
- BD - bipolar disorder
- SSD - Somatic symptom disorder
- ANS - autonomic nervous system
- GABA - Gamma-Aminobutyric Acid
- GAD - Glutamate Decarboxylase
- LAB - Lactic Acid Bacteria
- NMDA - N-methyl-D-aspartate
- AβP - Amyloid Beta-Peptide
- BACE1 - β-site APP-cleaving enzyme
- cAMP - Cyclic adenosine monophosphate
- CREB - cAMP response element-binding protein
- BDNF - Brain-Derived Neurotrophic Factor
- DOPA - dihydroxyphenylalanine
- SCZ - Schizophrenia
- HPA - Hypothalamus-Pituitary-Adrenal
- RCT - Randomized controlled trial
- DSM-V - Diagnostic and Statistical Manual of Mental Disorders-5
- OCD - Obsessive-compulsive disorder
- CFU - Colony Forming Units
- SSRI - Selective Serotonin Inhibitor
- ACTH - adrenocorticotropic hormone and corticotropin
- FDA - Food and Drug Administration

11. References

1. Rao M, Gershon MD. Enteric nervous system development: What could possibly go wrong?. Nature Reviews Neuroscience. 2018; 19(9):552-65. https://doi.org/10.1038/s41583-018-0041-0
2. Morais LH, Schreiber HL, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. Nature Reviews Microbiology. 2021; 19(4):241-55. https://doi.org/10.1038/s41579-020-00460-0
3. Musso G, Gambino R, Cassader M. Gut microbiota as a regulator of energy homeostasis and ectopic fat deposition: Mechanisms and implications for metabolic disorders. Current Opinion in Lipidology. 2010; 21(1):76-83. https://doi.org/10.1097/MOL.0b013e3283347ebb
4. Needham BD, Kaddurah-Daouk R, Mazmanian SK. Gut microbial molecules in behavioural and neurodegenerative conditions. Nature Reviews Neuroscience. 2020; 21(12):717-31. https://doi.org/10.1038/s41583-020-00381-0
5. Raval U, Harary JM, Zeng E, Pasinetti GM. The dichotomous role of the gut microbiome in exacerbating and ameliorating neurodegenerative disorders. Expert Review of Neurotherapeutics. 2020; 20(7):673-86. https://doi.org/10.1080/14737175.2020.1775585
6. Wang B, Yao M, Lv L, Ling Z, Li L. The human microbiota in health and disease. Engineering. 2017; 3(1):71-82. https://doi.org/10.1016/J.ENG.2017.01.008
7. Luca M, Di Mauro M, Di Mauro M, Luca A. Gut microbiota in Alzheimer's disease, depression, and type 2 diabetes mellitus: The role of oxidative stress. Oxidative medicine and cellular longevity. 2019; 2019. https://doi.org/10.1155/2019/5698132
8. Cox LM, Schafer MJ, Sohn J, Vincentini J, Weiner HL, Ginsberg SD, *et al*. Calorie restriction slows age-related microbiota changes in an Alzheimer's disease model in female mice. Scientific Reports. 2019; 9(1):1-4. https://doi.org/10.1038/s41598-019-54187-x
9. Dupont JR, Jervis HR, Sprinz H. Auerbach's plexus of the rat cecum in relation to the germfree state. Journal of Comparative Neurology. 1965; 125(1):11-8. https://doi.org/10.1002/cne.901250103
10. Neufeld KAM, Mao YK, Bienenstock J, Foster JA, Kunze WA. The microbiome is essential for normal gut intrinsic primary afferent neuron excitability in the mouse. Neurogastroenterology and Motility. 2013; 25(2):183-e88. https://doi.org/10.1111/nmo.12049
11. Collins SM, Bercik P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. Gastroenterology. 2009; 136(6):2003-14. https://doi.org/10.1053/j.gastro.2009.01.075
12. Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. Nature Reviews Microbiology. 2012; 10(11):735-42. https://doi.org/10.1038/nrmicro2876
13. Kabouridis PS, Lasrado R, McCallum S, Chng SH, Snippert HJ, Clevers H, *et al*. Microbiota controls the homeostasis of glial cells in the gut lamina propria. Neuron. 2015; 85(2):289-95. https://doi.org/10.1016/j.neuron.2014.12.037
14. Baird AD. Exstrophy in the adolescent and young adult population. Seminars in Pediatric Surgery. WB Saunders; 2011. p. 109-112. https://doi.org/10.1053/j.sempedsurg.2010.12.006
15. Booth DM, Murphy JA, Mukherjee R, Awais M, Neoptolemos JP, Gerasimenko OV, *et al*. Reactive oxygen species induced by bile acid induce apoptosis and protect against necrosis in pancreatic acinar cells. Gastroenterology. 2011; 140(7):2116-25. https://doi.org/10.1053/j.gastro.2011.02.054
16. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Science Translational Medicine. 2014; 6(263). https://doi.org/10.1126/scitranslmed.3009759
17. Xu D, Gao J, Gillilland M, Wu X, Song I, Kao JY, *et al*. Rifaximin alters intestinal bacteria and prevents stress-induced gut inflammation and visceral hyperalgesia in rats. Gastroenterology. 2014; 146(2):484-96. https://doi.org/10.1053/j.gastro.2013.10.026
18. Llopis M, Antolin M, Carol M, Borruel N, Casellas F, Martinez C, *et al*. Lactobacillus casei downregulates commensals' inflammatory signals in Crohn's disease mucosa. Inflammatory bowel diseases. 2009; 15(2):275-83. https://doi.org/10.1002/ibd.20736
19. Yano MJ, Yu K, Donaldson G, Shastri G. Ann P, Ma L, *et al*. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015; 161(2):264-76. https://doi.org/10.1016/j.cell.2015.02.047
20. Zhengkang H, Wang G, Yao W, Zhu WY. Isoflavonic phytoestrogens-new prebiotics for farm animals: A review on research in China. Current Issues in Intestinal Microbiology. 2006; 7(2):53-60.
21. Zhuo-Teng Y, Yao W, Wei-Yun Z. Isolation and identification of equol-producing bacterial strains from cultures of pig faeces. FEMS Microbiology

Letters. 2008; 282(1):73-80. https://doi.org/10.1111/j.1574-6968.2008.01108.x
22. Yu W, Wang Y, Zhou DX, Zhao LM, Li GR, Deng XL. Equol is neuroprotective during focal cerebral ischemia and reperfusion that involves p-Src and gp91phox. Current Neurovascular Research. 2014; 11(4):367-77. https://doi.org/10.2174/1567202611666140908094517
23. Kennedy DO. Polyphenols and the human brain: Plant "secondary metabolite" ecologic roles and endogenous signaling functions drive benefits. Advances in Nutrition. 2014; 5(5):515-33. https://doi.org/10.3945/an.114.006320
24. Cryan JF, O'Riordan KJ, Cowan CS, Sandhu KV, Bastiaanssen TF, Boehme M, *et al*. The microbiota-gut-brain axis. Physiological Reviews. 2019. https://doi.org/10.1152/physrev.00018.2018
25. Browning JS, Houseworth JH. Development of new symptoms following medical and surgical treatment for duodenal ulcer. Psychosomatic Medicine. 1953; 15(4):328-36. https://doi.org/10.1097/00006842-195307000-00006
26. Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, Sørensen HT. Vagotomy and subsequent risk of Parkinson's disease. Annals of Neurology. 2015; 78(4):522-529. https://doi.org/10.1002/ana.24448
27. Sgritta M, Dooling SW, Buffington SA, Momin EN, Francis MB, Britton RA, Costa-Mattioli M. Mechanisms underlying microbial-bediated changes in social behavior in mouse models of autism spectrum disorder. Neuron. 2019; 101(2):246-59. https://doi.org/10.1016/j.neuron.2018.11.018
28. Ropelle ER, da Silva ASR, Cintra DE, de Moura LP, Teixeira AM, Pauli JP. Physical exercise: A versatile anti-inflammatory tool involved in the control of hypothalamic satiety signaling. Exercise Immunology Review. 2021; 27.
29. El-Ansary AK, Bacha AB, Kotb M. Etiology of autistic features: The persisting neurotoxic effects of propionic acid. Journal of Neuroinflammation. 2012; 9:1-14. https://doi.org/10.1186/1742-2094-9-74
30. Skonieczna-Żydecka K, Grochans E, Maciejewska D, Szkup M, Schneider-Matyka D, Jurczak A, *et al*. Faecal short chain fatty acids profile is changed in Polish depressive women. Nutrients. 2018; 10(12):1939. https://doi.org/10.3390/nu10121939
31. Sherwin E, Sandhu KV, Dinan TG, Cryan JF. May the force be with you: The light and dark sides of the microbiota-gut-brain axis in neuropsychiatry. CNS Drugs. 2016; 30(11):1019-1041. https://doi.org/10.1007/s40263-016-0370-3
32. Lim PS, Chang YK, Wu TK. Serum lipopolysaccharide-binding protein is associated with chronic inflammation and metabolic syndrome in hemodialysis patients. Blood purification. 2019; 47(1-3):28-36. https://doi.org/10.1159/000492778
33. Genedi M, Janmaat IE, Haarman BB, Sommer IE. Dysregulation of the gut-brain axis in schizophrenia and bipolar disorder: Probiotic supplementation as a supportive treatment in psychiatric disorders. Current Opinion in Psychiatry. 2019; 32(3):185-195. https://doi.org/10.1097/YCO.0000000000000499
34. Severance EG, Gressitt KL, Stallings CR, Origoni AE, Khushalani S, Leweke FM, *et al*. Discordant patterns of bacterial translocation markers and implications for innate immune imbalances in schizophrenia. Schizophrenia Research. 2013; 148(1-3):130-137. https://doi.org/10.1016/j.schres.2013.05.018
35. Foster JA, Baker GB, Dursun SM. The relationship between the gut microbiome-immune system-brain axis and major depressive disorder. Frontiers in Neurology. 2021; 12:721126. https://doi.org/10.3389/fneur.2021.721126
36. Carlessi AS, Borba LA, Zugno AI, Quevedo J, Réus GZ. Gut microbiota-brain axis in depression: The role of neuroinflammation. European Journal of Neuroscience. 2021; 53(1):222-235. https://doi.org/10.1111/ejn.14631
37. Marx W, McGuinness AJ, Rocks T, Ruusunen A, Cleminson J, Walker AJ, *et al*. The kynurenine pathway in major depressive disorder, bipolar disorder, and schizophrenia: A meta-analysis of 101 studies. Molecular Psychiatry. 2021; 26(8):4158-4178. https://doi.org/10.1038/s41380-020-00951-9
38. Beaver MH, Wostmann BS. Histamine and 5-hydroxytryptamine in the intestinal tract of germ-free animals, animals harbouring one microbial species and conventional animals. British Journal of Pharmacology and Chemotherapy. 1962; 19(3):385-393. https://doi.org/10.1111/j.1476-5381.1962.tb01443.x
39. Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. Clinical Nutrition. 2019; 38(2):522-528. https://doi.org/10.1016/j.clnu.2018.04.010
40. Purton T, Staskova L, Lane MM, Dawson SL, West M, Firth J, *et al*. Prebiotic and probiotic supplementation

and the tryptophan-kynurenine pathway: A systematic review and meta analysis. Neuroscience and Biobehavioral Reviews. 2021; 123:1-3. https://doi.org/10.1016/j.neubiorev.2020.12.026
41. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine. Journal of Applied Microbiology. 2012; 113(2):411-417. https://doi.org/10.1111/j.1365-2672.2012.05344.x
42. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences. 2011; 108(38):16050-16055. https://doi.org/10.1073/pnas.1102999108
43. Bhatia NY, Jalgaonkar MP, Hargude AB, Sherje AP, Oza MJ, *et al*. Gut-brain axis and neurological disorders-how microbiomes affect our mental health. CNS and Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS and Neurological Disorders). 2022. https://doi.org/10.2174/1871527321666220822172039
44. Cheon MJ, Lim SM, Lee NK, Paik HD. Probiotic properties and neuroprotective effects of Lactobacillus buchneri KU200793 isolated from Korean fermented foods. International Journal of Molecular Sciences. 2020; 21(4):1227. https://doi.org/10.3390/ijms21041227
45. Kovalenko TN, Ushakova GA, Osadchenko I, Skibo GG, Pierzynowski SG. The neuroprotective effect of 2-oxoglutarate in the experimental ischemia of hippocampus. Journal of Physiology and Pharmacology. 2011; 62(2):239.
46. Villena J, Suzuki R, Fujie H, Chiba E, Takahashi T, Tomosada Y, *et al*. Immunobiotic Lactobacillus jensenii modulates the Toll-like receptor 4-induced inflammatory response via negative regulation in porcine antigen-presenting cells. Clinical and Vaccine Immunology. 2012; 19(7):1038-1053. https://doi.org/10.1128/CVI.00199-12
47. Kumar MR, Azizi NF, Yeap SK, Abdullah JO, Khalid M, Omar AR, *et al*. Clinical and preclinical studies of fermented foods and their effects on Alzheimer's disease. Antioxidants. 2022; 11(5):883. https://doi.org/10.3390/antiox11050883
48. Yang HJ, Weon JB, Lee B, Ma CJ. The alteration of components in the fermented Hwangryunhaedok-tang and its neuroprotective activity. Pharmacognosy Magazine. 2011; 7(27):207. https://doi.org/10.4103/0973-1296.84234
49. Yoo KY, Hwang IK, Lim BO, Kang TC, Kim DW, Kim SM, *et al*. Berberry extract reduces neuronal damage and N-Methyl-D-aspartate receptor 1 immunoreactivity in the gerbil hippocampus after transient forebrain ischemia. Biological and Pharmaceutical Bulletin. 2006; 29(4):623-628. https://doi.org/10.1248/bpb.29.623
50. Mocanu MM, Nissen A, Eckermann K, Khlistunova I, Biernat J, Drexler D, *et al*. The potential for β-structure in the repeat domain of tau protein determines aggregation, synaptic decay, neuronal loss, and coassembly with endogenous Tau in inducible mouse models of tauopathy. Journal of Neuroscience. 2008; 28(3):737-48. https://doi.org/10.1523/JNEUROSCI.2824-07.2008
51. Kumar A, Singh A. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological Reports. 2015; 67(2):195-203. https://doi.org/10.1016/j.pharep.2014.09.004
52. Agahi A, Hamidi GA, Daneshvar R, Hamdieh M, Soheili M, Alinaghipour A, *et al*. Does severity of Alzheimer's disease contribute to its responsiveness to modifying gut microbiota? A double blind clinical trial. Frontiers in Neurology. 2018; 9:662. https://doi.org/10.3389/fneur.2018.00662
53. Bonfili L, Cecarini V, Cuccioloni M, Angeletti M, Berardi S, Scarpona S, *et al*. SLAB51 probiotic formulation activates SIRT1 pathway promoting antioxidant and neuroprotective effects in an AD mouse model. Molecular Neurobiology. 2018; 55(10):7987-8000. https://doi.org/10.1007/s12035-018-0973-4
54. Azm SAN, Djazayeri A, Safa M, Azami K, Ahmadvand B, Sabbaghziarani F, *et al*. Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in β-amyloid (1-42) injected rats. Applied Physiology, Nutrition, and Metabolism. 2018; 43(7):718-26. https://doi.org/10.1139/apnm-2017-0648
55. Honarpisheh P, Reynolds CR, Conesa MPB, Manchon JFM, Putluri N, Bhattacharjee MB, *et al*. Dysregulated gut homeostasis observed prior to the accumulation of the brain amyloid-β in Tg2576 mice. International Journal of Molecular Sciences. 2020; 21(5):1711. https://doi.org/10.3390/ijms21051711
56. Wang F, Xu T, Zhang Y, Zheng T, He Y, He F, *et al*. Long-term combined administration of Bifidobacterium bifidum TMC3115 and Lactobacillus plantarum

45 alleviates spatial memory impairment and gut dysbiosis in APP/PS1 mice. FEMS Microbiology Letters. 2020; 367(7). https://doi.org/10.1093/femsle/fnaa048
57. Wang QJ, Shen YE, Wang X, Fu S, Zhang X, Zhang YN, *et al*. Concomitant memantine and Lactobacillus plantarum treatment attenuates cognitive impairments in APP/PS1 mice. Aging (albany NY). 2020; 12(1):628. https://doi.org/10.18632/aging.102645
58. Yeon SW, You YS, Kwon HS, Yang EH, Ryu JS, Kang BH, *et al*. Fermented milk of Lactobacillus helveticus IDCC3801 reduces beta-amyloid and attenuates memory deficit. Journal of Functional Foods. 2010; 2(2):143-152. https://doi.org/10.1016/j.jff.2010.04.002
59. Lee DH, Lee DH, Lee JS. Characterization of a new antidementia β-secretase inhibitory peptide from Saccharomyces cerevisiae. Enzyme and Microbial Technology. 2007; 42(1):83-8. https://doi.org/10.1016/j.enzmictec.2007.08.003
60. Jung IH, Jung MA, Kim EJ, Han MJ, Kim DH. Lactobacillus pentosus var. plantarum C29 protects scopolamine-induced memory deficit in mice. Journal of Applied Microbiology. 2012; 113(6):1498-1506. https://doi.org/10.1111/j.1365-2672.2012.05437.x
61. Lee J, Fukumoto H, Orne J, Klucken J, Raju S, Vanderburg CR, *et al*. Decreased levels of BDNF protein in Alzheimer temporal cortex are independent of BDNF polymorphisms. Experimental neurology. 2005; 194(1):91-96. https://doi.org/10.1016/j.expneurol.2005.01.026
62. Yoshimura M. Cortical changes in the parkinsonian brain: a contribution to the delineation of "diffuse Lewy body disease". Journal of Neurology. 1983; 229(1):17-32. https://doi.org/10.1007/BF00313493
63. Jenco JM, Rawlingson A, Daniels B, Morris AJ. Regulation of phospholipase D2: Selective inhibition of mammalian phospholipase D isoenzymes by α-and β-synucleins. Biochemistry. 1998; 37(14):4901-4909. https://doi.org/10.1021/bi972776r
64. Abeliovich A, Schmitz Y, Fariñas I, Choi-Lundberg D, Ho WH, Castillo PE, *et al*. Mice lacking α-synuclein display functional deficits in the nigrostriatal dopamine system. Neuron. 2000; 25(1):239-252. https://doi.org/10.1016/S0896-6273(00)80886-7
65. Schapira AH. Dopamine agonists and neuroprotection in Parkinson's disease. European Journal of Neurology. 2002; 9:7-14. https://doi.org/10.1046/j.1468-1331.9.s3.9.x
66. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. Journal of Neurochemistry. 2016; 139:318-324. https://doi.org/10.1111/jnc.13691
67. Nishiwaki H, Hamaguchi T, Ito M, Ishida T, Maeda T, Kashihara K, *et al*. Short-chain fatty acid-producing gut microbiota is decreased in Parkinson's disease but not in rapid-eye-movement sleep behavior disorder. MSystems. 2020; 5(6):e00797-20. https://doi.org/10.1128/mSystems.00797-20
68. Nuzum ND, Loughman A, Szymlek-Gay EA, Hendy A, Teo WP, Macpherson H. Gut microbiota differences between healthy older adults and individuals with Parkinson's disease: a systematic review. Neuroscience and Biobehavioral Reviews. 2020; 112:227-241. https://doi.org/10.1016/j.neubiorev.2020.02.003
69. Georgescu D, Ancusa OE, Georgescu LA, Ionita I, Reisz D. Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: is there hope?. Clinical Interventions in Aging. 2016; 11:1601. https://doi.org/10.2147/CIA.S106284
70. Cassani E, Privitera G, Pezzoli G, Pusani C, Madio C, Iorio L, *et al*. Use of probiotics for the treatment of constipation in Parkinson's disease patients. Minerva gastroenterologica e dietologica. 2011; 57(2):117-121.
71. Cassani E, Barichella M, Cancello R, Cavanna F, Iorio L, Cereda E, *et al*. Increased urinary indoxyl sulfate (indican): New insights into gut dysbiosis in Parkinson's disease. Parkinsonism and Related Disorders. 2015; 21(4):389-393. https://doi.org/10.1016/j.parkreldis.2015.02.004
72. Dobbs, R.J., S.M. Dobbs, C. Weller, et al. 2008. Helicobacter hypothesis for idiopathic parkinsonism: before and beyond. Helicobacter 13: 309-322.https://doi.org/10.1111/j.1523-5378.2008.00622.x
73. Çamcı G, Oğuz S. Association between Parkinson›s disease and Helicobacter pylori. Journal of Clinical Neurology. 2016; 12(2):147-150. https://doi.org/10.3988/jcn.2016.12.2.147
74. Hashim H, Azmin S, Razlan H, Yahya NW, Tan HJ, Manaf MR, *et al*. Eradication of Helicobacter pylori infection improves levodopa action, clinical symptoms and quality of life in patients with Parkinson's disease. PLoS One. 2014; 9(11):e112330. https://doi.org/10.1371/journal.pone.0112330
75. Pompei A, Cordisco L, Amaretti A, Zanoni S, Matteuzzi D, Rossi M. Folate production by bifidobacteria as a potential probiotic property. Applied and Environmental Microbiology. 2007; 73(1):179-185. https://doi.org/10.1128/AEM.01763-06

76. Surwase SN, Jadhav JP. Bioconversion of L-tyrosine to L-DOPA by a novel bacterium Bacillus sp. JPJ. Amino acids. 2011; 41(2):495-506. https://doi.org/10.1007/s00726-010-0768-z
77. Dinan TG, Borre YE, Cryan JF. Genomics of schizophrenia: time to consider the gut microbiome?. Molecular Psychiatry. 2014; 19(12):1252-1257. https://doi.org/10.1038/mp.2014.93
78. Nemani K, Ghomi RH, McCormick B, Fan X. Schizophrenia and the gut-brain axis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2015; 56:155-160. https://doi.org/10.1016/j.pnpbp.2014.08.018
79. Na KS, Jung HY, Kim YK. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2014; 48:277-286. https://doi.org/10.1016/j.pnpbp.2012.10.022
80. Okubo R, Koga M, Katsumata N, Odamaki T, Matsuyama S, Oka M, *et al*. Effect of bifidobacterium breve A-1 on anxiety and depressive symptoms in schizophrenia: A proof-of-concept study. Journal of Affective Disorders. 2019; 245:377-385. https://doi.org/10.1016/j.jad.2018.11.011
81. Severance EG, Gressitt KL, Stallings CR, Katsafanas E, Schweinfurth LA, Savage CL, *et al*. Probiotic normalization of Candida albicans in schizophrenia: A randomized, placebo-controlled, longitudinal pilot study. Brain, behavior, and immunity. 2017; 62:41-45. https://doi.org/10.1016/j.bbi.2016.11.019
82. Tomasik J, Yolken RH, Bahn S, Dickerson FB. Immunomodulatory effects of probiotic supplementation in schizophrenia patients: a randomized, placebo-controlled trial. Biomarker Insights. 2015; 10:BMI-S22007. https://doi.org/10.4137/BMI.S22007
83. Dickerson FB, Stallings C, Origoni A, Katsafanas E, Savage CL, Schweinfurth LA, *et al*. Effect of probiotic supplementation on schizophrenia symptoms and association with gastrointestinal functioning: A randomized, placebo-controlled trial. The primary care companion for CNS disorders. 2014; 16(1):26294. https://doi.org/10.4088/PCC.13m01579
84. Dokuyucu R, Kokacya H, Inanir S, Copoglu US, Erbas O. Antipsychotic-like effect of minocycline in a rat model. International Journal of Clinical and Experimental Medicine. 2014; 7(10):3354.
85. Jhamnani K, Shivakumar V, Kalmady S, Rao NP, Venkatasubramanian G. Successful use of add-on minocycline for treatment of persistent negative symptoms in schizophrenia. The Journal of Neuropsychiatry and Clinical Neurosciences. 2013; 25(1):E06-E07. https://doi.org/10.1176/appi.neuropsych.11120376
86. Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, Trivedi MH, *et al*. American Psychiatric Association practice guidelines for the treatment of patients with major depressive disorder. American Journal of Psychiatry. 2010; 167(Suppl 10):9-118.
87. Gruenberg AM. Manic-depressive illness: Bipolar disorders and recurrent depression, by FK Goodwin and KR Jamison.(Pp. 1288; $99.00; ISBN 0195135794.) Oxford University Press: New York. 2007. Psychological Medicine. 2008; 38(1):147-148. https://doi.org/10.1017/S0033291707001936
88. Gitlin MJ, Swendsen J, Heller TL, Hammen C. Relapse and impairment in bipolar disorder. The American Journal of Psychiatry. 1995.
89. Dickerson F, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C, *et al*. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: a randomized controlled trial. Bipolar Disorders. 2018; 20(7):614-621. https://doi.org/10.1111/bdi.12652
90. Reininghaus EZ, Wetzlmair LC, Fellendorf FT, Platzer M, Queissner R, Birner A, *et al*. The impact of probiotic supplements on cognitive parameters in euthymic individuals with bipolar disorder: A pilot study. Neuropsychobiology. 2020; 79(1-2):63-70. https://doi.org/10.1159/000492537
91. McGuinness AJ, Davis JA, Dawson SL, Loughman A, Collier F, O'Hely M, *et al*. A systematic review of gut microbiota composition in observational studies of major depressive disorder, bipolar disorder and schizophrenia. Molecular Psychiatry. 2022; 27(4):1920-1935. https://doi.org/10.1038/s41380-022-01456-3
92. Nemeroff CB. The role of GABA in the pathophysiology and treatment of anxiety disorders. Psychopharmacology Bulletin. 2003; 37(4):133-146.
93. Gallo AT, Hulse GK. A theory of the anxiolytic action of flumazenil in anxiety disorders. Journal of Psychopharmacology. 2022.
94. Swartz M, Landerman R, George LK, Melville ML, Blazer D, Smith K. Benzodiazepine anti-anxiety agents: prevalence and correlates of use in a southern community. American Journal of Public Health.

1991; 81(5):592-596. https://doi.org/10.2105/AJPH.81.5.592
95. Reis DJ, Ilardi SS, Punt SE. The anxiolytic effect of probiotics: A systematic review and meta-analysis of the clinical and preclinical literature. PloS One. 2018; 13(6):e0199041. https://doi.org/10.1371/journal.pone.0199041
96. Foster JA, Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. Trends in neurosciences. 2013; 36(5):305-312. https://doi.org/10.1016/j.tins.2013.01.005
97. Hadizadeh M, Hamidi GA, Salami M. Probiotic supplementation improves the cognitive function and the anxiety-like behaviors in the stressed rats. Iranian Journal of Basic Medical Sciences. 2019; 22(5):506.
98. Eskandarzadeh S, Effatpanah M, Khosravi-Darani K, Askari R, Hosseini AF, Reisian M, *et al*. Efficacy of a multispecies probiotic as adjunctive therapy in generalized anxiety disorder: A double blind, randomized, placebo-controlled trial. Nutritional Neuroscience. 2021; 24(2):102-108. https://doi.org/10.1080/1028415X.2019.1598669