InSight Bulletin: A Multidisciplinary Interlink International Research Journal
Peer Reviewed International, Open Access Journal.
ISSN : 3065-7857 / Website: https://ibrj.us / Volume-2, Issue-4 / April - 2025

Original Article

Gut–Brain Axis: Role of Gut Microbiota on Neurological Diseases and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to improve Brain Functions

Shruti Narayankar
D.S.T.S Mandal's College of Pharmacy, Solapur, Maharashtra, India.

Manuscript ID:
IBMIIRJ -2025-020412

Submitted: 03Mar 2025

Revised: 17 Mar 2025

Accepted: 04 Apr 2025

Published: 30 Apr 2025

ISSN: 3065-7857

Volume-2

Issue-4

Pp. 66-72

April 2025

Correspondence Address:
Shruti Narayankar
D.S.T.S Mandal's College of Pharmacy, Solapur, Maharashtra, India.
Email:
shrutinarayankar2002@gmail.com

OPEN ACCESS

Quick Response Code:

Web. https://ibrj.us

DOI: 10.5281/zenodo.16153283

DOI Link:
https://doi.org/10.5281/zenodo.16153283

Creative Commons

Abstract

The gastrointestinal tract (GIT) has the largest and most vulnerable surface, and the gut microbiota plays a crucial role in observing meals, nutrients, and environmental variables as well as differentiating commensals from invasive infections.In the context of health and illness, it is commonly known that the stomach and the central nervous system (CNS) are closely related. A healthy gut with a diverse range of bacteria is essential for normal brain and emotional functioning. Most of the gastrointestinal physiology is also under direction of the central nervous system. Gut homeostasis and healthy digestion are maintained by the intricate and reciprocal molecular interactions between the gut/microbiome and the central nervous system. A number of other processes, including as neuronal, endocrine, toll-like receptor, and metabolite-dependent pathways, have also been hypothesized. Since the pathophysiology of neurological and gastrointestinal problems is associated with changes in the reciprocal interaction between the GIT and CNS, the microbiota/gut-and-brain axis is a new and well recognized idea. In this review, we highlight the most current research demonstrating the immune system and gut microbiota's roles in both the development of neurological illnesses and the preservation of brain function. Furthermore, using the gut–brain axis idea, we emphasize the current developments in the treatment of neurological disorders through the use of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation.

Keywords : *Gut microbiota; gut-brain axis; neurological disorder; Alzheimer's disease; probiotics; prebiotics; synbiotics*

Introduction

The majority of microorganisms are known as gut microbiota (GM) and are found in the human gastrointestinal system. The GM's population and composition are influenced by a number of variables. As a result, it can vary according on the type of host. Two minor phyla (Verrucomicrobia and Fusobacteria) and four major phyla (Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria) make up the GM. [1] In order to preserve gut homeostasis and boost host immunity, these commensal bacteria not only interact with one another but also with the host gut epithelium. When the host is well, the gut-dwelling bacteria have a number of positive benefits; but, when the host is ill or disrupted, they have been linked to the development of a number of illnesses, including neurological conditions. [2] There is mounting evidence that the stomach and brain communicate strongly in both directions, which is essential for preserving gut homeostasis and brain function. The bidirectional relationship is thought to be altered by neurological conditions like stress, multiple sclerosis (MS), autistic spectrum disorder (ASD), Parkinson's disease (PD), and Alzheimer's disease (AD). Irritable bowel syndrome (IBS) and other brain-gut problems are believed to emerge as a result of this [3,4]. Furthermore, the pathophysiology of gut-brain illnesses has been linked to the alteration of gut bacterial composition and the loss of gut homeostasis, which are frequently linked to dietary patterns, antibiotic use, and bacterial and viral infections.

How to cite this article:
Narayankar, S. (2025). Gut–Brain Axis: Role of Gut Microbiota on Neurological Diseases and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to improve Brain Functions. Insight Bulletin: A Multidisciplinary Interlink International Research Journal, 2(4), 66–72. https://doi.org/10.5281/zenodo.16153283

[5]The chemical process underlying the bidirectional link between the gut and the brain, however, is still the subject of intense debate. Compared to specific pathogen-free (SPF) and GF-conventional mice, germ-free (GF) mice show abnormalities in the development of the gastrointestinal tract, indicating the importance of commensal gut bacteria for the early postnatal development [6,7]. Similarly, GM restores normal gut-brain communication and intrinsic and extrinsic nerve function in GF rats, according to McVey et al. [8]. These studies support the crucial function of the GM and its effects on the central nervous system's (CNS) early development. Thus, this review offers a summary of the available data indicating that the gut microbiota, together with its metabolites and cellular constituents, play a role in the development of a number of neurological disorders. Additionally, the many therapy approaches that are employed to treat these conditions are discussed.

Interaction of Gut and Nervous System: Gut–Brain Axis

Anatomically speaking, the gut-brain axis is a complicated and reciprocal connection between the gut and the central nervous system that interacts in both healthy and sick states [3]. The central nervous system (CNS), which regulates reflexes and mood swings, may be impacted by gut sensory visceral signals that go down the vagus nerve as a result of this crosstalk. These signals are subsequently used by the brain to alter gut physiology and other functions (Figure 1). Afferent (a neuron that receives signals) and efferent (a neuron that transmits signals) neurons are involved in connecting neuronal pathways and transferring signals through a variety of pathways, such as the hypothalamic–pituitary–adrenal (HPA) axis, sympatho-adrenal axis, descending monoaminergic pathways, autonomic nervous system (ANS), and enteric nervous system (ENS) [3,9]. A complex network of neurons called the ENS is primarily responsible for the intrinsic innervation of gastrointestinal functions. It is made up of the myenteric and submucosal plexuses, two ganglionated plexuses that control secretion, absorption, and intestinal movement (peristalsis)[10].

Sensation peregrination via primary afferent neurons and vagal afferent pathways in gut–brain transmission, while the ENS uses intestinofugal neurons to transmit information from the central nervous system(CNS) to the sympathetic nervous system(SNS) ganglia [10]. The sympathetic (Splanchic) and parasympathetic (vagal–sacral) nerves make up the ANS, a neural relay network [3]. The ANS regulates breathing, heartbeat, and CNS-mediated alterations in the gut and its functions, such as digestion, gut motility and permeability, bile secretion, glucose levels, mechanical distortion of the mucosa, maintenance of epithelial fluid level, luminal osmolality, mucus production, and mucosal immune response, in parallel with neuronal and neuroendocrine signaling [3,11]. By sending direct neurological reactions to the stomach through the central nervous system, the ANS alters the physiology of the gut. Through their metabolites, which are detected by the host cells, the gut microbiota interacts with the ANS gut synapses and exchanges information [12]. Furthermore, by altering how gut immune cells react to bacteria or by switching the roles of microbes and gut immune cells, the ANS can directly or indirectly influence the mechanisms of the gut epithelium that contribute to immune system activation [13].

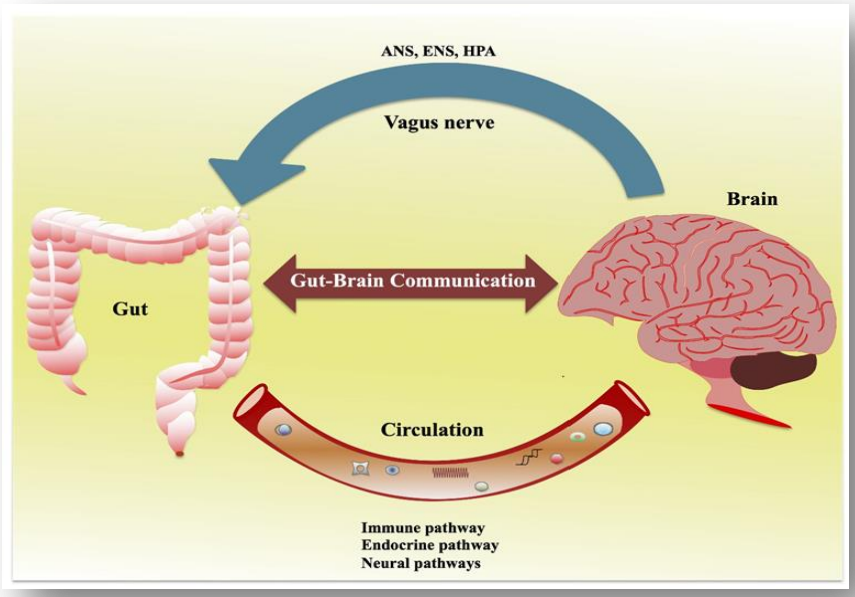

Figure 1: Diagrammatic representation showing how the brain and gastrointestinal tract interact. Numerous pathways, including the autonomic nervous system (ANS), enteric nervous system (ENS), hypothalamic-pituitary-adrenal (HPA), immunological processes, endocrine systems, and brain pathways, have a substantial impact on this two-way link.

Gut–Brain Axis and the Microbiota:

There is mounting evidence that the gut microbiota is a major player in the gut–brain axis [3]. As a result, changes in the composition of gut bacteria may have an impact on brain processes and vice versa [14]. Pattern recognition receptors (PRRs), such as Toll-like receptors 2 and 4 (TLR2 and TLR4), may be impacted by the gut microbiota in connection with the endocrine and central nervous systems' development, functions, and diseases [9,15]. The progression and development of various neurological diseases are caused by gut dysbiosis and the associated loss of intestinal permeability and gut barrier integrity, which allow gut-bacteria-derived metabolites and microbes-associated molecular patterns (MAMPs) to increase in translocation into mesenteric lymphoid tissues [16,17]. Enteric bacteria have a determinable effect on ENS tropism, as evidenced by an animal study that found mice with altered gut microbiota composition or lacking enteric bacterial composition had fewer

myenteric neurons and a higher incidence of bowel motor dysfunctions [6]. In comparison to standard control mice, the GF animals also showed altered neurotransmission, altered amino acid metabolism, dysregulated hormone signaling, and decreased expression of brain-derived neurotrophic factor (BDNF) [18,19,20]. According to a different study done on Drosophila, gut microorganisms increased the production of metabolites, which in turn controlled locomotor activity [21].The frontal cortex, striatum, and hippocampus of GF mice showed reduced expressions of occludin and claudin-5 and an elevated blood–brain barrier (BBB) [22]. In GF mice, colonization by B. thetaiotaomicron and C. tyrobutyricum increased the expression levels of tight-junction proteins, which decreased paracellular permeability [22]. Furthermore, GF mice's ENS showed notable abnormalities, but these abnormalities disappeared once the GF mice colonized with altered Schaedler flora (ASF), suggesting that the particular bacterial flora plays a part in the development of ENS [7]. When GF mice were colonized with microbiota from specific pathogen-free(SPF) donor mice, their intrinsic sensory signaling, which is crucial for CNS communication, was similarly restored [8]. Additionally, alterations in the makeup of the antibiotic-mediated gut microbiota impact neurochemistry, ENS shape and function, and the quantity of ganglia-resident enteric glial cells in vivo [23]. There is evidence that the unique function of native gut bacteria in GF adult mice in controlling the migration and homeostasis of the network of mucosal enteric glial cells is not restricted to the postnatal period [24]. Additionally, the pathogenic bacterial effects on the neurological system, which are mediated through the stimulation of the host immune system, were accessed through infection in a mouse model. Via vagal sensory neurons, the infected Campylobacter rodentium-infected mice displayed anxiety-like behavior; yet, their plasma levels of proinflammatory cytokines were identical to those of the control group [25] A Campylobacter jejuni infection in the medulla oblongata of mice causes c-Fos, a neuronal activation marker in the nucleus tractus solitaries (NTS) and vagal sensory ganglia, to become active.[26]. These investigations suggest that the gut-brain link is bidirectional, which is a key factor in explaining how the gut microbiota and host work together to access the gut-brain axis signaling to control host behavior, emotions, and moods [27].

Gut Microbiota on CNS and ENS Disorders

In addition to preserving health, gut-brain crosstalk has been linked to the emergence of neurological and psychological disorders when the gut-brain axis is disrupted [28,29].However, gut microorganisms and their neuroactive metabolites and other components are translocated due to increased intestinal permeability, which triggers a neuroinflammatory response in the brain.

Alzheimer's Disease

Dementia in older adults is the collective term for Alzheimer's disease (AD), a prevalent neurological ailment characterized by a decline in thinking, language, activities, memory, and cognitive abilities. The overproduction and deposition of Aβ, together with the translocation of microorganisms and their products into the brain, where they may promote neuroinflammation and neurodegeneration changes, are the main reasons why AD is often associated with a growing cerebral accumulation of Aβ [30, 31]. When proteases cleave the amyloid precursor protein (APP), a 40–42 amino acid peptide known as Aβ42 is produced. Because it triggers the neuroinflammatory response, it plays a significant part in the pathophysiology of AD [32]. Additionally, when GF APP transgenic (TG) mice were compared to control mice with gut microbiota, a significant reduction in the degree of cerebral Aβ amyloid pathology was observed. It's interesting to note that TG animals colonized with wild-type mouse gut microbiota had lesser effects on raising cerebral Aβ levels than TG mice given gut microbiota from typical APP transgenic mice, which led to an increase in cerebral Aβ pathology [33]. Bauerl et al. [34] have documented comparable results, noting alterations in the composition of the gut microbiota in the transgenic APP/PS1 mouse model of AD. It was shown that the inflammatory-related Erysipelotrichaceae family was more common in TG mice compared to wild-type control mice [34]. Additionally, compared to normal mice, transgenic APP/PS1 animals displayed decreased Aβ pathology [35], suggesting that the gut microbiota may play a role in the pathophysiology of both AD and Aβ pathology. In a different in vivo study, TG APPswe/PS1dE9 mice exhibited increased brain deposition of Aβ peptide, Tau protein, COX-2, and CD11b, and decreased expression of synapsin I and postsynaptic density protein 95 (PSD-95) [36]. TG animals that were given a transplant of the fecal microbiota from WT mice demonstrated improvements in gut microbiota composition, amyloid peptide, p-tau protein level, and synaptic plasticity compared to WT mice [36].As evidenced by the elevated intestinal Aβ burden, AβPP, CD68, and p-Tau positivity observed in both AD patients and APP/PS1 mice, the intestines of AD patients may reflect the brain and induce inflammatory and immunological changes linked to AβPP and Aβ pathology [37]. Furthermore, studies on the modulatory action of prebiotics against AD have shown that fructooligosaccharides reduced neurodegeneration and cognitive deficits in TG APP/PS1 mice by downregulating p-JNK and GLP1R and upregulating PSD-95, synapsin I, and GLP-1 [38]. The newly created animal model of AD, known as TG mice, has been shown to exhibit amyloid plagues, neurofibrillary tangles, reactive gliosis in the brain with memory deficits, intestinal inflammation, and loss of intestinal barrier integrity.Transplanting the intestinal microbiota from wild type mice helped to ameliorate these symptoms [39]. Reactive gliosis (microgliosis and astrocytosis) and amyloid-β plaque development are not essential for the production of cognitive deficits in the APP knock-in mice (APPNL-G-F/NL/G-F) model of AD [40]. Furthermore, they observed that APPNL-G-F/NL/G-F mice lacked spatial memory, whereas APPNL/NL animals exhibited intact spatial learning and memory, which was on par with WT mice [40].Furthermore, Reference Leblhuber et al. [41] investigated the amount of calprotectin in the feces of 22 AD patients. Furthermore, AD patients showed changed gut microbial composition, which may be related to the pathophysiology of AD [42]. In vivo, older AD patients showed a larger percentage of taxa linked to neurological illnesses (Odoribacter splanchnicus) and proinflammatory states (Bacteroides vulgatus, B. fragilis, and Eggerthella lenta) and a reduced abundance of butyrate-producing bacteria [43].Symptomatic AD animals showed altered gut microbiota and dysregulated gut homeostasis [44]. Furthermore, compared to individuals who were matched for age and sex, Vogt et al. [45], who detailed the taxonomic composition of the fecal microbiota from 25 AD patients, found a decreased microbial diversity that varied compositionally.These alterations were closely linked to Aβ pathology and p-tau protein in the patient subgroup [45]. The abundance of inflammatory taxa Escherichia/Shigella increased with higher levels of IL-1β, CXCL2, NLRP3, and Aβ peptide, while the abundance of anti-inflammatory E.rectale and B.fragilis decreased in older patients compared to healthy controls and subjects with cognitive impairment but no Aβ pathology [46]. Additionally, they lacked conclusive AD [47–

48]. Furthermore, it has been shown that proinflammatory gut bacteria such as Salmonella, Bacillus, Mycobacterium, E. coli, and Staphylococcus can induce dysbiosis, which can lead to neuroinflammation and cerebral Aβ accumulation in AD patients [49].Not only can bacteria have an impact on the pathophysiology of AD, but viruses have also been linked to the disease [50]. To fully comprehend the impact of the microbiome on the gut–brain axis in AD, more research is still required.

Parkinson's Disease

With an estimated seven to ten million people affected worldwide, Parkinson's disease (PD) is the second most common neurological disease [51]. The presence of both motor and non-motor symptoms is what essentially defines Parkinson's disease. Slowness of movement, rigidity, and resting tremors are the most prominent signs of motor complaints. For non-motor symptoms, cognitive issues, depression, mood changes, sensory alterations, sleep disturbances, and autonomic dysfunctions significantly contribute to disability. This extensive clinical variety highlights the buildup of α-synuclein in both the central and peripheral nervous systems [52, 53]. Most PD patients experience gastrointestinal (GI) symptoms. People with Parkinson's disease (PD) have been found to exhibit a variety of gastrointestinal symptoms, such as defecatory dysfunction, constipation, nausea, dysphagia, hypersalivation, and changes in bowel patterns [54]. In PD, enteric α-synucleinopathy results from the migration of gut bacteria and other microbiological components that promote inflammation and oxidative stress in the ENS due to elevated intestinal permeability [55]. Helicobacter pylori (HP) infection and its related consequences (gastric ulcers) have been connected with Parkinson's disease (PD) since the 1960s [56].Treating HP infection with medications improves PD symptoms [57]. Several studies provide supporting evidence that hypothesizes a connection between the gut and the resident microbiota and PD. Increased occurrences of postural instability and aberrant gait were positively connected with these alterations [58]. α-synuclein, a presynaptic neuronal protein linked to motor impairment and neuroinflammatory disorders, was found to increase in GF mice that were given fecal microbiota from PD patients [59]. Changes in the composition of the gut microbiota were also found in an animal investigation using a model of PD mice that was chemically created [60]. A recent study indicated that the relative abundance of mucin-degrading Verrucomicrobiae and LPS-producing Gammaproteobacteria was found to be greater in both PD patients and a human α-synuclein overexpressing mice model of PD (Thy-αSyn) when compared with healthy and wild-type controls. At 10 weeks, Thy-αSyn mice's early motor symptoms were made worse by LPS therapy [61]. In a mouse model of Parkinson's disease, they found that fecal microbiota transplantation (FMT) increased striatal DA and 5-HT while decreasing microbial dysbiosis, fecal SCFAs, and physical deficits. Additionally, they observed that FMT protects PD animals by reducing TLR4/TNF-α signaling in the gut and brain, as well as the activation of microglia and astrocytes [62]. The authors also showed that rotenone treatment may repair or lessen similar gut and neurological abnormalities in TLR4-KO mice, indicating that TLR4-induced inflammatory signaling is important for gut and brain inflammation in Parkinson's disease [63]. LPS-induced PD mouse models showed a drop in ferroportin (Fpn) levels and an increase in microglial activation levels, proinflammatory cytokine production, and heme oxygenase-1 (HO-1) [64].

Multiple Sclerosis

Another prevalent neurological condition affecting the central nervous system that causes an immunological reaction that damages the myelin layer is multiple sclerosis (MS). It is characterized by symptoms include changes in sensory perception, motor dysfunction, and impaired vision. [65] Several studies have found that the gut microbiota profile in MS patients differs from that of healthy individuals [66, 67]. Proinflammatory T cell activation is reduced by the rise in regulatory T cells (Treg) brought on by the changes in gut microorganisms [68]. Increased blood–brain barrier (BBB) permeability and CNS inflammation were the outcomes of the elevated amounts of circulating Th1 and Th17 cells [65]. Importantly, autoimmune encephalomyelitis (EAE) was more common in transgenic mice that received fecal microbiota from MS patients than in mice that received microbiota from healthy people [68]. In a mouse model of EAE, mice treated with a variety of antibiotics did not experience axon damage or motor impairment, while bacterial recolonization hampered both [69]. In mice with EAE, they also found that antibiotic-induced microbiota depletion could improve learning and memory abilities while lowering hippocampus BDNF. In EAE-induced rats, they also observed reductions in symptoms associated with sadness and increases in anxiety-like behavior and hippocampus TNF-a and IL-1β [70]. The relationship between gut microbiota and the degree of neurological illness in the progressive MS model was confirmed by these studies.

Gut Microbiota on Depression

Although depression is a common illness, major depressive disorder (MDD) is currently recognized as the most serious mental health problem in the world. In both human [71] and animal depressed models, MDD has been observed to be associated with increased levels of proinflammatory cytokines and altered gut microbiota composition [72,73]. Patients with depression were shown to have higher amounts of Bacteroidetes and Proteobacteria and lower levels of Firmicutes [71].
Recently, in a large cohort study focusing on microbiomes, Dialister and Coprococcus spp. were found to be reduced in individuals experiencing depression [74]. Compared to patients with depression who did not commit suicide and to normal control subjects, patients who died by suicide had significantly lower urinary outputs of DOPAC and homovanillic acid as well as lower total body outputs of sum dopamine [75]. Using a PubMed literature search, a study team recently investigated the relationship between gut microbiota and MDD [48].The researchers indicated that a higher prevalence of nine genera (Anaerostipes, Blautia, Clostridium, Klebsiella, Lachnospiraceae incertae sedis, Parabacteroides, Parasutterella, Phascolarcobacterium, and Streptococcus) and a lower presence of six genera (Bifidobacterium, Dialister, Escherichia/Shigella, Faecalibacterium, and Ruminococcus) were identified in MDD [48]. In conclusion, gut microbes have the potential to improve neurological diseases and brain function.

Therapeutic Treatment

Probiotics/Prebiotics/Synbiotics/Antibiotics

As of right now, pro/pre/synbiotics are being used more often in a variety of fields, especially in the clinical and medical fields. According to their definition, probiotics are live bacteria that, when consumed in sufficient quantities, benefit the host's health. Prebiotics are indigestible dietary fibers that specifically increase the growth and activity of gut microorganisms, mainly Lactobacillus and Bifidobacterium, hence improving host health [76]. Prebiotics and probiotics are combined to form what

are known as synbiotics. Improving intestinal and immunological homeostasis and restoring gut microbiota are the most commonly reported positive benefits of probiotics [77, 78]. Moreover, it has been documented that probiotics exhibit modulatory effects on CNS diseases, including the normalization of behaviors resembling anxiety and depression [79, 80] along with a decrease in ASD [81]. According to a randomized, double-blind, placebo-controlled study, taking probiotic L. plantarum PS128 for four weeks significantly reduced ASD symptoms when compared to the placebo group [82]. In mice using an AD model, the probiotic treatment markedly improved brain function [83]. In rats with AD, Razaeiasi et al. [84] looked into how probiotics affected memory and spatial learning in addition to a few other factors. Additionally, after 10 weeks, rats given oral probiotics (L. reuteri, L. rhamnosus, and B. infantis) showed a significant improvement in spatial memory as well as a decrease in oxidative (MDA), inflammatory (IL-1β and TNF-α), and Aβ plaques [85]. By modifying gut microbiota and an anti-inflammatory peripheral immune response, probiotics (L. paracasei, L. plantarum, L. acidophilus, L. delbrueckii, B. longum, B. infantis, B. breve, and Streptococcus thermophilus) given daily for two months alleviated MS symptoms in MS patients [86]. Furthermore, in mice that received a multiple sclerosis peptide vaccination, the probiotic S. thermophilus ST285 reduced pro-inflammatory (IL-1β and IFN-γ) and anti-inflammatory (IL-4, IL-5, and IL-10) cytokines [87]. Probiotic formulation SLAB51 has been observed to reduce Aβ aggregation, brain damage, neuronal proteolysis, and cognitive impairment in AD animals [88].

In a model of AD mice, it also increases antioxidant and neuroprotective properties via activating the SIRT1 pathway [89]. After taking probiotics (L. acidophilus, B. bifidum, and B. longum) along with selenium for 12 weeks, AD patients showed improvements in a number of metabolic markers and cognitive abilities [90]. Compared with selenium alone and a placebo, probiotic and selenium consumption significantly reduced high sensitivity CRP, insulin, serum lipids, HOMA-IR, VLDL, and LDL levels and significantly increased total antioxidant capacity [90]. Seniors with memory problems who used B. breve A1 supplements for 12 weeks showed improved cognitive performance in a randomized, double-blind, placebo-controlled study [91].Consuming the same strain, B. breve A1, at four weeks significantly improved the Positive and Negative Syndrome Scale (PANSS) and the hospital anxiety and depression scale (HADS) score in an open-label single-arm research [92]. According to a meta-analysis of randomized controlled studies, probiotic use improved cognitive abilities in participants with AD and moderate cognitive impairment (MCI), possibly by lowering oxidative and inflammatory marker levels [93]. On the other hand, a meta-analysis of randomized controlled trials found no discernible difference in the reduction of anxiety and depression symptoms between probiotics/prebiotics and a placebo [94, 95].By altering the brain-derived neurotrophic factor (BDNF) pathway and improving the P13K/Akt, pTrK, pERK5, and p-CREB pathways while decreasing the p-JNK, ERK-1, and P75 pathways in human neuroblastoma cells, the probiotic formulation SLAB51 recently showed a neuroprotective effect in vitro. Additionally, probiotics have been demonstrated to protect dopaminergic neurons in the substantia nigra and striatum of PD rats and amplify behavioral abnormalities [96].Probiotics L. salivarius (LS01) and L. acidophilus (LA02) significantly reduced the levels of pro-inflammatory cytokines and reactive oxygen species (ROS) and increased the anti-inflammatory cytokines in Peripheral blood mononuclear cells (PBMCs) from PD patients and healthy controls [97]. Consuming fermented milk that contains various probiotic strains and prebiotic fibers has been shown to help PD patients with constipation in a randomized, double-blind, placebo-controlled research [98]. Patients with Parkinson's disease who drank fermented milk with L. casei Shirota reported less bloating and stomach pain in addition to improvements in stool consistency [99]. Furthermore, the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and specific metabolic profiles in PD patients improved after taking probiotics in the form of capsules (L. acidophilus, L. reuteri, L. fermentum, and B. bifidum) for 12 weeks [100]. When compared to a placebo, probiotic consumption has also been shown to increase glutathione and insulin sensitivity while decreasing levels of insulin, insulin resistance, malondialdehyde, and high-sensitivity C-reactive protein [100].Memory impairments, cerebral neuronal and synaptic damage, microglia activation, and microbial composition in the feces and brains of elderly mouse models were all improved by probiotic-4 (B. lactis, B. bifidum, L. casei, and L. acidophilus) supplementation [101]. Chronic stress-induced sadness and anxiety-like behavior were reversed in mice treated with B. breve CCFM1025, and changes in the gut microbiome were observed in vivo [102]. It has decreased the pCREB-c-Fos signaling pathway and raised BDNF, SCFAs, and 5-hydroxytryptophan (5-HTP) levels. A type of gut bacterium called Akkermansia muciniphila (Akk) has probiotic properties that help prevent a number of illnesses.When given to APP/PS1 animals, Akk led to a decrease in cerebral Aβ 40–42 in vivo, as well as a drop in fasting blood glucose, lipids, and serum diamine oxidase [103]. Also, prebiotics have been shown to improve brain function and prevent neurological conditions such ASD [108], PD [107], IBS [106], AD [104], and dementia [105]. By focusing on the microbiota-gut-brain axis, the fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) therapies improve behaviors associated with anxiety and depression in mice under chronic stress [109].The use of prebiotics was successful in elevating cecal short-chain fatty acids (SCFAs) such as acetate and propionate while decreasing proinflammatory cytokines and corticosterone induced by chronic stress in affected mice [110]. According to a preliminary trial, giving synbiotics to patients with hepatic encephalopathy increased their cognitive abilities [111]. In both in vitro and humanized mice models, human milk oligosaccharides (HMOS) have demonstrated symbiotic effects when used in conjunction with B. longum subsp. infantis as infant prebiotics [112]. A transgenic humanized Drosophila model of Alzheimer's disease showed improved motility and survival, while acetylcholinesterase activity and Aβ buildup were reduced by a new synbiotic that included Triphala and L. plantarum, L. fermentum, and B. longum subsp. infantis [113].By activating the PPAR-γ pathway, it also reduced oxidative, immunological, and inflammatory indicators in addition to mitochondrial stress. Treatment for this mood disorder included a probiotic mixture [118], synbiotics [114], and several strain probiotics, including L. acidophilus, L. casei, and B. bifidum [115], L. rhamnosus HN001 [116], and C. butyricum [117]. Furthermore, the best adjunctive therapy for depressive disorders are supplements that contain polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA), and folate-based N-acetylcysteine [119]. According to a systematic study, probiotics, prebiotics, and synbiotics offer beneficial therapeutic strategies for improving cognitive abilities and reducing behavioral and psychiatric symptoms in individuals with dementia [105]. As previously stated, gut microbes play a crucial role in neurological disorders like AD. It has been shown that taking antibiotics alters the bacterial composition of the stomach, which may or may not affect how the brain operates [120,121]. In AD patients, the medications omeprazole, amoxicillin, and clarithromycin improved brain function by lowering Helicobacter pylori levels [122]. Non-absorbable antibiotic therapy reduces the amount of motor impairment in the PD rat model, the generation of proinflammatory cytokines in the striatum, and the

dopaminergic neuronal death brought on by 6-hydroxydopamine (6-OHDA) [123]. In AD mice, the treatment of minocycline, rapamycin, and rifampicin decreased microglial activity, inflammatory cytokine levels, and Aβ [124,125,126].

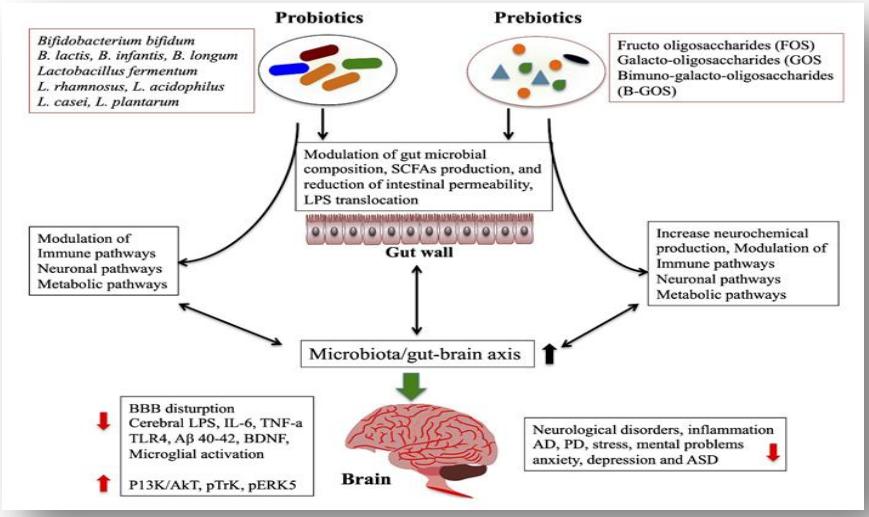

Figure 2: Probiotics and prebiotics' impact on improving the gut-brain axis and microbiota. By increasing the production of SCFAs and neurochemicals, reducing intestinal permeability, and changing the gut microbial structure, as well as immune, metabolic, and neural pathways, the presence of probiotics, prebiotics, or both has been demonstrated to exacerbate neurological problems. (Up and down-regulation are indicated by ↑ ↓).

Conclusion

To sum up, different neurological viewpoints on the gut–brain axis suggest that the gut microbiota have strong two-way communication with the central nervous system (CNS) and control the growth and influence the development and activity of the central nervous system (CNS), which subsequently helps maintain balance within the gut environment. Brain dysfunction affects GI physiology, affecting digestion and gut microbial diversity. The mechanisms behind this axis are very complex, involving multiple pathways directly and indirectly. Intestinal permeability is a promising factor influencing or impacting CNS/ENS functions. Metabolites and gut-derived components are important components that migrate to the brain, disrupt the blood-brain barrier, activate microglia, and set off inflammatory immune pathways. Nevertheless, the mechanisms that directly impact CNS/ENS functions through gut-derived metabolites/components remain ambiguous. It would be extremely helpful to assess treatment strategies like probiotics, prebiotics, dietary components, and FMT in patients with neurological conditions and altered gut microbiota composition. This would help us better understand the beneficial or detrimental effects of gut microbiota on the brain through the gut–brain axis.

Acknowledgements

I would like to express my special thanks of gratitude to the management of D.S.T.S Mandal's College of Pharmacy, Solapur, India. The authors of this review paper, Gut–Brain Axis: Role of Gut Microbiota on Neurological Diseases and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to improve Brain Functions, would also like to thank their teaching staff and friends for their invaluable assistance.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1. Eckburg, P.B.; Bik, E.M.; Bernstein, C.N.; Purdom, E.; Dethlefsen, L.; Sargent, M.; Gill, S.R.; Nelson, K.E.; Relman, D.A. Diversity of the human intestinal microbial ora. *Science* **2005**, *308*, 1635–1638. [CrossRef] [PubMed]
2. Gubert, C.; Kong, G.; Renoir, T.; Hannan, A.J. Exercise, diet and stress as modulators of gut microbiota: Implications for neurodegenerative diseases. *Neurobiol. Dis.* **2020**, *134*, 104621. [CrossRef] [PubMed]
3. Mayer, E.A. Gut feelings: The emerging biology of gut-brain communication. *Nat. Rev. Neurosci.* **2011**, *12*, 453–466. [CrossRef] [PubMed]
4. Pellegrini, C.; Antonioli, L.; Colucci, R.; Blandizzi, C.; Fornai, M. Interplay among gut microbiota, intestinal mucosal barrier and enteric neuro-immune system: A common path to neurodegenerative diseases? *Acta Neuropathol.* **2018**, *136*, 345–361. [CrossRef] [PubMed]
5. Rogers, G.B.; Keating, D.J.; Young, R.L.; Wong, M.L.; Licinio, J.; Wesselingh, S. From gut dysbiosis to altered brain function and mental illness: Mechanisms and pathways. *Mol. Psychiatry* **2016**, *21*, 738–748. [CrossRef] [PubMed]
6. McVey Neufeld, K.A.; Mao, Y.K.; Bienenstock, J.; Foster, J.A.; Kunze, W.A. The microbiome is essential for normal gut intrinsic primary afferent neuron excitability in the mouse. *Neurogastroenterol. Motil.* **2013**, *25*,183. [CrossRef]
7. Collins, J.; Borojevic, R.; Verdu, E.F.; Huizinga, J.D.; Ratcliffe, E.M. Intestinal microbiota influence the early postnatal development of the enteric nervous system. *Neurogastroenterol. Motil.* **2014**, *26*, 98–107. [CrossRef]
8. McVey Neufeld, K.A.; Perez-Burgos, A.; Mao, Y.K.; Bienenstock, J.; Kunze, W.A. The gut microbiome restores intrinsic and

extrinsic nerve function in germ-free mice accompanied by changes in calbindin. *Neurogastroenterol. Motil.* **2015**, *27*, 627–636. [CrossRef]
9. .Heiss, C.N.; Olofsson, L.E. The role of the gut microbiota in development, function and disorders of the central nervous system and the enteric nervous system. *J. Neuroendocrinol.* **2019**, *31*, e12684. [CrossRef]
10. .Furness, J.B. The enteric nervous system and neurogastroenterology. *Nat. Rev. Gastroenterol. Hepatol.* **2012**, *9*, 286–294. [CrossRef]
11. Wehrwein, E.A.; Orer, H.S.; Barman, S.M. Overview of the Anatomy, Physiology, and Pharmacology of the Autonomic Nervous System. *Compr. Physiol.* **2016**, *6*, 1239–1278. [PubMed]
12. Rhee, S.H.; Pothoulakis, C.; Mayer, E.A. Principles and clinical implications of the brain- gut-enteric microbiota axis. *Nat. Rev. Gastroenterol. Hepatol.* **2009**, *6*, 306–314. [CrossRef] [PubMed]
13. Alonso, C.; Guilarte, M.; Vicario, M.; Ramos, L.; Ramadan, Z.; Antolín, M.; Martínez, C.; Rezzi, S.; Saperas, E.; Kochhar, S.; et al. Maladaptive intestinal epithelial responses to life stress may predispose healthy women to gut mucosal inflammation. *Gastroenterology* **2008**, *135*, 163–172. [CrossRef] [PubMed]
14. Cryan, J.F.; O'Riordan, K.J.; Sandhu, K.; Peterson, V.; Dinan, T.G. The gut microbiome in neurological disorders. *Lancet Neurol.* **2020**, *19*, 179–194. [CrossRef]
15. Hyland, N.P.; Cryan, J.F. Microbe-host interactions: Influence of the gut microbiota on the enteric nervous system. *Dev. Biol.* **2016**, *417*, 182–187. [CrossRef] [PubMed]
16. .Tremlett, H.; Bauer, K.C.; Appel-Cresswell, S.; Finlay, B.B.; Waubant, E. The gut microbiome in human neurological disease: A review. *Ann. Neurol.* **2017**, *81*, 369–382. [CrossRef] [PubMed]
17. Tyler Patterson, T.; Grandhi, R. Gut Microbiota and Neurologic Diseases and Injuries. *Adv. Exp. Med. Biol.***2020**, *1238*, 73– [PubMed]
18. Neufeld, K.M.; Kang, N.; Bienenstock, J.; Foster, J.A. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol. Motil.* **2011**, *23*, 255–264. [CrossRef] [PubMed]
19. .Park, H.; Poo, M.M. Neurotrophin regulation of neural circuit development and function. *Nat. Rev. Neurosci.***2013**, *14*, 7–23. [CrossRef]
20. Kawase, T.; Nagasawa, M.; Ikeda, H.; Yasuo, S.; Koga, Y.; Furuse, M. Gut microbiota of mice putatively modifies amino acid metabolism in the host brain. *Br. J. Nutr.* **2017**, *117*, 775–783. [CrossRef]
21. Chen, K.; Luan, X.; Liu, Q.; Wang, J.; Chang, X.; Snijders, A.M.; Mao, J.H.; Secombe, J.; Dan, Z.; Chen, J.H.; et al. *Drosophila* histone demethylase KDM5 regulates social behavior through immune control and gut microbiota maintenance. *Cell Host Microbe* **2019**, *25*, 537–552. [CrossRef] [PubMed]
22. Braniste, V.; Al-Asmakh, M.; Kowal, C.; Anuar, F.; Abbaspour, A.; Toth, M.; Korecka, A.; Bakocevic, N.; Ng, L.G.; Kundu, P.; et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci. Transl. Med.* **2014**, *6*, 263ra158. [CrossRef] [PubMed]
23. Caputi, V.; Marsilio, I.; Filpa, V.; Cerantola, S.; Orso, G.; Bistoletti, M.; Paccagnella, N.; De Martin, S.; Montopoli, M.; Dall'Acqua, S.; et al. Antibiotic-induced dysbiosis of the microbiota impairs gut neuromuscular function in juvenile mice. *Br. J. Pharmacol.* **2017**, *174*, 3623–3639. [CrossRef] [PubMed]
24. Kabouridis, P.S.; Lasrado, R.; McCallum, S.; Chng, S.H.; Snippert, H.J.; Clevers, H.; Pettersson, S.; Pachnis, V. Microbiota controls the homeostasis of glial cells in the gut lamina propria. *Neuron* **2015**, *85*, 289–295. [CrossRef] [PubMed]
25. Lyte, M.; Li, W.; Opitz, N.; Gaykema, R.P.; Goehler, L.E. Induction of anxiety-like behavior in mice during the initial stages of infection with the agent of murine colonic hyperplasia *Citrobacter Rodentium*. *Physiol. Behav.* **2006**, *89*, 350–357. [CrossRef] [PubMed]
26. Goehler, L.E.; Gaykema, R.P.; Opitz, N.; Reddaway, R.; Badr, N.; Lyte, M. Activation in vagal afferents and central autonomic pathways: Early responses to intestinal infection with *Campylobacter jejuni*. *Brain Behav. Immun.* **2005**, *19*, 334–344. [CrossRef]
27. .Cryan, J.F.; Dinan, T.G. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci.* **2012**, *13*, 701–712. [CrossRef]
28. Patrick, K.L.; Bell, S.L.; Weindel, C.G.; Watson, R.O. Exploring the "Multiple-Hit Hypothesis" of neurodegenerative disease: Bacterial infection comes up to bat. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 138. [CrossRef]
29. Pellegrini, C.; Antonioli, L.; Calderone, V.; Colucci, R.; Fornai, M.; Blandizzi, C. Microbiota-gut-brain axis in health and disease: Is NLRP3 inflammasome at the crossroads of microbiota-gut-brain communications? *Prog. Neurobiol.* **2020**, *191*, 101806. [CrossRef]
30. Soscia, S.J.; Kirby, J.E.; Washicosky, K.J.; Tucker, S.M.; Ingelsson, M.; Hyman, B.; Burton, M.A.; Goldstein, L.E.; Duong, S.; Tanzi, R.E.; et al. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS ONE* **2010**, *5*, e9505. [CrossRef]