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REVIEW

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Gut microbiome and neurodegenerative disorders: therapeutic implications

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This article belongs to the Special Issue: The gut microbiome for improving neurological health

Abstract

The gut microbiome, home to 100 trillion microorganisms, and its influence on brain health and disease via the gut-brain axis has encouraged interdisciplinary studies. The gut-brain axis is the two-way communication network connecting the gut microbiome to the central nervous system. Gut microbes produce neurotransmitters such as serotonin and gamma-aminobutyric acid, which can impact mood and cognitive function. The microbial imbalance can lead to systemic inflammation, which may contribute to neuroinflammation and further cause neurodegeneration. Additionally, it modulates immune responses and results in autoimmune disorders. Every day, new and progressive findings are surfacing related to microbiota-mediated neurodegenerative disorders, their mechanistic approach, and different therapeutic approaches to ameliorate these conditions. In this review, we aim to unfold the intricate relationship of the microbiota-gut-brain axis to overlay a better understanding of the microbiota-mediated pathogenesis of neurodegenerative disorders, popularly known as Alzheimer's and Parkinson's disease, including amyotrophic lateral sclerosis, multiple sclerosis, and Huntington's disease. Aging accelerates neurodegeneration by modulating microbial composition, altering metabolic processes and immune functions. Moreover, possible therapeutic strategies such as the use of probiotics, prebiotics, synbiotics and various dietary modulations to ameliorate neurodegenerative conditions have been outlined in both preclinical and clinical studies. As the gut microbiome is highly individualistic, designing personalized prebiotic or probiotic formulations according to each person's microbiome profile is a future challenge. More research is needed to fully understand how the gut microbiota influences neurodegenerative processes at a mechanistic level. The long-term effects of microbiome-based interventions on neurodegenerative diseases need to be thoroughly investigated to establish their safety and efficacy.

Keywords: Gut microbiota, gut-brain axis, neurodegenerative disorders, probiotics, prebiotics, aging

Introduction

The gut microbiome is an environment composed of both beneficial and pathogenic microbes that plays an important role in various functions related to health and disease [1]. *Cytophaga-flavobacterium bacteroides* (CFB) and *Firmicutes* are the beneficial bacteria present in the gut microbiota of an individual. The CFB group consists of *Bacteroides* with the majority of *Prevotella*, *Porphyromonas*, and *Bifidobacterium*, whereas *Firmicutes* are classified into *Bacilli*, *Clostridia*, *Erysipelotrichia*, *Lactobacillus*, *Limnochordia*, *Clostridia*, *Negativicutes*, *Thermolithobacteria*, and *Tissierellia* [2]. These beneficial bacteria play a very important role in unlocking the nutrients we need from our food and also create beneficial by-products like short-chain fatty acids (SCFAs), consisting of butyrate, propionate, and acetate, which contribute to gut health and even influence mood, cognition, and brain function [3].

They are also involved in various other functions such as

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absorption of minerals, production of vitamins, regulation of gut motility, conversion of bile acids and steroids, metabolism of xenobiotics, and destruction of mutagens, toxins, and genotoxins [4]. Apart from these, some harmful bacteria, consisting of *Clostridium perfringens*, *Staphylococcus*, and *Escherichia coli* (*E.coli*), also reside in our intestines, which inhibit health by promoting aging and triggering various diseases [5]. When the natural equilibrium between these beneficial and pathogenic bacteria is altered, it leads to gut dysbiosis that contributes to various diseases such as obesity, diabetes, cancer, neurodegenerative, psychiatric, cardiovascular, and inflammatory bowel

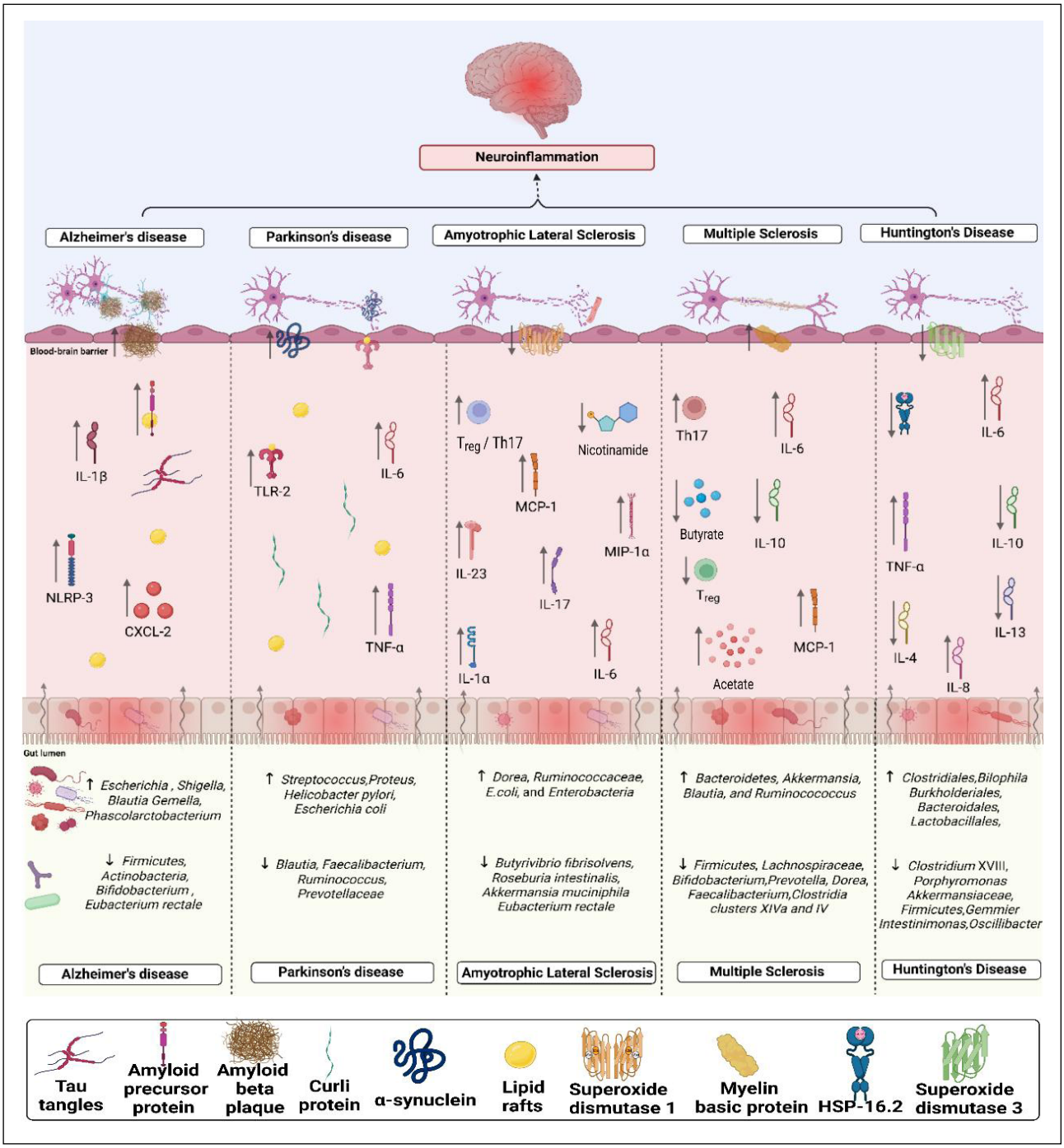

Figure 1. Pictorial presentation of neuropathogenesis of gut microbiota-mediated neurodegenerative diseases. Dysbiosis of the gut microbiota leads to disruption of the intestinal barrier, resulting in increased intestinal permeability. With a compromised intestinal barrier, pathogens enter the intestine and trigger the release of multiple pro-inflammatory factors such as C-X-C motif chemokine ligand 2 (CXCL-2), NOD-like receptor protein-3 (NLRP-3), Toll-like receptor-2 (TLR-2), tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha (MIP-1α), and disruption of the immune balance between T helper 17 (Th17) cells and regulatory T cells (Tregs). Loss of beneficial bacteria in a given disease resulted in altered expression of certain proteins, such as amyloid precursor protein (APP), tau protein, curli protein, superoxide dismutase, myelin basic protein, heat shock protein-16.2 (HSP-16.2), and reduced levels of nicotinamide. Levels of SCFAs were also affected by disruptions in the gut microbiota, such as increased acetate and decreased butyrate in a given disease. Neuroinflammation is facilitated by gut dysbiosis, which significantly decreases levels of anti-inflammatory interleukins (IL-4, IL-10, IL-13) and increases levels of pro-inflammatory interleukins (IL-1β, IL-6, IL-17, IL-23, IL-8).

diseases [6]. Recent research has revealed the existence of a bidirectional communication channel between the gut microbiome and the brain through the microbiota-gut-brain axis (MGBA) [7]. Despite the anatomical separation of the brain and gut, several pathways have been suggested for the gut bacteria to interact with the central nervous system (CNS). These include the generation of neuroactive compounds, metabolites, and hormones that modulate the neuroendocrine system, vagus nerve, enteric neurological system (ENS), immune system, and cardiovascular system [8]. Research has demonstrated that the gut microbiota is capable of producing neurotransmitters such as γ-aminobutyric acid (GABA), dopamine, and serotonin [9]. When these neurotransmitter levels are affected, it leads to various neurodegenerative diseases such as depression and anxiety, Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and so on [10]. The association of the abundance of different microorganisms in the respective neurodegenerative disorders has been depicted in Figure 1 [11].

To replenish the beneficial bacteria, prebiotics, probiotics, or synbiotics are given to enhance the body's defense system, improve nutrient absorption, and reduce digestive discomfort [12]. Prebiotics are defined as "a nondigestible dietary component that selectively stimulates the growth and/or activity of a limited number of bacteria in the colon, hence improving host health and providing a beneficial impact on the host". The common prebiotics include inulin, resistant starch, fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and trans-galacto-oligosaccharides (TOS) [13]. In a recent study, mice fed a high-fat diet (HFD) that disrupted the gut microbiome and then treated with FOS and GOS showed reduced signs of depression and anxiety. This behavioral improvement contributed to a reduction in dysbiosis, an increase in bacteria that produced acetate (*Bacillus acidifaciens* and *Bacillus dorei*), and a decrease in intestinal permeability that eventually resulted in a reduction in both peripheral and central inflammation [14]. Probiotics are defined as microorganisms that, when administered in sufficient quantities, provide health benefits to the host [15]. A recent study showed the effect of a probiotic diet (*Lactobacillus plantarum* KY1032 and *Lactobacillus curvatus* HY7601) on the transgenic 3xTg-AD mouse that inhibited the progression of mild cognitive impairment and neurodegeneration in AD pathology [16]. A recent preclinical study was conducted on a cuprizone-induced demyelination model in rats by administering probiotic *Bifidobacterium breve* which alleviated demyelination and oxidative stress levels in the corpus callosum and may be used as a supplementary strategy for the treatment of MS [17]. Synbiotics are a combination of probiotics and prebiotics employed to replenish the gut with beneficial microbes in situations where the microbiome is disrupted due to severe disease or clinical care treatments [18]. A recent preclinical study suggested that a 5xFAD transgenic AD mouse model, when treated with a synbiotic formulation (*Clostridium sporogenes* and xylan) for 30 days, promoted gut-derived indole-3-propionic acid and markedly enhanced cognitive performance, spatial memory as well as reduced amyloid-beta (Aβ) accumulation in the hippocampus and cortex of the brain [16]. Despite significant advances in drug development, many medications used to treat neurodegenerative diseases that lead to a range of side effects. This often complicates treatment decisions and can significantly impact a patient's quality of life [19]. The connection between diet and neurodegenerative diseases is an area of growing interest. While research is ongoing, there is compelling evidence that dietary choices can significantly impact brain health and potentially reduce the risk or slow the progression of neurodegenerative conditions such as AD, PD, MS, depression, and anxiety [20]. This review summarizes the possible mechanisms, current advances, and development of potential novel probiotic, prebiotic, and synbiotic interventions that may manage and treat AD, PD, ALS, MS, and HD in Figure 2.

Gut microbiome and neurodegenerative disorders

Alzheimer's disease (AD)

AD is a neurodegenerative disease that worsens over time, causing damage to the neurons associated with memory, language, and thinking, resulting in early symptoms such as memory loss, impaired thinking, and confusion [21]. Worldwide, 35.6 million people have dementia, and the number is expected to double by 2030 (65.7 million) and triple by 2050 (11.4 million). Currently, 6.9 million Americans age 65 and older are reported to have Alzheimer's dementia. Without medical advances to prevent or treat AD, this number could rise to 13.8 million by 2060 [22]. Alzheimer's dementia affects 5.0% of people aged 65 to 74, 13.1% of people aged 75 to 84, and 33.3% of people aged 85 and older. Data show that AD progresses with age, which is one of the most important risk factors for AD [23]. AD treatments consist primarily of cholinesterase inhibitors, including donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). These medications increase acetylcholine levels to temporarily reduce cognitive dysfunction [24]. However, they have significant limitations: they do not slow disease progression, they can cause side effects such as nausea and insomnia that can affect patient adherence, and their effectiveness often decreases over time [25]. Ultimately, while they provide some symptomatic relief, they do not improve AD pathology. Due to these undesirable side effects, research is more focused on alternative strategies that may have a more comprehensive safety profile and efficacy.

AD is mainly driven by a complex interaction of lifestyle, genetic, and environmental variables that lead to neuronal degeneration in the brain. Aβ peptides accumulated in the brain to form insoluble plaques, which play a vital role in the pathophysiology of AD by impairing neuronal communication and triggering inflammatory responses [26]. Microglia are exposed to Aβ through amyloid compaction, which also plays a critical role in microglial activation

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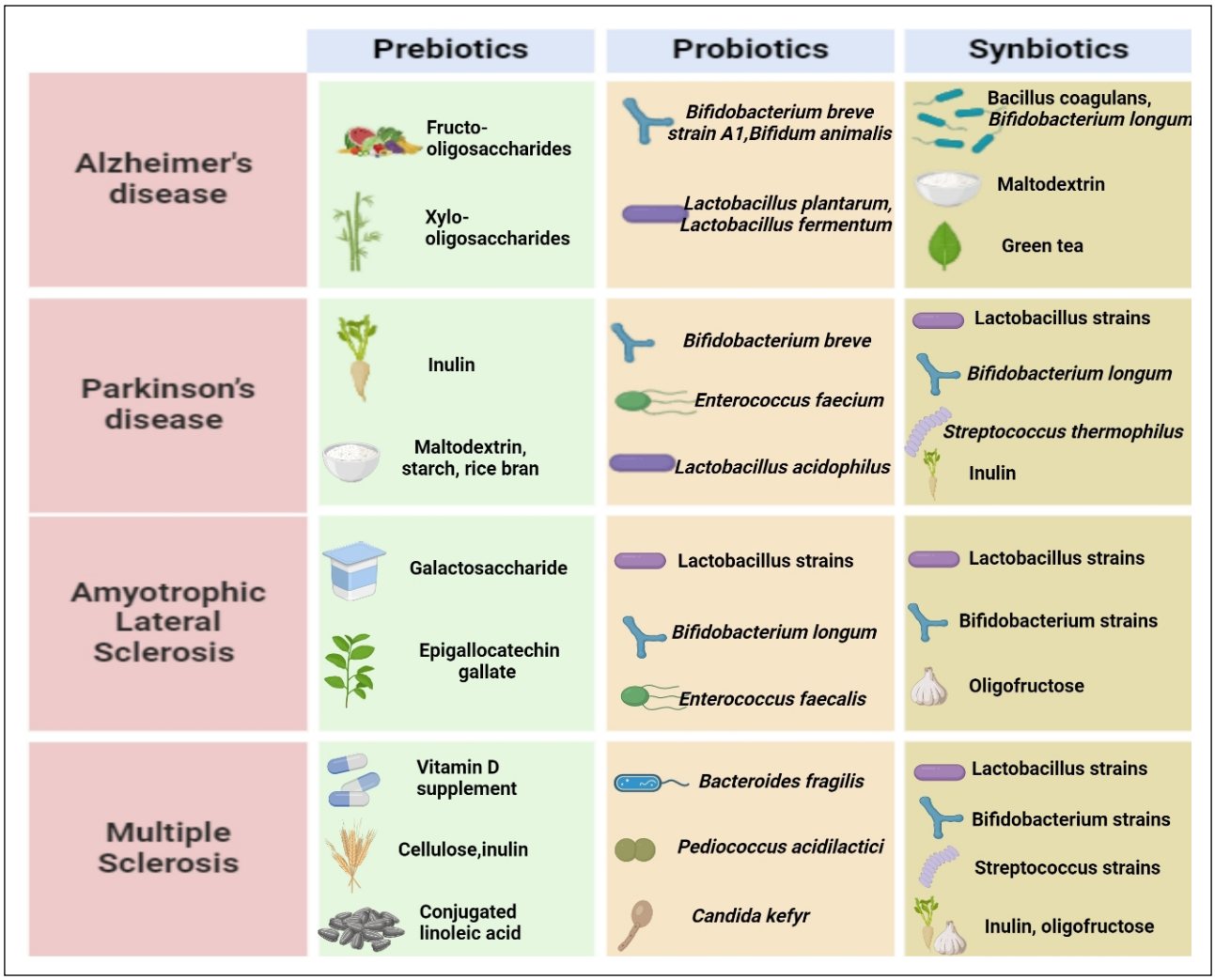

Figure 2. Consumption of different prebiotics, probiotics and synbiotics in ameliorating neurodegenerative diseases conducted in preclinical and clinical studies. Prebiotics are indigestible fibers that promote the development of beneficial gut flora. The consumption of probiotics, which are live bacteria, can have beneficial effects on our health. Synbiotics improve the survival and colonization of good bacteria in the gut by combining both probiotics and prebiotics. All of these elements are essential for maintaining the balance of the gut microbiota and overall health.

through NOD-like receptor and toll-like-receptor (TLR) signaling, resulting in the production of proinflammatory cytokines [27]. Aβ accumulation is also linked to compromised synaptic signaling and plasticity, both of which are crucial for learning and memory [28]. Aβ accumulation, impaired brain glucose metabolism, and impaired phosphorylation, dephosphorylating pathway enhances tau hyperphosphorylation, which results in the development of neurofibrillary tangles [29]. In healthy neurons, tau protein plays a crucial role in stabilizing microtubules, key components of the cytoskeleton that help transport cellular materials within axons and dendrites [30]. When tau protein becomes hyperphosphorylated, it undergoes structural changes that interfere with its ability to effectively bind to microtubules [31]. This destabilization leads to microtubule disruption, which disrupts the transport of vital proteins, organelles, and other molecules necessary for proper neuronal function and survival [32]. The cholinergic hypothesis of AD suggests that a significant decrease in the neurotransmitter acetylcholine (ACh) contributes to the cognitive decline observed in the disease [33]. A more recent theory, known as the lipid invasion model, postulates that disruptions in the blood-brain barrier allow external lipids to enter the brain, triggering neuroinflammation and oxidative stress [34]. This model indicates that lipid influx may play a role in the formation of amyloid plaques and neurodegeneration, offering a different perspective on the mechanisms underlying AD [35]. Genetic mutations in APP [36], presenilin (PSEN1 and PSEN2) [37], and apolipoprotein E (APOE ε4 allele) [38], greatly elevate the likelihood of developing AD.

Although there are several theories explaining AD, the most well-known of which is the Aβ hypothesis, researchers are now focusing more on gut dysbiosis, which is assumed to be involved in the etiology of the disease [39]. The term "dysbiosis" describes the disruptions in the microbial population of the intestine, its local deposition patterns, its metabolic features, and the gut epithelial barrier when compared with the healthy individual's microbiota [40]. In both clinical and murine research, a marked shift toward pro-inflammatory microorganisms and a reduction in the variety of bacteria have been linked to AD [41]. According to a recently published study, the abundance of *Firmicutes* families such as *Turicibacteraceae*, *Pepto-*

streptococcaceae, *Clostridiaceae*, *Ruminococcaceae*, and *Mogibacteriaceae* decreases, while the abundance of the genera *Phascolarctobacterium*, *Blautia*, and *Gemella* increases in AD [42]. The primary indicator of gut dysbiosis has been associated with an increase in the *Firmicutes/Bacteroidetes* ratio since the early stages of AD, which is subsequently associated with APP accumulation in the gut [43]. Elevations of Aβ in the central nervous system and deficits in memory and spatial learning have been associated with alterations in the gut microbiome of APP/PS1 mice [44]. Increased levels of bile acids (BAs) produced by bacteria in the bloodstream may cause tight junction rupture, increasing blood-brain barrier (BBB) permeability and allowing peripheral cholesterol or BAs to enter the central nervous system. As cellular cholesterol builds up in the brain, it binds directly to APP, making it easier for APP to enter into the phospholipid monolayers that constitute the lipid rafts where the formation of Aβ occurs, eventually promoting the production and accumulation of Aβ [45]. An essential component of the *Actinobacteria phylum*, *Bifidobacterium* controls the GBA, and its degeneration contributes to the pathophysiology of tau, leading to the build-up of tangles that cause cell damage and inflammation in AD [46]. Elevated levels of CXCL2, IL-1β, and NOD-like receptor protein-3 (NLRP3) have been related to increased levels of proinflammatory bacteria such as *Escherichia*, *Shigella* along with decreased levels of anti-inflammatory bacteria such as *Eubacterium rectale* were found in the plasma of patients suffering from brain amyloidosis and cognitive impairment [47]. Different pathways suggesting a link between gut microbiota and AD have been investigated in different studies and are summarized in Figure 3.

Prebiotics, probiotics, and synbiotics may prove useful as novel biological prophylactics in the treatment of AD because of their ability to improve cognition and metabolic activity, their antioxidant and anti-inflammatory properties, and their ability to produce metabolites essential for the gut and brain [48]. The most extensively studied prebiotic is FOS, which is naturally present in many fruits and vegetables and serves as a substrate for the growth of *Bifidobacterium* and *Lactobacillus*, thus promoting their production in AD patients [49]. When FOS was administered to transgenic AD mice, there was an increase in glucagon-like peptide-1 (GLP-1), a protein that readily crosses the BBB, stimulates pancreatic insulin production, and promotes delayed gastric emptying. As a result of the delayed glucose metabolism associated with AD patients, this increase in cerebral GLP-1 prevents CNS insulin resistance and slows neuronal death [50]. Enhancing the diversity of the gut microbiota through the introduction of xylooligosaccharides (XOS), which are naturally obtained from honey, fruits, bamboo sprouts, vegetables, and more recently from sugar cane biomass, showed reduced intestinal inflammation by lowering levels of immunosuppressive cytokine-like IL-10 as well as pro-inflammatory cytokines such as IL-1β and IL-6, which were elevated in APP/PS1 mice [51]. Probiotic species such as *Bifidum animalis*, *Lactobacillus plantarum*, and *Lactobacillus fermentum* have shown the ability to produce antioxidants in large quantities [52]. According to Kobayashi *et al*., the probiotic strains *Bifidobacterium infantis* and *Bifidobacterium breve* strain A1 enhanced the proportion of superoxide dismutase (SOD) and decreased the deposition of IL-1, Aβ, and TNF-α in the hippocampal region of the brain in Aβ-induced AD rats [53]. Administration of *Bifidobacterium* increases hippocampal plasma acetate levels, which improves cognitive function and inhibits the production of immune-reactive genes. From this, it can be deduced that *Bifidobacterium* can prevent neuroinflammation and control the immune response that arises from Aβ toxic exposure in brain tissue [54]. *Bifidobacterium breve* MCC1274 treatment in wild-type (WT) mice decreased the AD-related pathologies by lowering the levels of phosphorylated tau, presenilin 1 protein, and soluble hippocampal Aβ1-42. Also, it enhanced synaptic proteins and decreased neuroinflammation [55]. In astrocytes, *Lactobacillus reuteri* can reduce neuroinflammation by promoting the synthesis of indole-3-propionic acid and indole-3-aldehyde by subsequently passing through the BBB [56]. For neural defense, nuclear factor erythroid-related factor 2 (NRF-2) is essential because it can stimulate the expression of genes that are cytoprotective, anti-inflammatory, and antioxidant, which are reduced in the pathology of AD [57]. Curcumin, found in saffron, has neuroprotective qualities. According to Patel *et al*., curcumin and *Lactobacillus rhamnosus* may work together as an adjuvant to enhance memory and learning and raise antioxidant enzyme levels in mice with scopolamine-induced dementia [58]. Synbiotic powder (containing vitalon probiotics (VP) powder - *Bifidobacterium longum*, *Bacillus coagulans*, *Bifidobacterium breve*, protease, and maltodextrin) and prebiotics (composed of 650 mL of healthy green tea that contains 2.5% inulin freeze-dried into powder) were mixed in a 1:7 ratio and dissolved in water at 0.5 g/mL and administered to 3-month-old APP and wild-type (WT) mice [48]. The results showed a significant decrease in Aβ42 levels between the treatment and control groups. Thus, the consumption of synbiotics was able to effectively reduce the accumulation of Aβ42, the most pathogenic species among the different Aβ lengths. Doublecortin (DCX), a marker of neurogenesis, was also found to be significantly increased in APP mice treated with the symbiotic mixture, indicating that the symbiotic treatment can promote neurogenesis. Levels of pro-inflammatory cytokines such as TNF-α were also reduced between groups [59]. An interesting study was conducted on a transgenic humanized Drosophila melanogaster model that exhibited an AD phenotype caused by BACE1-APP. The insects were given the synbiotic containing the polyphenol-rich plant prebiotic Triphala and three metabolically active probiotics (*Lactobacillus fermentum*, *Lactobacillus plantarum*, and *Bifidobacterium longum spp. infantis*), and the results showed suppression of Aβ aggregation as well as a reduction in neuroinflammation by generating a secondary source of antioxidants [60].

Parkinson's disease (PD)

PD is a complex neurodegenerative disease that progress-

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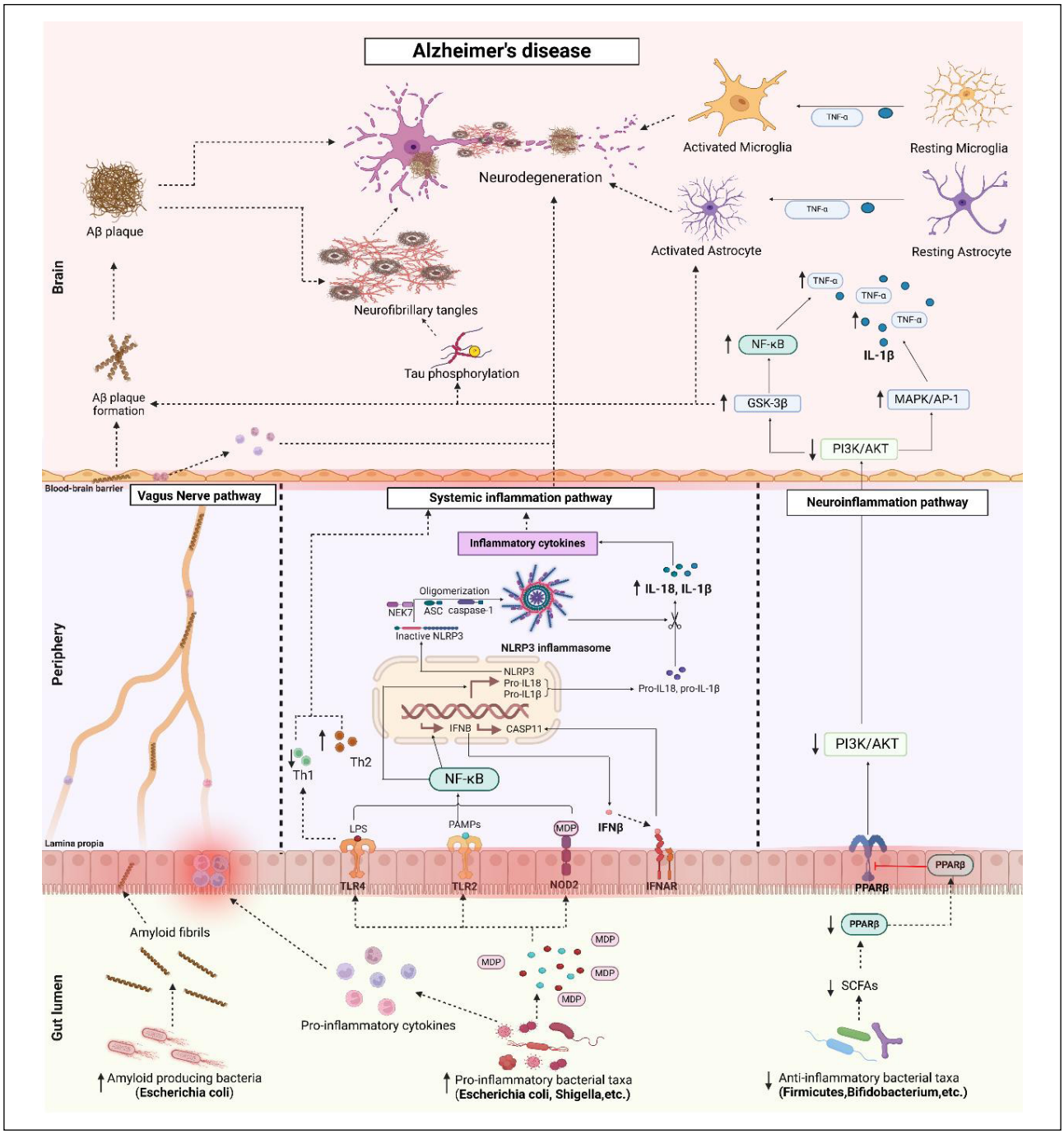

Figure 3. Potential signaling pathways linking gut dysbiosis with AD. The abundance of pro-inflammatory bacterial taxa over anti-inflammatory bacterial taxa resulting in gut dysbiosis may mediate AD. 1) Vagus nerve pathway: Pro-inflammatory bacteria secrete pro-inflammatory cytokines that cause increased intestinal permeability and inflammation, referred to as leaky gut. These pro-inflammatory cytokines travel through the vagus nerve and into the brain, where they cause neuroinflammation and neurodegeneration. Increased pro-inflammatory bacteria, particularly *E. coli*, also known as amyloid-producing bacteria, secrete amyloid into the intestinal lumen, which travels through the leaky gut and enters the vagus nerve. Amyloid travels through the vagus nerve and crosses the BBB, resulting in the formation of Aβ plaques. 2) Systemic inflammatory pathway: Gut dysbiosis leads to increased production of lipopolysaccharide (LPS), pathogen-associated molecular patterns (PAMPs), and muramyl dipeptide (MDP). Upon recognition of these stimuli by TLR4, TLR2 and NOD2 receptors, NF-κB is activated, leading to the production of interferon-beta (IFN-β) and the transcription of NLRP3 and other pro-inflammatory genes. Activation of IFN-β by IFNAR leads to activation of the CASP11 and NLRP3 inflammasomes. Activation of the NLRP3 inflammasome involves oligomerization of the inactive NLRP3 protein, an adaptor protein called ASC, caspase-1, and NEK7. The NLRP3 inflammasome converts pro-IL-18 and pro-IL-1β to their active forms, IL-18 and IL-1β. These pro-inflammatory cytokines lead to systemic inflammation, followed by neuroinflammation and neurodegeneration. Stimulation of TLR4 by LPS leads to an imbalance between Th1 and Th2 cells, contributing to systemic inflammation. 3) Neuroinflammatory pathway: Reduced levels of SCFAs lead to decreased expression of PPARβ, which inhibits the PI3K/AKT pathway and activates the GSK-3β and MAPK/AP-1 pathways, resulting in the production of IL-18 and TNF-α. The GSK-3β pathway stimulates tau phosphorylation and Aβ plaque formation, leading to neurofibrillary tangles and AD progression. All of these pathways lead to AD pathogenesis. TLR, Toll-like-receptors; NOD2, nucleotide-binding oligomerization domain containing 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; CASP11, caspase 11; NLRP3, NOD-like receptor protein 3; ASC, apoptosis-associated speck-like protein; NEK7, NIMA-related kinase 7; IFNAR, interferon beta receptor; IL, interleukin; Th, T helper cells; PPAR-β, peroxisome proliferator-activated receptor beta; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; GSK-3β, glycogen synthase kinase 3 beta; MAPK/AP-1, mitogen-activated protein kinase/activator protein 1; TNF-α, tumor necrosis factor alpha.

es with age and results in uncontrollable or unintended movements, including stiffness, tremor, and difficulty with balance and coordination [61]. Worldwide, approximately 10 million people are affected by PD, with approximately one million people in the United States, which is expected to increase to 1.2 million by 2030. According to a survey conducted by the 2022 Parkinson's Foundation, approximately 90,000 Americans are diagnosed with PD each year, a sharp increase of 50% from the previously estimated rate of 60,000 diagnoses per year [62]. PD affects 0.3% of individuals between the ages of 55 and 64, 1.0% of individuals between the ages of 65 and 74, 3.1% of individuals between the ages of 75 and 84, and 4.3% of individuals over the age of 85 [63]. The facts clearly indicate that PD accelerates with age, making it one of the most significant risk factors for the disease. First-line treatment for PD consists of levodopa, often combined with carbidopa (Sinemet), and dopamine agonists such as pramipexole (Mirapex) and ropinirole (Requip) [64]. Levodopa is highly effective for motor symptoms by increasing dopamine levels, while dopamine agonists are useful in the early stages or as adjunctive therapy. However, long-term use of levodopa can lead to reduced efficacy and motor fluctuations, and dopamine agonists can cause side effects such as nausea and sleep disturbances [65]. Importantly, neither treatment addresses the non-motor symptoms that greatly impact a patient's quality of life. As a result of these undesirable side effects, prebiotics, probiotics, or synbiotic treatments are receiving more attention in research as they may have a better safety profile and greater efficacy.

A mechanistic link between aging and PD has been established through various pathways, including decreased dopamine levels, abnormal accumulation of alpha-synuclein, loss of protein homeostasis, neuroinflammation, genomic instability, oxidative damage, and impaired stress responses [66]. Dopamine is a neurotransmitter responsible for coordinating millions of nerve and muscle cells involved in movement and is broken down by an enzyme called monoamine oxidase B (MAO-B), which leads to a reduction in dopamine levels. Dopamine levels decline by about 13% each decade after age 45 in brain regions associated with motor and cognitive function. This decline coincides with an increase in brain levels of MAO-B [67]. The dopamine transporter (DAT) is the primary defense mechanism of dopaminergic neurons against this oxidative stress. DAT transports the damaging dopamine to the nerve terminal where it can be repackaged into synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2). There have been reports of a decline in DAT expression in the dorsal layer of the substantia nigra (SN) with age, which may explain some of the neuronal vulnerability to loss in PD [68]. The abnormal accumulation of alpha-synuclein protein as Lewy bodies is a key feature of PD. These aggregates disrupt cellular function and induce neuronal toxicity, leading to the degeneration of dopaminergic neurons in the substantia nigra [69]. This neuronal loss leads to the motor symptoms of PD, including tremor, rigidity, and bradykinesia. Lewy bodies not only characterize the disease, but also highlight the pathogenic processes that drive its progression [70]. Approximately 15% of individuals with PD have a family history of the disease, and these can be caused by genetic abnormalities in a variety of genes, such as α-synuclein (α-Syn), LRRK2, PARK2, PARK7, PINK1, or the SNCA genes [71].

While there are many theories to explain PD, a growing variety of research suggests a connection between gut dysbiosis and the development and progression of PD. The potential pathobionts are from the genera *Escherichia*, *including Shigella*, *Streptococcus*, *Proteus*, *Enterococcus*, *Enterobacteriaceae*, and *Helicobacter pylori* were significantly increased, whereas *Blautia*, *Faecalibacterium*, *Ruminococcus*, *Prevotellaceae*, and *Enterobacteriaceae* were significantly decreased in PD subjects compared to healthy controls [72]. Curli is one of the amyloid proteins produced by *E. coli* and other strains of Gram-negative bacteria that form biofilms that promote bacterial adhesion and colonization. Repeated oral administration of Curli-producing bacteria to aged wild-type (WT) rats resulted in the formation of intestinal α-Syn deposits, and brain samples from these animals showed increased levels of TLR-2, IL-6, TNF, along with enhanced microgliosis, astrogliosis, and neuronal α-Syn deposition in both the intestinal and brain tissues of α-Syn-overexpressing rats [73]. α-Syn aggregates cause dysfunction in presynaptic and postsynaptic transmission and disrupt dopaminergic transmission. In this way, CURLI subunits may facilitate the development of Parkinson's disease [74]. It has been observed that variations in gut microbiota populations are influenced by dopamine production through changes in levels of the gut hormone ghrelin. Ghrelin is a gastrointestinal hormone that controls appetite and obesity and is found in the endogenous ghrelin receptor (GHSR) located in the hypothalamus [75]. The intestinal mucus barrier becomes more permeable due to the growth of the Akkermansia genus, which breaks down the mucus layer and uses the mucus as energy to perform its function. [76]. Variations in the intestinal microbiota population affect the integrity and permeability of the BBB by altering tight junctions such as occludin, claudin, and zonula occludens-1 (ZO-1), which maintain normal BBB permeability. The altered subcellular distribution of ZO-1 and occludin, as well as the decreased expression level of colonic occludin, have shown that intestinal permeability is altered in PD patients [77]. The potential pathways linking gut dysbiosis to PD are summarized in Figure 4.

Probiotics, prebiotics, or synbiotics may prevent and alleviate Parkinson's disease (PD) symptoms by regulating intestinal microecology, reducing oxidative stress damage and inflammatory response, and enhancing neurotrophic factor and dopamine production through the gut-brain axis (Figure 2). A recent open-label, non-randomized study was conducted in a small cohort of PD participants who received a prebiotic fiber intervention consisting of rice bran, inulin, resistant maltodextrin, and resistant starch incubated with human stool obtained from healthy controls. The bacterial population enriched by the administration of the prebiotic intervention was from the genera *Ruminococaceae*, *Prevotella*, and *Lachnospiraceae* promoted by resistant starch; the genera *Ruminoccocus, Bacteroides*,

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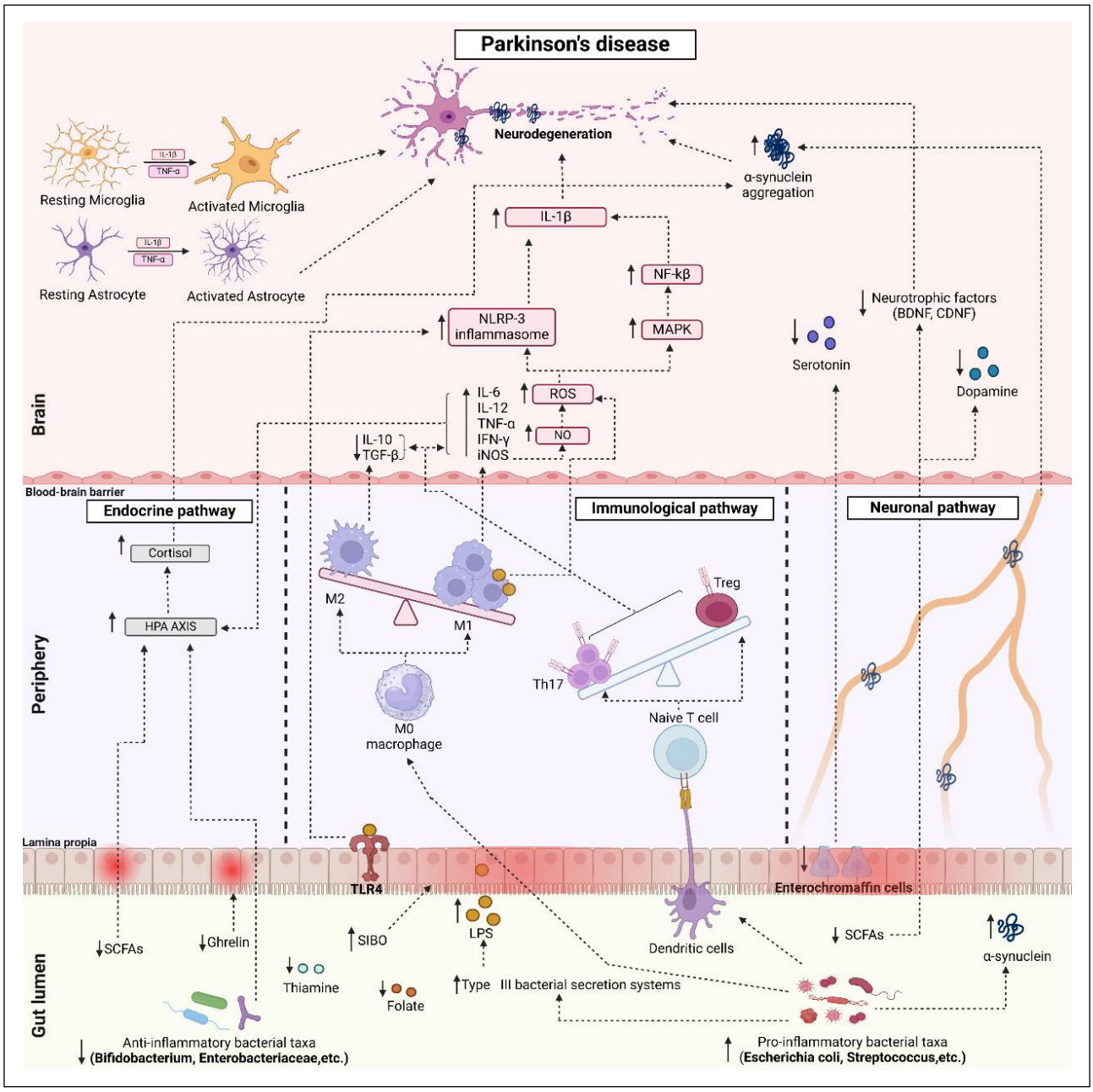

Figure 4. Potential signaling pathways of pathogenesis of gut microbiota-mediated Parkinson's disease. The dominance of pro-inflammatory bacterial taxa over anti-inflammatory bacterial taxa (gut dysbiosis) initiates different pathways for the pathogenesis of PD. 1) Endocrine pathway: Gut dysbiosis results in decreased production of SCFAs, thiamine, folate, and ghrelin, and increased levels of LPS (via an enhanced type III bacterial secretion system). Reduced SCFAs and increased LPS lead to activation of the HPA axis and release of stress hormones. Increased plasma levels of cortisol promote α-syn aggregation and neurodegeneration. Reduced levels of SCFAs and ghrelin cause intestinal inflammation and leaky gut by reducing mucin secretion. In addition, ghrelin is responsible for maintaining and protecting the normal function of nigrostriatal dopaminergic neurons. 2) Immunological pathway: Gut dysbiosis increases SIBO, which increases intestinal permeability and creates an imbalance between Th17 and Treg and M1 and M2 macrophages leading to the formation of ROS, Inos. It induces the production of pro-inflammatory cytokines (TNF-α, IFN-γ, IL-6, and IL-12) and decreases the anti-inflammatory cytokines IL-10 and TGF-β. iNOS produces NO and potentiates ROS production. Similarly, depletion of Treg cells and increase in Th17 produce pro-inflammatory cytokines and ROS. Increased ROS can activate the NLRP-3 inflammasome and the MAPK/NF-κβ pathway. In addition, the presence of inflammatory cytokines such as TNF-α and IL-1β activates astrocytes and microglia leading to neurodegeneration. 3) Neuronal pathway: Decrease in SCFAs and enterochromaffin epithelial cells affects the formation of serotonin, dopamine and brain-derived neurotrophic factor (BDNF) in the brain via the vagus nerve and accelerates the accumulation of α-syn. All of these factors contribute to neurodegeneration in PD. SIBO, small intestinal bacterial overgrowth; SCFA, short chain fatty acid; LPS, lipopolysaccharides; α-syn, alpha synuclein; HPA, hypothalamus-pituitary adrenal; ROS, reactive oxygen species; IL, interleukin; IFN-γ, interferon γ; TNFα, tumor necrosis factor α; iNOS, inducible nitric oxide synthase; NO, nitric oxide.

and *Dorea* promoted by rice bran; the genera *Bifidobacterium*, *Blautia*, and *Anaerostipes* promoted by inulin; and the genus *Parabacteroides* promoted by resistant maltodextrin. In addition, changes in the gut microbiota, increased SCFA, decreased calprotectin (responsible for intestinal inflammation) and zonulin (a potential indicator of intestinal barrier inflammation) were observed, along with a small statistically significant decrease in NfL (a

neurodegenerative marker). [78]. A four-strain probiotic comprised of *Lacticaseibacillus rhamnosus*, *Enterococcus faecium*, *Lactiplantibacillus plantarum*, and *Lactobacillus acidophilus* was administered to PD patients in a multi-center randomized controlled trial that resulted in significant decrease in plasma levels of IL-6 and TNF-α as well as improvements in both motor and non-motor symptoms [79]. A recent preclinical study was conducted in female Sprague-Dawley (SD) rats to evaluate the effect of the probiotic *Bifidobacterium breve* (*Bif11*) and it was observed that the probiotic ameliorated motor symptoms in the methylphenyl tetrahydropyridine hydrochloride (MPTP) induction rat model assessed by the rotarod test. The results indicated the downregulation of tyrosine hydroxylase (TH) in the midbrain by MPTP, which was reversed by a higher dosage of *Bif11*, suggesting a potential compensatory mechanism in midbrain biosynthesis and signaling. TH is recognized as a potential indicator in the onset and progression of PD. It is also the rate-limiting enzyme in the biosynthesis of dopamine, and it has been reported that TH levels tend to decline in both animal models of PD patients with the disease. The neuroprotection provided by *Bif11* may be a result of reduced levels of reactive nitrogen species (RNS) and reactive oxygen species (ROS), as well as inflammatory cytokines such as IL-1β and IL-6, and the corresponding inflammatory protein expression [80]. A double-blind, placebo and randomized controlled trial was carried out on PD patients to evaluate the effect of synbiotic sachet comprised of five strains of beneficial probiotics, including *Lactobacillus acidophilus* (LA-5), *Lactobacillus plantarum* (LAP-10), *Lactobacillus rhamnosus* (LAR-7), *Bifidobacterium longum* (BIA-8), *Streptococcus thermophilus* along with 4 g of inulin that served as a prebiotic which showed a significant reduction in serum oxidative stress index (OSI), malondialdehyde (MDA), and increase in serum glutathione (GSH) level and total antioxidant capacity (TAC) and led to significant improvement in depression, cognitive dysfunction and improvement in the activities of daily living which was hindered in PD patients was measured by the scale known as Parkinson's disease quality of life (PDQ-39) [81].

Amyotrophic lateral sclerosis (ALS)

ALS is defined as a degenerative motor neuron disease, often associated with pathogenic neuronal hyperexcitability, characterized by impairment of motor neurons in the spinal cord, primary motor cortex, and brain stem [82]. According to the National ALS Registry, the age-adjusted prevalence estimate is 6.6 per 100,000. According to a 2023 study, the prevalence of ALS in the United States is approximately 9.1 cases per 100,000 people [83]. The age range of 18 to 39 years old had the lowest incidence rates (0.6 age-adjusted rates per 100,000), whereas the age categories of 60–69 (4.2–4.4 age-adjusted rates per 100,000) and 70–79 (19.5 age-adjusted rates per 100,000) age groups had the highest incidence rates across all years, suggesting that aging is a significant risk factor for disease progression [84]. The only ALS drug approved by the U.S. Food and Drug Administration (FDA) is riluzole, which works by blocking glutamatergic transmission and lowering glutamate levels to protect motor neurons from degeneration caused by excitotoxicity [85]. The most common side effects associated with riluzole are dizziness, general malaise, and elevated liver enzyme levels, which may indicate possible liver damage [86]. Prebiotics, probiotics and synbiotic therapies are gaining importance due to these unfavorable side effects because of their better safety profile and higher efficacy in the treatment of ALS [87].

Remarkably, the pathological features of ALS common to both hereditary and sporadic variants coincide with markers of aging, including telomere attrition, disrupted intercellular communication, inflammation, loss of proteostasis, mitochondrial failure, cellular senescence, and genomic instability/DNA damage. [88]. In the $SOD1^{G93A}$ rodent model, telomerase knockout promotes telomere shortening and an accelerated ALS phenotype [89]. Connexin-based gap junctions, such as Cx43, facilitate communication between astrocytes. Astrocytic-mediated neurotoxicity is associated with abnormally elevated Cx43 expression in mSOD1 mice and in cortical and spinal cord (SC) astrocytes of ALS patients [90]. The $SOD1^{G93A}$ transgenic rat has elevated expression of pro-inflammatory markers like IL-1β, NF-κB, and IL-18 along with NLRP3 inflammasome and caspase-1. Active caspase 1, IL-18, and apoptosis-associated speck-like proteins containing a caspase-1 recruitment domain (ASC) are also found in higher concentrations of the spinal cord astrocytes of $SOD1^{G93A}$ mice and sporadic ALS patients [91]. Furthermore, with aging, oxidative damage from reactive oxygen species (ROS) or sugars can modify proteins post-translationally, which leads to the creation of advanced glycation end products (AGEs) [92]. This AGE accumulation in neurofilament protein prolongs neuronal damage in ALS patients by producing superoxide, blocking nitric oxide-mediated responses, and causing covalent cross-linking [93]. When compared to non-transgenic or asymptomatic transgenic rats, senescence markers such as loss of nuclear lamin B1 expression and significantly elevated levels of matrix metalloproteinase-1 (MMP-1), p53 and $p16^{INK4a}$ were observed [94]. Senescence in naturally aging neurons may therefore impair their viability and make them more susceptible to various diseases. However, more research is needed to elucidate the relationship between senescence and the pathogenesis of ALS [95].

Although there are several theories to explain ALS, a growing collection of research indicates a link between intestinal dysbiosis and the development and progression of ALS. When compared to controls, the genus Dorea was overexpressed, while the genera *Anaerostipes*, *Lachnospira*, and *Oscillibacter* were comparatively underexpressed in ALS patients [96]. Apart from this, specific species like *Butyrivibrio fibrisolvens*, *Roseburia intestinalis*, *Akkermansia muciniphila*, and *Eubacterium rectale* were also decreased along with a decrease in *Firmicutes/Bacteroidetes* (F/B) ratio along with lower abundance of *Clostridium* and some yeasts [97, 98]. In the ALS group, a higher proportion of uncultured *Ruminococcaceae*, *E. coli*, and *Enterobacteria* were also found [99]. Certain taxa, including *Sphingomonas*, *Gaiella*, *Lachnospiraceae*, and *Klebsiella*,

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have been identified to be significant ALS predictors [100]. Increased risk of ALS was shown to be related to *Enterobacteriaceae* and unclassified *Acidaminococcaceae*. It is probable that γ-glutamyl amino acids may have a negative correlation with the possibility of developing the disease where γ-glutamyl phenylalanine is a specific risk factor for the condition. It was discovered that both of its metabolites, 3-methyl-2-oxobutyrate and 1-arachidonoyl-GPI, increase the possibility of developing ALS, whereas higher 4-acetylaminobutyric acid levels may lower the incidence of ALS [101]. It was reported that butyrate-producing bacteria (*e.g*., *Butyrivibrio Fibrisolvens*) are substantially reduced in ALS patients than in healthy controls. These changes affect not only the generation of SCFAs but also exhibit the potential to aggravate gut inflammation locally and initiate a neuroinflammatory or systemic response [102]. According to Niccolai *et al*., stool samples from patients with ALS showed considerably greater levels of inflammatory biomarkers, including IL-1α, IL-6, IL-18, and IL-27, monocyte chemoattractant protein-1 (MCP-1) as well as macrophage inflammatory protein-1 alpha (MIP-1α). Additionally, it has been shown that the serum and CSF fluid of ALS patients contained higher amounts of circulating inflammatory cytokines, such as IL-23 and IL-17, which indicated a Treg/Th17 imbalance [103]. Sagi *et al*. reported that alterations in the gut microbiota and F/B ratio were linked with significant metabolic abnormalities in mice lacking the antioxidant enzyme superoxide dismutase 1 (SOD1), a well-known animal model of ALS [104]. SOD1 deficiency increased oxidative stress, which prevented hepatic gluconeogenesis and facilitated lipid accumulation. Furthermore, a crucial enzyme in glycolysis, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), was linked to increased nitrosylation and subsequent deactivation in relation to redox imbalance. Chronic variations in the metabolism of carbohydrates might negatively affect the energy balance and progression of the ALS disease [105]. The presence of *Akkermansia muciniphila* (*A. muciniphila*) has been linked to better clinical outcomes, a possible increase in motor neuron survival, and a rise in nicotinamide, which is also linked to improvements in motor and functional abilities in ALS patients [106]. The immediate link of bacteria, *A. muciniphila* is highlighted due to its capacity to elevate GABA/glutamate ratios in the hippocampus in the pathogenesis of the disease [107].

Prebiotics, probiotics and synbiotics offer a promising avenue for exploring novel therapeutic strategies by modulating the gut microbiome and gut-brain axis function, reducing inflammation and conferring neuroprotection for debilitating disease [108]. A common prebiotic is galactosaccharide (GOS), which, when administered along with prebiotic curd rich in GOS to $SOD1^{G93A}$ mice, their life duration significantly increased, motor neuron loss was also decreased, and the production of inflammatory markers TNF-α and iNOS was also blocked [109]. According to a study conducted on $SOD1^{G93A}$ mice, the polyphenol Epigallocatechin gallate (EGCG) present in green tea is the main ingredient promoting the increase in *A. muciniphila* levels. Additionally, EGCG can boost SCFA levels substantially and particularly promote the proliferation of *Bifidobacterium* and *Lactobacillus*, thereby alleviating the symptoms of the disease [110]. The ALS mice expressing human mutant of transactive response DNA binding protein of 43 kDa (TDP43) were treated with probiotic formulation VSL#43 (comprised of *Streptococcus thermophilus*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*, *Lactobacillus helveticus*, *Bifidobacterium breve*, *Lactobacillus paracasei*, *Bifidobacterium longum* and *Bifidobacterium infantis*) by oral gavage for three weeks daily. The probiotic therapy enhanced *Butyrivibrio fibrisolvens*, Butyryl-coenzyme A CoA transferase as well as smooth muscle actin (α-SMA), ZO-1, and Claudin-5 in the colon, spinal cord, and brain. It also decreased the expression of inflammatory cytokines (IL-6, IL-17, and IFN-γ), GFAP, and TDP43 [111]. A longitudinal study was carried out to assess the changes in the morphology of the colon and ileum in mutant $SOD1^{G93A}$ transgenic mice models of ALS by using immunofluorescence and Western blotting. A multistrain probiotic combination (LBE) comprised of live bacteria of *Enterococcus faecalis, Bifidobacterium longum*, and *Lactobacillus acidophilus* was given to the mice beginning from 60 days of age and continued until the disease reached its fatal stage. Oral administration of LBE- not only protected the neuronal cells in the gut but also in the spinal cord of $SOD1^{G93A}$ mice, decreased abnormal SOD1 aggregation, and improved the pro-inflammatory response. Additionally, intestinal microbiota, SCFA levels, and autophagy function were all enhanced through LBE therapy [112]. Another interesting finding from prospective longitudinal research, including 50 ALS patients and 50 controls, demonstrated an imbalance between microbial groups that may be beneficial, such as *Bacteroidetes*, and those that may be neurotoxic or have pro-inflammatory functions, like *Cyanobacteria*. Moreover, *Cyanobacteria* produce additional neurotoxic compounds such as nodularin, which damages the cytoskeleton [113]; saxitoxin, which paralyzes voluntary muscle contraction [114]; and also microcystins, which are undesirable for the brain [115]. The microbial groups that altered the most over time were Bacteroidetes, and related families serve as a defense mechanism against neurotoxicity because of their many roles in the generation of butyrate, the activation of T cell-mediated responses, the metabolism of toxic and/or mutagenic compounds, and the synthesis of bile acid [116]. These findings may serve as a basis for further research on compounds associated with cytotoxic-related *Cyanobacteria* in the blood of ALS patients in order to validate the theory that these bacteria play a role in the pathogenesis of the disease [116]. The most widely used synbiotics are mostly made up of oligofructose and *Bifidobacterium* or *Lactobacillus* [117]. The impact of synbiotics on ALS patients or animal models has not been extensively studied in research [97].

Multiple sclerosis (MS)

MS is an autoimmune neurodegenerative disease characterized by progressive destruction of the myelin sheath surrounding nerve fibers by reactive T cells. Demyelination of nerve fibers causes axonal inflammation and results in a lack of coordination in walking and standing,

including tremors, muscle spasms, irregular bowel movements, and cognitive impairment [118]. It is thought to be of non-traumatic origin and predominates in young women. MS has been subdivided into benign MS (BMS), progressive relapsing MS (PRMS), primary progressive MS (PPMS), relapsing and remitting MS (RRMS) and secondary progressive MS (SPMS). In RRMS patients, relapses are mostly reversible with occasional exacerbations, whereas in SPMS there is continuous disease progression with or without relapses. PPMS is characterized by the recurrence of neurological symptoms with continuous disease progression and no response to treatment [119].

Although the origin of MS is still unknown, current research suggests that gut microbiota dysbiosis promotes the development and progression of MS [120]. The microbial diversity is affected in all subcategories of MS patients [121]. The significant drop in relative abundance of *Bifidobacterium*, *Firmicutes*, *Lachnospiraceae*, *Prevotella*, *Roseburia*, *Coprococcus*, *Dorea*, *Lachnospira*, *Faecalibacterium*, and *Butyricicoccus* has been reported in gut microbiome of MS patients including a marked increment in *Bacteroidetes*, *Akkermansia*, *Blautia*, and *Ruminococcoccus* population compared to healthy people [122]. The depletion of *Prevotella* concentration is responsible for relapsing episodes of RRMS patients and the expansion of Th17 cells [123]. Another study reported reduced levels of *Clostridia* clusters XIV and IV, resulting in less amount of SCFAs, Treg cells, and anti-inflammatory cytokines like 1L-10 production in RRMS patients [124, 125]. *Clostridium* is known for the production of Treg cells and anti-inflammatory cytokines like IL-10. *Firmicutes*, *Bifidobacterium*, and *Prevotella* are mainly responsible for the production of explicit microbial metabolite, SCFAs, and immune regulation. Therefore, SCFA levels in the serum of MS patients were observed low [126, 127], mainly butyrate [128, 129]. Similarly, *Coprococcus*, *Butyricicoccus*, *Lachnospira* and *Roseburia* are butyrate-producing bacteria. *Faecalibacterium* can convert other SCFAs, such as acetate and lactate, into butyrate. Therefore, the low concentration of the above-mentioned significant butyrate-producing bacteria in MS patients results in low SCFAs and butyrate molecules. SCFAs and butyrate have anti-inflammatory properties and have important immunomodulatory functions by enhancing Treg cells [130]. Moreover, SCFAs can cross BBB and can reduce the neuro-inflammatory cytokines [131], which trigger an inflammatory state favouring neuroinflammation in MS patients. *Akkermansia* is a mucin degrading bacteria and mucin degradation may cause intestinal inflammation [132, 133]. *Blautia* can release acetate, which stimulates insulin release and encourages hyperglyceridemia, fatty liver disease, and insulin resistance [134]. The reduced alpha diversity of gut microbiota was detected in RRMS patients [126]; however, an increase in alpha diversity was shown in PPMS [127]. The population of *Adlercreutzia* was lessened in MS patients, resulting in enhancement in oxidative stress, including inflammatory cytokines (IL-6) and chemo-attracting proteins-1 [135]. The consequences of the gut microbial community in MS are generally studied on an experimental autoimmune encephalomyelitis (EAE) animal model [136] (Figure 1).

The introduction of various therapeutic agents such as probiotics and prebiotics to improve the condition of MS patients by modulating gut dysbiosis, reducing oxidative stress and improving mental health has been studied [137]. Probiotic supplementation has slowed the onset and progression of the disease, including improved motor coordination by regulating immune and inflammatory factors [138]. The two probiotics named *Lactobacillus plantarum* and *Lactobacillus paracasei* restrained neurological symptoms in the EAE animal model [139]. The administration of probiotics *Lactobacillus casei shirota*, *Bacteroides fragilis*, *Bifidobacterium bifidum*, and *Bifidobacterium animalis* in EAE mice, suppressed TNF-α, IL-17 which further reduced Th1 and Th17 immune cells and triggers Treg and IL-10 secretion and improves the diseased condition [140]. Many more probiotics like *Candida kefir* [141], *Lactobacillus lactis* [142], *Lactobacillus* and *Bifidobacterium* [143], *Bifidobacterium animalis* and *Pediococcus acidilactici* [144], a combination of *L. plantarum* and *B. animalis* has proven the positive effect in EAE animal model. Similar results have been observed in clinical studies as well. Various probiotics individually [145, 146], as well as a combination of probiotics (*L. casei*, *L. fermentum*, *L. acidophilus*, and *B. bifidum*) [147], have made MS disease progression sluggish. The intake of different prebiotics in the form of non-fermentable dietary fiber (cellulose-rich diet) has healed gut dysbiosis by enriching *Ruminococcaceae*, *Helicobacteraceae*, and *Enterococcaceae* and lowering the *Sutterellaceae* and *Coriobacteriaceae* and prevents EAE in animals. Further, it reduces Th2 immune responses [148]. Recently, in randomized and cross-over trials, prebiotics (Prebiotin, containing oligofructose enriched inulin) and probiotics (Visbiome, containing *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* species) were administered to MS patients for six weeks. Both the supplements were well tolerated, but prebiotics were preferable to probiotics among MS patients; however, probiotics significantly improved bowel control than prebiotics [149] (Figure 2).

Moreover, few techniques like fecal microbial transplantation (FMT) have been reported the successful amelioration of MS symptoms [150, 151]. Diet modification studies in MS patients have shown promising results in alleviating the chronic symptoms of MS. Intervention with vitamin D supplements in a low-calorie diet and intake of dietary polyphenols like resveratrol, quercetin has rebalanced the gut microbiota, consequently leading to improved mitochondrial function [152], reduced oxidative biomarkers, better motor function and balance. Additionally, these diet modifications hampered the production of inflammatory cytokines (TNF-α) and autoimmune T cells and demyelination in MS and contributed to a better quality of life in MS patients [141-143]. A ketogenic diet consumed for 6 months by MS patients reversed the composition of the gut microbiome to normal, especially the abundance of *Akkermansia* strains [144]. One more method that has recently drawn attention in combating MS symptoms is intermittent fasting (IF), which enriched the gut population

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of *Bacteroidaceae*, *Lactobacillaceae*, and *Prevotellaceae* in EAE animals. Additionally, it showed an immunomodulatory effect by reducing Th17 and stimulating Treg cells [153, 154]. Many other variations in diet such as oral supplementation of SCFAs and introduction of polyunsaturated fatty acids (PUFAs) like omega-3 have indicated a therapeutic potential for MS. SCFAs such as propionate or butyrate treatment has promoted neuroprotection and remyelination, axonal density was also recovered with better immune responses which slowed relapse rate and severity of disease progression [152, 155]. Conjugated linoleic acid supplementation lowered CNS inflammation and demyelination, which corresponded with proliferation in *Porphyromonadaceae*, *Lachnospiraceae*, *Bacteroides*, *Lactobacillus*, and *Akkermansia* in EAE animals [156].

Thus, the imbalance between beneficial and pathogenic bacteria in the gut microbiome is an important player in the onset and progression of MS, and its modulation through various therapeutic interventions has been shown to benefit MS patients.

Huntington's disease (HD)

HD is an inherited autosomal dominant neurodegenerative disorder characterized by progressive cognitive decline and behavioral disturbances along with movement disorders such as dystonia and chorea [157]. Recent advances in the study of the gut microbiome have established a link between gut dysbiosis and the development of HD. Both wild-type (WT) male and female mice with HD exhibit a characteristic gut bacterial dominance. WT male HD mice had dominance of *Clostridiales*, *Bacteroidales*, and *Lactobacillales* compared to control WT male mice which showed bacterial gut dominance of *Clostridiales*, *Bacteroidales*, *Deferribacterales*, *Erysipelotrichales*, and *Lactobacillales*. Similarly in WT female HD mice, the abundance of *Clostridiales*, *Bacteroidales*, and *Lactobacillales* were reported in compared with control WT female mice where abundance of *Coriobacteriales*, *Clostridiales*, *Erysipelotrichales*, *Bacteroidales*, and *Burkholderiales* were observed [143]. In transgenic R6/1 HD mice, the increased level of *Bacteroidetes* and decreased level of *Firmicutes* was noted however in R6/2 mice *Firmicutes* were found in lower quantities whereas *Proteobacteria* and *Bacteroidetes* were found in greater quantities [158, 159]. Similar results, as depleted population of *Firmicutes*, *Lachnospiraceae* and *Akkermansiaceae* were observed in HD gene expansion carriers (HDGECs) male mice [160]. HD patients have a significant drop in a metabolite named 4-hydroxyphenyl acetic acid level which is derived from the diet [161]. In HD patients, lower species abundance of both α-diversity and β-diversity of gut microbiota were observed. Significant differences in phylum level of *Euryarchaeota*, *Firmicutes*, and *Verrucomicrobia* were noticed in HD male patients compared to healthy control. Additionally, in family level of *Enterobacteriaceae*, *Bacteroidaceae*, *Peptostreptococcaceae*, *Bifidobacteriaceae*, *Erysipelotrichaceae*, *Christensenellaceae*, *Peptococcaceae*, *Coriobacteriaceae*, *Flavobacteriaceae*, *Akkermansiaceae*, *Eggerthellaceae*, *Lachnospiraceae*, *Methanobacteriaceae*, *Rikenellaceae*, *Acidaminococcaceae*, and *Clostridiaceae* differences were highlighted however no major differences were observed in women. These observations were correlated with the cognitive inability of HD patients [162]. Another study results depicted, the lower abundance of genus *Intestinimonas* and higher abundance of genus *Bilophila* indicated the modulation of immune responses of HD patients as plasma level of anti-inflammatory cytokines (IL-4) was decreased and proinflammatory IL-6 level was increased. The gut population of *Porphyromonas* was positively correlated with the plasma concentration of IL-4, IL-10, and IL-13, whereas *Oscillibacter* and Gemmier were negatively correlated with IL-6 and *Clostridium_XVIII* were also negatively correlated with TNF-α and IL-8 [163] (Figure 1).

With the advancement of research, various therapies have been proposed to prevent the pathogenesis and progression of HD. The use of various polyphenols such as rutin, resveratrol, and grape seed polyphenol extract has counteracted neuroinflammation and neurodegeneration progression in HD. Rutin induces nuclear localization of DAF-16, which normalizes SOD-3 and HSP-16.2 gene expression, which disrupts sensory terminals and provides neuroprotection in *C. elegans* models of HD [164]. Resveratrol stimulates *Lactobacillus* and Aβ clearance of R6/2 transgenic HD mice which prevents apoptosis and Bax gene and stimulates Bcl-2 genes. This cascade of process delays neurodegeneration [165]. The grape seed polyphenol extract delays motor incoordination and enhances longevity in R6/2 transgenic HD mice [166]. Other polyphenols such as fisetin, hesperidin, and hesperetin significantly enrich *Lachnospiraceae* and activate ERK/MAPK signalling, which ameliorates the pathogenesis of HD [167-169].

The most widely used probiotic strain, *Lactobacillus* and *Bifidobacterium*, provides neuroprotection in other neurodegenerative disorders, including HD [170]. The other probiotics including *Lactobacillus rhamnosus*, *Lactobacillus reutri*, *Lactobacillus casei* or *Lactobacillus acidophilus*, *Saccharomyces* modulate gut dysbiosis and related immune response [171]. These probiotics benefit in recovering intestinal permeability and promoting anti-inflammatory responses. Additionally, the production of SCFAs can be stimulated and can significantly ameliorate the neuropathogenesis of HD by lowering neuroinflammation and neurodegeneration [172]. Well-planned studies, both pre-clinical as well as clinical, needed to be carried out to analyse the ideal probiotic for HD and to understand its microbiota-based molecular mechanism. Other microbiota-based therapeutic approaches for HD are modifications in diet, for example, the introduction of a high-fiber diet [173], ketogenic diet [174], or Mediterranean diet to HD patients [175]. These diets promote an abundance of beneficial bacteria, push gut dysbiosis to eubiotics, promote SCFA production, and cease oxidative stress and neuronal dysfunction, which may positively influence the neurogenesis of HD. However, advanced research is needed to choose the prime dietary regimen for HD patients and to interpret the mechanisms to control HD pathogenesis and progression [173]. The other major technique that is usually beneficial in other neurodegenerative diseases is

Table 1. Application of different prebiotics, probiotics, or synbiotics in neurodegenerative disorders in ongoing clinical trials.

Sl. No.	Neurodegenerative diseases	Therapeutic intervention	Trial outcome	Title of the study	Phase	NCT Number
1	AD	Probiotic blend capsule [20 million CFU (*Bifidobacterium breve, Lactobacillus helveticus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus rhamnosus*)].	• Pro-inflammatory cytokines (IL-6, IL-1β, CXCL2, NLRP3) and anti-inflammatory cytokines (IL-10) are peripheral inflammation indicators linked to the pathophysiology of mild AD separated from plasma in blood. • 16S rDNA gene sequencing for bacterial identification, taxonomic profiling.	Effect of probiotics on cognitive functioning of patients with mild Alzheimer's disease	Early Phase 1	NCT06181513
2	PD	Ecologic® Barrier 849 [Maize starch, maltodextrin, vegetable protein, potassium chloride, +/- probiotic bacteria (*L. casei W56, B. lactis W51, B. lactis W52, L. acidophilus W37, L. brevis W63, L. salivarius W24, Lc. lactis W19, Lc. lactis W58, B. bifidum W23*; ≥ 2.5×10^9 CFU/g), magnesium sulphate, manganese sulphate sachet, two times daily dosing for a total of 2 g (viable cell count of 2.5×10^9 CFU/g) per day].	• The 12-item Parkinson anxiety scale (PAS) is a self-reported measure with three subscales: avoidance behavior, episodic anxiety, and persistent anxiety; a likert scale (0–4) is employed to rate it. • The beck depression inventory (BDI) is a multiple-choice, 21-question self-report measure with a 0-to-3 scale.	Treating anxiety in Parkinson's disease with a multi-strain probiotic—a randomized, placebo-controlled trial	Phase 2	NCT03968133
		Prebiotic fibers and a probiotic [*Lactobacillus acidophilus*-10 billion CFU]	• The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) will be used to assess patients clinically both at baseline and 3 months later. • Blood samples will be collected at baseline and after 3 months	Clinical study evaluating the efficacy and safety of synbiotic as an adjuvant therapy in the treatment of Parkinson's disease	Phase 3	NCT05576818
3	ALS	Probiotic formulation containing 15 billion CFU.	• The study aimed to assess the changes in lipidomic profiles within and between placebo and probiotic groups after 24 weeks of intervention. • The study aimed to evaluate changes in polar metabolite profiles within and between probiotic and placebo groups during a 24-week period. Key microbiota metabolites that will be targeted, includes SCFAs, trimethylamine N-oxide (TMAO), and tryptophan-derived metabolites.	Effects of probiotics on lipidomic profile and disease evolution in ALS-FTDSD patients: a randomized multicenter, double-blind, phase II, placebo-controlled, parallel trial.	Phase 2	NCT06051123
4	MS	Vivomixx® [1.800 bio bacteria/day] Conjugated linoleic acid (CLA/Tonalin® FFA 80)	• T2 lesions were selected as the main outcome because they have been utilized in a number of recent MS studies as a surrogate indicator of treatment effectiveness. • The number of new or growing T2-weighted hyperintense lesions after 48 weeks of intervention is determined by comparing the brain MRI images to baseline.	Effects of incorporating conjugated linoleic acid (CLA/Tonalin® FFA 80) with probiotics (Vivomixx®/VSL#3) as add-on to a first-line immunotherapy in the treatment of RRMS.	Not applicable	NCT05920018
		Bouchard Belgian dark chocolate probiotic Napolitains, containing *Bifidobacterium longum*	• Percent change in Treg cells from baseline to week 6. • Percent change in SCFA levels from baseline to week 6.	The effects of probiotics on inflammatory biomarkers in MS patients and their family members with MS.	Not applicable	NCT06475183

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FMT. FMT can restore the gut microbiota and its function and modulate the brain axis; therefore, well-planned clinical trials are needed to confirm the safety and beneficial effects of FMT in HD patients and to identify the precise gut microbiota and metabolites that could act as therapeutic targets [174].

Clinical trials and evidence

Many clinical trials are currently underway to understand the clinical significance of various prebiotics, probiotics, or synbiotics and their mechanistic approach to ameliorating neurodegenerative disorders, which are listed in Table 1 [176].

Future directions

Research on the gut-brain axis is advancing rapidly, providing exciting new opportunities to explore the potential benefits of probiotics, prebiotics and synbiotics in the treatment of age-related and neurodegenerative diseases. Elucidate the mechanisms by which the gut microbiota influences neurodegenerative disease, such as the production of neuroactive metabolites, immune modulation, and gut-brain axis signaling, and characterize the distinct gut microbiome composition of patients to identify specific strains or microbial imbalances that could be targeted. Determining the specific indicators that distinguish neurodegenerative disease patients from healthy individuals and characterizing the gut flora in neurodegenerative disease are critical challenges. To address such challenges, high-quality metabolomic data from multiple long-term cohort studies and strain-level resolution metagenomic data would be extremely beneficial. Furthermore, precise mechanistic knowledge of the pathways by which gut microbes and their by-products affect the brain is still lacking. Designing personalized prebiotic or probiotic formulations according to each person's microbiome profile may help identify specific bacteria that are important for disease development or progression and prevention. Investigating the possibilities of integrating probiotics, prebiotics, and synbiotics with additional therapeutic treatments, including drugs or dietary changes, may help alleviate disease.

Conclusions

The continued rise in the prevalence of neurodegenerative diseases worldwide, coupled with the ineffectiveness of FDA-approved drugs, highlights the need for a different approach to identifying effective therapeutic targets. Modern technologies are helping us to understand the complex interactions between gut bacteria and the brain in neurodegenerative diseases. Interventions that modulate the microbiome, such as probiotics, synbiotics, and prebiotics, could reduce the severity of symptoms by decreasing pro-inflammatory bacteria and increasing SCFA production, which may reduce the inflammatory tone associated with neurodegenerative diseases. This review aims to explore the various possible pathways and mechanisms related to gut dysbiosis and aging in various neurodegenerative diseases such as AD, PD, ALS, MS, and HD. Various studies have shown that prebiotics, probiotics and synbiotics can improve brain function and overall health and can be used as an alternative treatment strategy, thereby improving the overall quality of life of an individual diagnosed with a neurodegenerative disease.

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