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Possible Role of Probiotics on Parkinson's Disease

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Abstract: Parkinson's Disease (PD), a neurodegenerative disorder characterized by dopaminergic neuron loss in the substantia nigra, presents a significant unmet therapeutic need. While current treatments primarily focus on managing symptoms, increasing evidence suggests a potential role for probiotics in mitigating disease progression and improving patient outcomes. The gut-brain axis, a bidirectional communication pathway between the gut microbiota and the central nervous system, is increasingly recognized as a key player in PD pathogenesis. Dysbiosis, an imbalance in gut microbial composition, has been consistently observed in PD patients, characterized by reduced beneficial bacteria and increased pathogenic species. This dysbiosis may contribute to increased intestinal permeability ("leaky gut"), leading to inflammation and the translocation of bacterial products into the bloodstream, potentially triggering neuroinflammation and exacerbating neuronal damage in the brain. Probiotics, live microorganisms that confer health benefits upon ingestion, offer a promising therapeutic strategy by modulating gut microbiota composition and function. Preclinical studies using animal models of PD have demonstrated that specific probiotic strains, such as *Lactobacillus* and *Bifidobacterium* species, can attenuate motor deficits, reduce neuroinflammation, and improve gut barrier integrity. These effects are often associated with alterations in short-chain fatty acid (SCFA) production, known to possess neuroprotective properties. Furthermore, probiotics may influence the production of neurotransmitters such as serotonin and dopamine, impacting mood and motor control. However, human studies on probiotics and PD remain limited and often yield inconsistent results. Challenges include variations in probiotic strains, dosages, and study designs, hindering the establishment of clear efficacy. Future research should focus on identifying specific probiotic strains with demonstrable efficacy in larger, well-designed clinical trials, considering individual patient characteristics and gut microbiota profiles for personalized probiotic therapies. Nevertheless, the accumulating preclinical and early clinical evidence strongly suggests that exploring the therapeutic potential of probiotics in PD warrants further investigation, potentially offering a novel and safe adjuvant therapy to improve disease management and quality of life for patients.

Keywords: *Probiotics, Parkinson Disease*

Introduction.

Parkinson's disease is a common and complex neurological disorder. The first detailed description of Parkinson's disease was made almost two centuries ago, but the concept of the disease continues to evolve. At its core, Parkinson's disease is a neuro- degenerative disease with early prominent death of dopaminergic

neurons in the substantia nigra pars compacta (SNpc). The resultant dopamine deficiency within the basal ganglia leads to a movement disorder characterised by classical parkinsonian motor symptoms. (Bloem et al., 2021)

Parkinson's disease is also associated with numerous non-motor symptoms, some of which precede the motor dysfunction by more than a decade. The mainstay of Parkinson's disease management is symptomatic treatment with drugs that increase dopamine concentrations or directly stimulate dopamine receptors. However, Parkinson's disease involves neurotransmitters other than dopamine and regions of the nervous system outside the basal ganglia. (Tolosa et al., 2021)

Previously, Parkinson's disease was thought to be caused primarily by environmental factors, but research is revealing that the disease develops from a complicated interplay of genetics and environment. (Weintraub et al., 2022a)

Thus, Parkinson's disease is now viewed as a slowly progressive neurodegenerative disorder that begins years before diagnosis can be made, implicates multiple neuroanatomical areas, results from a combination of genetic and environmental factors, and manifests with a broad range of symptoms. These complexities of Parkinson's disease are accompanied by clinical challenges. (Jankovic & Tan, 2020)

In particular, diagnostic tests which allow for definitive diagnosis at early stages of the disease do not exist. The gold standard for diagnosis of Parkinson's disease has been the presence of SNpc degeneration and Lewy pathology at post-mortem pathological examination. Lewy pathology consists of abnormal aggregates of α-synuclein protein, called Lewy bodies and Lewy neurites. The association between Lewy pathology and pathogenesis of the disease is poorly understood. Management strategies for many of the disabling features that occur in late stages of the disease are poor. These features include motor symptoms that do not respond to dopaminergic therapies or develop as complications of long-term dopaminergic drug use, as well as an array of non-motor symptoms. (Fanning et al., 2020)

Disease-modifying treatments that reduce the rate of neurodegeneration or stop the disease process have remained elusive and are the greatest unmet therapeutic need in Parkinson's disease. However, the understanding of the pathogenesis of Parkinson's disease is expanding and thereby helping to identify potential targets for disease modification. (Abdukodirov et al., 2022)

Clinical features

The classical motor symptoms of Parkinson's disease have been recognised as prominent components of the disease since James Parkinson's initial description in the 19th century, later refined by Jean-Martin Charcot. These parkinsonian symptoms include bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment.(Váradi, 2020)

Motor features in patients with Parkinson's disease are heterogeneous, which has prompted attempts to classify subtypes of the disease. A consensus on the classification of Parkinson's disease subtypes has not yet been established, but empirical clinical observations suggest two major subtypes: tremor-dominant Parkinson's disease (with a relative absence of other motor symptoms) and non-tremor-dominant Parkinson's disease (which includes phenotypes described as akinetic-rigid syn- drome and postural instability gait disorder). (Cilia et al., 2020)

An additional subgroup of patients with Parkinson's disease has a mixed or indeterminate phenotype with several motor symptoms of comparable severity. Course and prognosis of disease differ between the subtypes; tremor-dominant Parkinson's disease is often associated with a slower rate of progression and less functional disability than non-tremor-dominant Parkinson's disease. Furthermore, the various Parkinson's disease subtypes are hypothesised to have distinct aetiologies and pathogenesis. (Bloem et al., 2021b)

Non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, autonomic dysfunction, pain, and fatigue. These symptoms are common in early Parkinson's disease and are associated with reduced health-related quality of life. (Weintraub et al., 2022b)

Non-motor features are also frequently present in Parkinson's disease before the onset of the classical motor symptoms. This premotor or prodromal phase of the disease can be characterised by impaired olfaction,

constipation, depression, excessive daytime sleepiness, and rapid eye movement sleep behaviour disorder (RBD. (Tolosa et al., 2021b)

In fact, mood disorders and constipation have both been shown to nearly double an individual's risk of subsequently developing Parkinson's disease. The premotor phase can be prolonged; for example, the average latency between onset of RBD and occurrence of parkinsonian motor symptoms is 12–14 years. (Hayashida et al., 2021)

Motor and non-motor symptoms coexist in Parkinson's disease (PD), a degenerative neurological condition (Sveinbjornsdottir 2016). A lack of dopamine in the substantia nigra pars compacta is linked to the symptoms of Parkinson's disease (PD) (Jankovic 2008). Evidence suggests that oxidative stress, inflammatory pathways, aquaporins, growth factors, and gut microbiota are all involved in the pathophysiology of PD, which contributes to the disease's complex etiology (Parashar and Udayabanu 2017; Hassanzadeh and Rahimmi 2018; Romano et al. 2021; Tamtaji et al. 2019a; Sidorova and Saarma 2020). The motor phenotype in PD has been suggested to be connected to the alteration in gut microbiota (Scheperjans et al. 2015).

Jankovic and Stacy (2007) state that symptomatic treatment with various dopaminergic medications seeks to control motor abnormalities. Furthermore, numerous dietary and supplemental approaches have demonstrated promise in managing PD and other age-related diseases. These include flavonoids (Tamtaji et al. 2020a), vitamins (Suzuki et al. 2013), fatty acids (Tamtaji et al. 2019b), melatonin (Tamtaji et al. 2020b), and probiotic bacteria (Magistrelli et al. 2019). There are a number of proposed methods by which probiotics might protect the central nervous system (CNS). According to the results of a complete gene expression study, a probiotic product made up of eight different strains of Gram-positive bacteria was able to control the amount of gene expression in brain tissue. Distrutti et al. (2014) found that probiotics may alter the expression of genes including synapsin and BDNF, which are involved in neural plasticity and inflammatory processes. According to Mohammadi et al. (2019), LPS seems to downregulate the expression of procaspase-3 protein and Bcl-2, but elevated the expression of Bax and cleaved caspase-3. However, the Bax/Bcl-2 ratio and Bax were both reduced by the prophylactic administration of probiotics (L. helveticus R0052+B. longum R0175), while Bcl-2 expression was increased. In addition, Muhammadi et al. (2019) found that pretreatment with bacterial probiotics greatly enhanced procaspase-3 expression while simultaneously decreasing the level of cleaved caspase-3 in target tissues. This led to a diminution of caspase-3 activity produced by LPS. In an animal model of Alzheimer's disease (AD), the injection of Lactobacillus plantarum enhances gut microbiota diversity (Tan et al. 2020). In an animal model of Alzheimer's disease, researchers found that administering probiotics reduced oxidative stress and improved spatial function (Asl et al. 2019). Animal models of multiple sclerosis have demonstrated that probiotics alleviate inflammation and clinical symptoms (Lavasani et al. 2010). Additionally, a study conducted by Rahimlou et al. in 2020 found that probiotic administration enhanced mental health, exhaustion, and discomfort in multiple sclerosis patients, as well as increasing BDNF and decreasing IL-6 levels. Seizure severity, spatial memory, and oxidative stress in rats caused with pentylenetetrazole can be ameliorated by administering probiotics (Bagheri et al. 2019). It has also been suggested that probiotics be used in order to manage PD. A number of clinical trials have shown that taking probiotic supplements can help with constipation, bowel habits, stool consistency, and even scores on the MDS-UPDRS, which is used in Parkinson's disease clinical trials. Furthermore, probiotics exacerbated motor-cognitive impairments in a PD animal model, according to animal research (Tamtaji et al. 2019c; Castelli et al. 2020; Alipour Nosrani et al. 2020). Because of their ability to decrease inflammatory reactions and oxidative stress while increasing brain-derived neurotrophic factors (BDNF), probiotics have been suggested as a potential treatment for Parkinson's disease (PD) (Tamtaji et al. 2019c; Castelli et al. 2020).

More research into the molecular and cellular mechanisms that mediate the anti-Parkinsonian benefits of probiotics might shed light on potential therapeutic options for Parkinson's disease. In this article, we will try to give interested readers a more up-to-date picture of the area by examining the present status of probiotic treatment in PD.

Gut microbiota and PD

Borre et al. (2014) found that gut microbes play a significant impact in brain development. According to Sarkar and Banerjee (2019), an imbalance in the microbiota in the gut might cause an overabundance of T helper cells, pro-inflammatory cytokines, and lipopolysaccharides, which in turn can enhance the permeability of the intestinal and blood-brain barriers. The pathophysiology of neurodegenerative illnesses like Alzheimer's and Parkinson's may thus include the gut microbiota (Sarkar and Banerjee 2019).

Intestinal microbial flora may have a role in the onset and progression of PD, according to some (Marizzoni et al. 2017). The gut bacteria impact brain cells and, by extension, the digestive tract, through a variety of methods. These microbes influence the brain-gut axis by possible neurological, immunological, and neuroendocrine routes. Some researchers have proposed a relationship between PD gastrointestinal symptoms and dysregulation of the brain-gut-microbiota axis. Systemic inflammation can occur when the innate immune system is overstimulated, which can be caused by gut dysbiosis, an overpopulation of tiny intestinal bacteria, or increased intestinal permeability. It is also possible for alpha-synuclein misfolding to begin with activation of glial cells and enteric neurons. Furthermore, human antigens reacting with bacterial proteins can disrupt the acquired immune system (Mulak and Bonaz 2015). One possible link between motor phenotypes in PD and changes in the composition of the gut microbiota has been proposed (Scheperjans et al. 2015). The following changes in microorganisms species were observed in PD; decreased Bacteroides, Dorea, Prevotella, Bacteroides massiliensis, Faecalibacterium, Stoquefichus massiliensis, Blautia glucerasea, Bacteroides coprocola, Dorea longicatena, Bacteroides plebeius, Bacteroidesdorei, Prevotella copri, Ruminococcus callidus, Coprococcus eutactus, and raised Catabacter, Christensenella, Lactobacillus, Bifidobacterium, Papillibacter cinnamivorans, Oscillospira, Christensenella minuta, Lactobacillus mucosae, Catabacter hongkongensis, and Ruminococcus bromii. The formation of Lewy bodies (LBs), inflammation, and α-synuclein aggregation could be the outcome of these changes (Petrov et al. 2017). Disease severity and motor impairment were shown to be correlated with low levels of Lacnospiraceae and high levels of Enterobacteriaceae families, according to reports from Hoehn and Yahr and MDS-UPDRS Part III (Pietrucci et al. 2019). Although some PD patients follow Braak's staging, others do not have LP in the dorsal motor nucleus of the vagal nerve (DMV) but higher brain regions are affected. It is important to highlight that not all PD patients comply to the exact pattern of LP spread suggested by Braak. Moreover, olfactory issues are unrelated to LP in the enteric nervous system (ENS), and approximately one-third of PD patients do not have any LP in the ENS.

An imbalance in the gut microbiota's makeup may also be regulated by probiotics. In addition to regulating apoptosis, cytokine production, and reactive oxygen species (ROS), they improve the function of the gut epithelial barrier (Azad et al. 2018). Research has demonstrated that the microbiota in the gut can produce endocrine signaling molecules in two ways: indirectly and directly.Acetate, propionate, and butyrate are important signaling molecules produced by the microbiota; these are known as short-chain fatty acids (SCFAs) (Westfall et al. 2017). Their important functions include stimulating neurotransmitter synthesis in both the central and peripheral nervous systems, inhibiting apoptosis through caspase cascades, and limiting the creation of reactive oxygen species (ROS) by upregulating FoxP transcription. Among the essential molecules produced by microbiota is ferulic acid, which suppresses inflammatory responses, production of caspase-3, ROS suppression through PRX/Trx signaling, and apoptosis suppression through CRMP2 inhibition (Westfall et al. 2017).

Additionally, there is evidence that the gut bacteria community was improved after probiotic delivery. Probiotic supplementation significantly increased the number of beneficial bacteria and decreased the number of harmful bacteria in the gut following symbiotic consumption. In addition, Hosseinifard et al. (2019) found that probiotics reduced glial cell function (GFAP and GDNF) and levels of TLR-2, IL-17, and IL-6 in the colon and brain. A number of taxa, including the more common Lactobacillus, Bifidobacterium, and Streptococcus species, showed an increase in abundance after VSL3 administration (Tankou et al. 2018). Inflammatory

indicators rise and dendritic cells (DCs), macrophages (MQs), and endothelial cells (ECs) attach to toll-like receptors (TLR-2, 4). One possible intracellular mechanism by which LPS increases intestinal permeability is the elevation of CD14 membrane expression, which is dependent on TLR-4 (Guo et al. 2013). On the other hand, cytokine release via TLRs (ECs, MQs, and DCs) may also mediate the anti-inflammatory and immunomodulatory effects generated by probiotics. Increased levels of TGF-β and IL-10 can be caused by their effects on the development and proliferation of immune cells, including T-reg cells, as well as B cells and CD cells. According to Morshedi et al. (2019), probiotics have the potential to increase gut permeability by weakening transepithelial junctions (TJs), which in turn decreases the entry of LPS and other pathogens into the circulation through the lumen.

Probiotics and PD

Probiotics and clinical symptom in PD

The symptoms of Parkinson's disease can be either motor or non-motor in nature (Sveinbjornsdottir 2016). The non-motor symptoms of Parkinson's disease include cognitive dysfunction, depression, anhedonia, apathy, and constipation (Sveinbjornsdottir 2016). Sveinbjornsdottir (2016) lists bradykinesia, falls, postural instability, speech disturbance, gait freezing, and tremor as motor symptoms of PD.

One strategy for managing PD is to take probiotics. According to Tamtaji et al. (2019c), some PD symptoms may be alleviated by taking a probiotic supplement that includes Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus fermentum, and Lactobacillus reuteri.Fermented milk with certain probiotic strains can help PD patients whose constipation is bad, according to research by Barichella et al. (2016). Furthermore, probiotics enhance PD patients' bowel habits and stool consistency. According to a 2011 study by Cassini et al. In a separate study conducted by Ibrahim et al. (2020), it was found that PD patients experiencing constipation might improve their entire gut transit time and bowel opening frequency with the use of a multi-strain probiotic (Hexbio®) eight weeks later. The use of probiotics was also shown to enhance the frequency of loose bowel movements by other researchers (Tan et al., 2021). Secondary outcomes, such as life quality as it pertains to constipation and stool consistency, also showed improvements after multiple comparisons were corrected. Further studies found that treating constipation with probiotics (Bifidobacterium infantis and Lactobacillus acidophilus) may be less effective than trimebutine, but may alleviate bloating and abdominal pain to the same extent (Georgescu et al. 2016). In a 6-OHDA-induced Parkinson's disease animal model, the probiotic formulation SLAB51 ameliorated motor dysfunction. (Fuentes et al., 2020). Furthermore, animal models of 6-OHDA-induced PD have demonstrated that a combination of probiotics, including Bifidobacterium bifidum, Lactobacillus fermentum, Lactobacillus acidophilus, and Lactobacillus reuteri, can enhance apomorphine-induced rotating behavior and spatial memory. (Nosrani et al. 2020, Alipour). Probiotics reduced the amount of 6-OHDA-induced spins in an animal model of Parkinson's disease, according to another study (Mirzanaeni et al. 2019). According to Visñuk et al. (2020), motor skills can be improved by giving Streptococcus thermophilus CRL 808, Lactobacillus plantarum CRL 2130, and Streptococcus thermophilus CRL 807. Furthermore, Sun et al. (2021) found that motor deficits in MPTP-induced PD were ameliorated by oral administration of Clostridium butyricum. Hsieh et al. (2020) found that motor impairments, including abnormal gait patterns, motor coordination, and balance, were reduced with daily dosing. While Lacticaseibacillus rhamnosus HA-114 probiotics did not influence anxiety-like behavior in a 6-OHDA-induced PD animal model, they did increase cognitive impairments (Xie and Prasad 2020). Lastly, a mouse model of PD was found to have contextual fear extinction restored after oral injection of B. breve A1 (Ishii et al. 2021).

Disadvantageous metabolic activities, insufficient immune responses, increased expression of genes involved in antibiotic resistance, systemic infections, and altered intestinal tract integrity can result from inadequate probiotic consumption, despite the benefits of probiotics (Daliri et al. 2019; Doron and Snydman 2015). Extensive clinical trials on probiotic efficacy have revealed their potential to modulate dysbiosis regulation in several pathological phenotypes and diseases (Jiménez-Pranteda et al., 2015). Next time we study people with dysbiosis, we need to make sure we collect consistent data on the kind of probiotics they take, how much of them, and for how long. In addition, for probiotics to have the desired effects, they must be administered in

accordance with established protocols for clinical trials. Several factors, including the bacterial probiotics' strain, the method of administration, and the ultimate therapeutic efficacy, might influence the appropriate dosages of probiotics (Ouwehand 2017). Forssten and Ouwehand (2020) note that most probiotic assays prioritise end outcomes and changed clinical factors over the creation of consensus guidelines for the correct administration of these probiotics. Without jeopardizing the integrity of science, clinical trials may give doctors and scientists the ability to check the outcomes of trials and look for new ways to apply trial results in parallel (Pencina et al. 2016). The vast majority of probiotic clinical trials, however, fail to provide sufficient data regarding bacterial strains, dosage, or administration method. Therefore, additional research is required to address this data gap, as it could enhance their potential for future clinical and translational advantages.

Recent research has investigated the therapeutic effects and clinical features of probiotic treatment in PD patients. Compared to a non-PD group that was age and sex-matched, people with PD had a higher prevalence of UTIs and RT infections in this research. Additionally, PD patients tended to have lengthier hospital stays (Su et al. 2018). According to Mogna et al. (2012) and (2016), certain probiotic strains have the potential to inhibit the growth of common microbial pathogens like E. coli and Klebsiella pneumoniae. Furthermore, it was discovered by Van Kessel et al. (2019) that some probiotics produce tyrosine decarboxylase, or TDC. TDC is an enzyme produced by bacteria that efficiently converts levodopa into dopamine in the gut. Contaminants like tyrosine or inhibitors of human decarboxylase do not affect this reaction. Patients with Parkinson's disease who had intestinal bacterial TDC had much lower levodopa levels in situ (van Kessel et al. 2019). The tdc gene family was discovered in the genomes of many different species of bacteria, most notably in the Enterococcus and Lactobacillus genera (Perez et al. 2016, 2015). A higher need for daily doses of levodopa has been linked to a high concentration of bacterial tdc in stool specimens of PD patients (van Kessel et al. 2019).

Probiotic and biochemical markers in PD

Wei et al. (2018) found that oxidative stress is a known factor in neurological illnesses, including PD. Dopaminergic cell death in Parkinson's disease is thought to be triggered by oxidative stress, a common underlying mechanism. Referenced in Sanders and Greenamyre (2013). An imbalance in the redox status, brought about by an excess of reactive oxygen species (ROS), is what causes oxidative stress. Various intracellular components, including as mitochondria, the endoplasmic reticulum, peroxisomes, Xanthine oxidases, and NADPH oxidases, are responsible for producing reactive oxygen species (ROS) (Kim et al. 2015). Microglia-mediated neurotoxicity involves NADPH oxidase. According to Block et al. (2007), it is the main way that microglia produce extracellular reactive oxygen species. (Lull and Block 2010; Kim and Joh 2006) When microglia are activated, they release cytotoxic substances like tumor necrosis factor (TNF), reactive oxygen species (ROS), and nitric oxide (NO). There is evidence that the release of IL-1β, IL-6, and TNF-α increases in PD. According to Bessler et al. as published in 1999. Neurodegeneration may result from the exacerbation of neuro-inflammation brought on by microglia-released pro-inflammatory cytokines (Ramirez et al. 2017). Additionally, PD patients whose illness severity is substantially connected with elevated serum inflammatory cytokine levels (Kouchaki et al. 2018).

The maintenance of dopaminergic neurons is a critical function of BDNF. Dopaminergic cell death in PD is accompanied by a decrease in BDNF. Therefore, neurons in PD are at risk of damage if their BDNF mRNA levels are low. In 2000, Wells et al. There is evidence linking the pathogenesis of Parkinson's disease to BDNF and TrkB, the receptor for this protein. In 2020, Jin published... Neurons in PD are protected from oxidative stress injury when the TrkB/PI3K/Akt signaling pathway activates Nrf2 (Hannan et al. 2020; Park et al. 2019; Ren et al. 2019).

There is a significant function for 4-hydroxynonenal in neurodegeneration. It has a role in the process of oxidative stress-induced neuronal death (Zarkovic 2003). According to Kraemer et al. (2014), 0.4-hydroxynonenal activates p75, which controls the production of α-synuclein in Parkinson's disease. In 2018, Chen et al. Furthermore, apoptosis is facilitated by p-JNK and p-ERK1,2 (Lee et al., 2003; Pan et al., 2007). One possible treatment for Parkinson's disease is the suppression of p-JNK and p-ERK1,2.References: (Wang et al., 2004; Dong et al., 2020).

Potential novel therapeutic techniques for neurological illnesses have emerged, including antioxidant and anti-inflammatory supplements. Probiotic microorganisms are one kind of dietary supplement. Our earlier research demonstrated that MS patients whose diets included probiotics including Lactobacillus fermentum, Bifidobacterium lactis, Lactobacillus casei, Bifidobacterium infantis, and Lactobacillus plantarum had lower levels of hs-CRP and IL-6 and higher levels of IL-10, an anti-inflammatory factor. Furthermore, MDA, 8-OHdG, and insulin resistance were all reduced when individuals consumed probiotics (Tamtaji et al. 2019c). Another study found that patients with PD whose diets include probiotics had an improvement in gene expression of TNF-α, IL-1, IL-8, and TGF-β. In 2018, Borzabadi et al. Furthermore, in an animal model of PD, lipid peroxidation was reduced by a mixture of probiotics that included Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacterium bifidum, and Lactobacillus fermentum. (Nosrani et al. 2020, Alipour). Probiotic strains reduced inflammation and oxidative stress in PD, according to an in vitro study. They also boosted levels of anti-inflammatory cytokines. (The quote is from Magistralli et al.2019). Castelli et al. (2020) found that in an in vitro model of PD, the probiotic formulation SLAB51 improved mBDNF, p-TrkB, p-ERK5, p-CREB, PI3K/Akt, HO-1, p-Nrf2, and PPARγ. Furthermore, according to Castelli et al. (2020), NF-κB, 4-hydroxynonenal, p-JNK, p-ERK1,2, and P75 were all downregulated in PD after administering the probiotic formulation SLAB51. According to Visñuk et al. (2020), the anti-inflammatory cytokine interleukin 10 was elevated in both the brain and serum, when Streptococcus thermophilus CRL 808, Lactobacillus plantarum CRL 2130, and Streptococcus thermophilus CRL 807 were administered. These microorganisms also decreased tumor necrosis factor-alpha in serum and inflammatory cytokine interleukin 6. At the same time, Clostridium butyricum heightened microglial activation in MPTP-induced PD. Additionally, Sun et al. (2021) found that therapy with Clostridium butyricum corrected the gut microbiota dysbiosis in the MPTP-induced PD. In contrast, Dwyer et al. (2021) found no evidence that VSL#3 mitigated inflammation in a mouse model of LPS-induced PD. Therefore, it is evident that further research into the function of probiotics in PD is warranted.

Probiotic and dopamine in PD

The brain's catecholamine production is limited by the rate-limiting enzyme tyrosine hydroxylase (TH). Zhu et al. (2012) found that PD results from a decrease in dopamine (DA) production caused by a decrease in TH expression. The downregulation of α-synuclein increases TH activity and DA production. Thus, α-synuclein acts as a regulator of DA in a negative manner (Liu et al. 2008). Furthermore, microglia are directly activated and pro-inflammatory cytokine production results from the overexpression of α-synuclein (Theodore et al. 2008). According to Scudamore and Ciossek (2018), Hashimota et al. (1999), and Souza et al. (2000), α-synuclein aggregation can be caused by elevated oxidative stress.

Dopaminergic neurons in the striatum and substantia nigra were rescued and TH immunoreactivity was increased by the probiotic formulation SLAB51 (Castelli et al. 2020). Furthermore, in PD experimental models, probiotic formulation restored PSD95 and reverted the decline in dopaminergic transporter levels. (Fuentes et al., 2020). The substantia nigrain is an animal model of PD generated by 6-OHDA. A mixture of probiotics containing Lactobacillus acidophilus, Lactobacillus reuteri, Bifidobacterium bifidum, and Lactobacillus fermentum reduced neuronal damage in this model (Alipour Nosrani et al. 2020). Hsieh et al. (2020) found that probiotic treatment retained TH-positive cells in the substantia nigra of PD mice. A study conducted by Visñuk et al. (2020) in an animal model of Parkinson's disease found that the brain TH-positive cell counts were increased after the administration of Streptococcus thermophilus CRL 808, Lactobacillus plantarum CRL 2130, and Streptococcus thermophilus CRL 807. In MPTP-induced PD, the probiotic Clostridium butyricum increased synaptic dysfunction and the death of dopaminergic neurons. According to Sun et al. (2021). However, in a lipopolysaccharide-induced PD mouse model, VSL#3 was unable to avert a decrease in substantia nigra dopamine neuron density (Dwyer et al. 2021). In PD animals, there was a notable drop in the levels of postsynaptic density protein-95 and synaptophysin mRNA expression in the hippocampus, along with an increase in the levels of neuropsin mRNA and protein. In addition, the number of CA1 apical spines decreased in mice with PD. Nevertheless, when PD mice were given B. breve A1, the effects were reversed and the CA1 spine density was returned to control levels. The results demonstrate that aberrant changes in hippocampal

synaptic plasticity are associated with increased neuropsin induction and that B. breve A1 inhibits its expression. Fear extinction was facilitated in PD mice after treatment, which corrected the aberrant hippocampus synaptic plasticity.

Parkinson's disease (PD) is a prevalent neurodegenerative illness that manifests in both motor and non-motor symptoms. One of the molecular processes of PD is increased inflammation and oxidative stress, which can occur prior to the motor symptoms. Another indication is gastrointestinal dysfunction. There is currently no cure for PD, however therapies can alleviate symptoms. Ideally, a solution would slow the disease's course.

The gut-brain axis can be regulated by administering probiotics, which may provide neuroprotection. Table 1 shows that some have hypothesized that probiotics reduce the incidence of neurological illnesses; nevertheless, this idea has to be further investigated and validated. The potential of probiotics in treating Parkinson's disease and other neurological illnesses can be better understood by studying the biochemical changes that occur when individuals with these conditions take probiotic supplements.

Authors	Years	Human/animal	Supplementation	Clinical results
Cassani et al. (2011)	2011	Patients with PD	Fermented milk drink containing 6.5 × 109 CFU of *Lactobacillus casei Shirota*	Improving stool consistency as well as bowel habits
Barichella et al. (2016)	2016	Patients with PD	Fermented milk, containing multiple probiotic strains and prebiotic fiber	Improving the constipation
Tamtaji et al. (2019c)	2019	Patients with PD	*Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri, and Lactobacillus fermentum*	Improving UPDRS
Mirzanaeni et al. (2019)	2019	Animal model of PD induced by 6-OHDA	Probiotic Bacillus coagulans	Improving apomorphine-induced rotational behavior
Castelli et al. (2020)	2020	Animal model of PD induced by 6-OHDA	Probiotic formulation SLAB51	Improving motor impairment
Alipour Nosrani et al. (2020)	2020	Animal model of PD induced by 6-OHDA	Probiotics including *Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri, and Lactobacillus fermentum*	Improving apomorphine -rotational behavior and spatial memory
Visñuk et al. (2020)	2020	Animal model of PD induced by MPTP	Lactobacillus plantarum CRL 2130, Streptococcus thermophilus CRL 807 and Streptococcus thermophilus CRL 808	Improving motor skills
Hsieh et al. (2020)	2020	A genetic MitoPark PD mouse model	*Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus rhamnosus, Lactobacillus rhamnosus* GG, *Lactobacillus plantarum* LP28, and *Lactococcus lactis* subsp. *Lactis*	Improving motor impairments in gait pattern, balance function, and motor coordination
Ibrahim et al. (2020)	2020	Patients with PD	Probiotic (Hexbio) in orange flavoring containing microbial cell preparation of (MCP1BCMC1) at 30 × 109 colony forming units (CFU), 2% fructooligosaccharide (FOS), and lactose. The microbial composition of the probiotics were: Lactobacillus acidophilus (BCMC1 12,130)—107 mg, Lactobacillus casei (BCMC1 12,313)—107 mg, Lactobacillus lactis (BCMC1 12,451)-107 mg, (BCMC1 02,290)—107 mg, Bifidobacterium infantis (BCMC1 02,129)—107 mg and Bifidobacterium longum (BCMC1 02,120)—107 mg	improving bowel opening frequency and whole gut transit time
Xie and Prasad (2020)	2020	Animal model of PD induced by 6-OHDA	Lacticaseibacillus rhamnosus HA-114	No impact on anxiety-like behavior Improving hippocampal dependent cognition deficits
Sun et al. (2021)	2021	Animal model of PD induced by MPTP	Probiotic *Clostridium butyricum*	Improving motor deficits
Tan et al. (2021)	2021	Patients with PD	*Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus gasseri, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Enterococcus faecalis, Enterococcus faecium*	Increasing spontaneous bowel movements Improving stool consistency and quality of life related to constipation
Ishii et al. (2021)		Animal model of PD induced by MPTP	*Bifidobacterium breve strain A1 [MCC1274] (B. breve A1)*	Restored facilitation of contextual fear extinction in PD mice

References

Alipour Nosrani E, Tamtaji OR, Alibolandi Z, Sarkar P, Ghazanfari M, Azami Tameh A, Taghizadeh M, Banikazemi Z, Hadavi R, Naderi Taheri M (2020) Neuroprotective effects of probiotics bacteria on animal model of Parkinson's disease induced by 6-hydroxydopamine: A behavioral, biochemical, and histological study. J Immunoassay Immunochem 42:106–120 [DOI] [PubMed] [Google Scholar]

Asl ZR, Sepehri G, Salami M (2019) Probiotic treatment improves the impaired spatial cognitive performance and restores synaptic plasticity in an animal model of Alzheimer's disease. Behav Brain Res 376:112183. [DOI] [PubMed] [Google Scholar]

Azad M, Kalam A, Sarker M, Li T, Yin J (2018) Probiotic species in the modulation of gut microbiota: an overview. BioMed Res Int. 10.1155/2018/9478630 [DOI] [PMC free article] [PubMed] [Google Scholar]

Bagheri S, Heydari A, Alinaghipour A, Salami M (2019) Effect of probiotic supplementation on seizure activity and cognitive performance in PTZ-induced chemical kindling. Epilepsy Behav 95:43–50 [DOI] [PubMed] [Google Scholar]

Barichella M, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, Pinelli G, Privitera G, Cesari I, Faierman SA (2016) Probiotics and prebiotic fiber for constipation associated with Parkinson disease: an RCT. Neurology 87(12):1274–1280 [DOI] [PubMed] [Google Scholar]

Bessler H, Djaldetti R, Salman H, Bergman M, Djaldetti M (1999) IL-1β, IL-2, IL-6 and TNF-α production by peripheral blood mononuclear cells from patients with Parkinson's disease. Biomed Pharmacother 53(3):141–145 [DOI] [PubMed] [Google Scholar]

Block ML, Zecca L, Hong J-S (2007) Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci 8(1):57–69 [DOI] [PubMed] [Google Scholar]

Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF (2014) Microbiota and neurodevelopmental windows: implications for brain disorders. Trends Mol Med 20(9):509–518 [DOI] [PubMed] [Google Scholar]

Borzabadi S, Oryan S, Eidi A, Aghadavod E, Kakhaki RD, Tamtaji OR, Taghizadeh M, Asemi Z (2018) The effects of probiotic supplementation on gene expression related to inflammation, insulin and lipid in patients with Parkinsonâ s disease: a randomized, double-blind, placebo-controlled trial. Arch Iran Med 21(7):289–295 [PubMed] [Google Scholar]

Cassani E, Privitera G, Pezzoli G, Pusani C, Madio C, Iorio L, Barichella M (2011) Use of probiotics for the treatment of constipation in Parkinson's disease patients. Minerva Gastroenterol Dietol 57(2):117–121 [PubMed] [Google Scholar]

Castelli V, d'Angelo M, Lombardi F, Alfonsetti M, Antonosante A, Catanesi M, Benedetti E, Palumbo P, Cifone MG, Giordano A (2020) Effects of the probiotic formulation SLAB51 in in vitro and in vivo Parkinson's disease models. Aging (Albany, NY) 12(5):4641. [DOI] [PMC free article] [PubMed] [Google Scholar]

Chen Y, Hou Y, Yang J, Du R, Chen C, Chen F, Wang H, Ge R, Chen J (2018) P75 involved in the ubiquitination of α-synuclein in rotenone-based Parkinson's disease models. Neuroscience 388:367–373 [DOI] [PubMed] [Google Scholar]

Daliri EBM, Lee BH, Oh DH (2019) Safety of probiotics in health and disease. In: Singh RB, Watson RR, Takahashi T (eds) The role of functional food security in global health. Academic Press, Cambridge, pp 603–622 [Google Scholar]

Distrutti E, O'Reilly JA, McDonald C, Cipriani S, Renga B, Lynch MA, Fiorucci S (2014) Modulation of intestinal microbiota by the probiotic VSL#3 resets brain gene expression and ameliorates the age-related deficit in LTP. PLoS ONE 9(9):e106503. 10.1371/journal.pone.0106503 [DOI] [PMC free article] [PubMed] [Google Scholar]

Dong L, Lu F, Zu J, Zhang W, Xu C, Jin G, Yang X, Xiao Q, Cui C, Xu R (2020) MiR-133b inhibits MPP+-induced apoptosis in Parkinson's disease model by inhibiting the ERK1/2 signaling pathway. Eur Rev Med Pharmacol Sci 24(21):11192–11198 [DOI] [PubMed] [Google Scholar]

Doron S, Snydman DR (2015) Risk and safety of probiotics. Clin Infect Dis 60(Suppl 2):129–134. 10.1093/cid/civ085 [DOI] [PMC free article] [PubMed] [Google Scholar]

Dwyer Z, Chaiquin M, Landrigan J, Ayoub K, Shail P, Rocha J, Childers CL, Storey KB, Philpott DJ, Sun H (2021) The impact of dextran sodium sulphate and probiotic pre-treatment in a murine model of Parkinson's disease. J Neuroinflammation 18(1):1–15 [DOI] [PMC free article] [PubMed] [Google Scholar]

Forssten S, Ouwehand AC (2020) Dose-response recovery of probiotic strains in simulated gastro-intestinal passage. Microorganisms. 10.3390/microorganisms8010112 [DOI] [PMC free article] [PubMed] [Google Scholar]

Georgescu D, Ancusa OE, Georgescu LA, Ionita I, Reisz D (2016) Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: is there hope? Clin Interv Aging 11:1601. [DOI] [PMC free article] [PubMed] [Google Scholar]

Guo S, Al-Sadi R, Said HM, Ma TY (2013) Lipopolysaccharide causes an increase in intestinal tight junction permeability in vitro and in vivo by inducing enterocyte membrane expression and localization of TLR-4 and CD14. Am J Pathol 182(2):375–387 [DOI] [PMC free article] [PubMed] [Google Scholar]

Hannan MA, Dash R, Sohag AAM, Haque M, Moon IS (2020) Neuroprotection against oxidative stress: phytochemicals targeting TrkB signaling and the Nrf2-ARE antioxidant system. Front Mol Neurosci 13:116. [DOI] [PMC free article] [PubMed] [Google Scholar]

Hashimoto M, Hsu LJ, Xia Y, Takeda A, Sisk A, Sundsmo M, Masliah E (1999) Oxidative stress induces amyloid-like aggregate formation of NACP/α-synuclein in vitro. NeuroReport 10(4):717–721 [DOI] [PubMed] [Google Scholar]

Hassanzadeh K, Rahimmi A (2018) Oxidative stress and neuroinflammation in the story of Parkinson's disease: could targeting these pathways write a good ending? J Cell Physiol 234(1):23–32. 10.1002/jcp.26865 [DOI] [PubMed] [Google Scholar]
Hosseinifard E-S, Morshedi M, Bavafa-Valenlia K, Saghafi-Asl M (2019) The novel insight into anti-inflammatory and anxiolytic effects of psychobiotics in diabetic rats: possible link between gut microbiota and brain regions. Eur J Nutr 58(8):3361–3375 [DOI] [PubMed] [Google Scholar]
Howells D, Porritt MJ, Wong J, Batchelor P, Kalnins R, Hughes A, Donnan G (2000) Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. Exp Neurol 166(1):127–135 [DOI] [PubMed] [Google Scholar]
Hsieh T-H, Kuo C-W, Hsieh K-H, Shieh M-J, Peng C-W, Chen Y-C, Chang Y-L, Huang Y-Z, Chen C-C, Chang P-K (2020) Probiotics alleviate the progressive deterioration of motor functions in a mouse model of Parkinson's disease. Brain Sci 10(4):206. [DOI] [PMC free article] [PubMed] [Google Scholar]
Ibrahim A, Ali RAR, Manaf MRA, Ahmad N, Tajurruddin FW, Qin WZ, Desa SHM, Ibrahim NM (2020) Multi-strain probiotics (Hexbio) containing MCP BCMC strains improved constipation and gut motility in Parkinson's disease: A randomised controlled trial. PLoS ONE 15(12):e0244680. [DOI] [PMC free article] [PubMed] [Google Scholar]
Ishii T, Furuoka H, Kaya M, Kuhara T (2021) Oral Administration of probiotic bifidobacterium breve improves facilitation of hippocampal memory extinction via restoration of aberrant higher induction of neuropsin in an MPTP-induced mouse model of Parkinson's disease. Biomedicines 9(2):167. [DOI] [PMC free article] [PubMed] [Google Scholar]
Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79(4):368–376 [DOI] [PubMed] [Google Scholar]
Jankovic J, Stacy M (2007) Medical management of levodopa-associated motor complications in patients with Parkinson's disease. CNS Drugs 21(8):677–692 [DOI] [PubMed] [Google Scholar]
Jiménez-Pranteda ML, Pérez-Davó A, Monteoliva-Sánchez M, Ramos-Cormenzana A, Aguilera M (2015) Food omics validation: towards understanding key features for gut microbiota, probiotics and human health. Food Anal Methods 8(2):272–289 [Google Scholar]
Jin W (2020) Regulation of BDNF-TrkB signaling and potential therapeutic strategies for Parkinson's disease. J Clin Med 9(1):257. [DOI] [PMC free article] [PubMed] [Google Scholar]
Kim YS, Joh TH (2006) Microglia, major player in the brain inflammation: their roles in the pathogenesis of Parkinson's disease. Exp Mol Med 38(4):333–347 [DOI] [PubMed] [Google Scholar]
Kim GH, Kim JE, Rhie SJ, Yoon S (2015) The role of oxidative stress in neurodegenerative diseases. Experimental Neurobiology 24(4):325. [DOI] [PMC free article] [PubMed] [Google Scholar]
Kouchaki E, Kakhaki RD, Tamtaji OR, Dadgostar E, Behnam M, Zaribaf A, Nikoueinejad H, Akbari H, Asemi Z (2018) Correlation of serum levels and gene expression of tumor necrosis factor-α-induced protein-8 like-2 with Parkinson disease severity. Metab Brain Dis 33(6):1955–1959 [DOI] [PubMed] [Google Scholar]
Kraemer BR, Snow JP, Vollbrecht P, Pathak A, Valentine WM, Deutch AY, Carter BD (2014) A role for the p75 neurotrophin receptor in axonal degeneration and apoptosis induced by oxidative stress. J Biol Chem 289(31):21205–21216 [DOI] [PMC free article] [PubMed] [Google Scholar]
Lavasani S, Dzhambazov B, Nouri M, Fåk F, Buske S, Molin G, Thorlacius H, Alenfall J, Jeppsson B, Weström B (2010) A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. PLoS ONE 5(2):9009. [DOI] [PMC free article] [PubMed] [Google Scholar]
Lee Y-J, Cho H-N, Soh J-W, Jhon GJ, Cho C-K, Chung H-Y, Bae S, Lee S-J, Lee Y-S (2003) Oxidative stress-induced apoptosis is mediated by ERK1/2 phosphorylation. Exp Cell Res 291(1):251–266 [DOI] [PubMed] [Google Scholar]
Liu D, Jin L, Wang H, Zhao H, Zhao C, Duan C, Lu L, Wu B, Yu S, Chan P (2008) Silencing α-synuclein gene expression enhances tyrosine hydroxylase activity in MN9D cells. Neurochem Res 33(7):1401–1409 [DOI] [PMC free article] [PubMed] [Google Scholar]
Lull ME, Block ML (2010) Microglial activation and chronic neurodegeneration. Neurotherapeutics 7(4):354–365 [DOI] [PMC free article] [PubMed] [Google Scholar]
Magistrelli L, Amoruso A, Mogna L, Graziano T, Cantello R, Pane M, Comi C (2019) Probiotics may have beneficial effects in Parkinson's disease: in vitro evidence. Front Immunol 10:969. [DOI] [PMC free article] [PubMed] [Google Scholar]
Marizzoni M, Provasi S, Cattaneo A, Frisoni GB (2017) Microbiota and neurodegenerative diseases. Curr Opin Neurol 30(6):630–638 [DOI] [PubMed] [Google Scholar]
Mirzanaeni S, Pakpour B, Navabian M (2019) The treatment effect of probiotic Bacillus coagulans on male Parkinson's rats. J Appl Microbiol Food Ind 5(3):17–30 [Google Scholar]
Mogna L, Deidda F, Nicola S, Amoruso A, Del Piano M, Mogna G (2016) In Vitro Inhibition of Klebsiella pneumoniae by Lactobacillus delbrueckii Subsp. delbrueckii LDD01 (DSM 22106): an Innovative Strategy to Possibly Counteract Such Infections in Humans? J Clin Gastroenterol 50(Suppl 2):S136–S139. 10.1097/mcg.0000000000000680 [DOI] [PubMed] [Google Scholar]
Mogna L, Del Piano M, Deidda F, Nicola S, Soattini L, Debiaggi R, Sforza F, Strozzi G, Mogna G (2012) Assessment of the in vitro inhibitory activity of specific probiotic bacteria against different Escherichia coli strains. J Clin Gastroenterol 46(Suppl):S29–32. 10.1097/MCG.0b013e31826852b7 [DOI] [PubMed] [Google Scholar]

Mohammadi G, Dargahi L, Naserpour T, Mirzanejad Y, Alizadeh SA, Peymani A, Nassiri-Asl M (2019) Probiotic mixture of Lactobacillus helveticus R0052 and Bifidobacterium longum R0175 attenuates hippocampal apoptosis induced by lipopolysaccharide in rats. 22(3):317–323. 10.1007/s10123-018-00051-3 [DOI] [PubMed] [Google Scholar]
Morshedi M, Hashemi R, Moazzen S, Sahebkar A, Hosseinifard E-S (2019) Immunomodulatory and anti-inflammatory effects of probiotics in multiple sclerosis: a systematic review. J Neuroinflammation 16(1):1–11 [DOI] [PMC free article] [PubMed] [Google Scholar]
Mulak A, Bonaz B (2015) Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol: WJG 21(37):10609. [DOI] [PMC free article] [PubMed] [Google Scholar]
Ouwehand AC (2017) A review of dose-responses of probiotics in human studies. Beneficial Microbes 8(2):143–151. 10.3920/bm2016.0140 [DOI] [PubMed] [Google Scholar]
Pan J, Zhao Y-x, Wang Z-Q, Jin L, Sun Z-K, Chen S-D (2007) Expression of FasL and its interaction with Fas are mediated by c-Jun N-terminal kinase (JNK) pathway in 6-OHDA-induced rat model of Parkinson disease. Neurosci Lett 428(2–3):82–87 [DOI] [PubMed] [Google Scholar]
Parashar A, Udayabanu M (2017) Gut microbiota: Implications in Parkinson's disease. Parkinsonism Relat Disord 38:1–7 [DOI] [PMC free article] [PubMed] [Google Scholar]
Park J-S, Leem Y-H, Park J-E, Kim D-Y, Kim H-S (2019) Neuroprotective effect of β-lapachone in MPTP-induced Parkinson's disease mouse model: involvement of astroglial p-AMPK/Nrf2/HO-1 signaling pathways. Biomol Ther 27(2):178. [DOI] [PMC free article] [PubMed] [Google Scholar]
Pencina MJ, Louzao DM, McCourt BJ, Adams MR, Tayyabkhan RH, Ronco P, Peterson ED (2016) Supporting open access to clinical trial data for researchers: The Duke Clinical Research Institute-Bristol-Myers Squibb Supporting Open Access to Researchers Initiative. Am Heart J 172:64–69. 10.1016/j.ahj.2015.11.002 [DOI] [PubMed] [Google Scholar]
Perez M, Calles-Enríquez M, Nes I, Martin MC, Fernandez M, Ladero V, Alvarez MA (2015) Tyramine biosynthesis is transcriptionally induced at low pH and improves the fitness of Enterococcus faecalis in acidic environments. Appl Microbiol Biotechnol 99(8):3547–3558. 10.1007/s00253-014-6301-7 [DOI] [PubMed] [Google Scholar]
Perez M, Ladero V, Del Rio B, Redruello B, de Jong A, Kuipers OP, Kok J, Martin MC, Fernandez M, Alvarez MA (2016) Transcriptome profiling of TDC cluster deletion mutant of Enterococcus faecalis V583. Genomics Data 9:67–69. 10.1016/j.gdata.2016.06.012 [DOI] [PMC free article] [PubMed] [Google Scholar]
Petrov V, Saltykova I, Zhukova I, Alifirova V, Zhukova N, Dorofeeva YB, Tyakht A, Kovarsky B, Alekseev D, Kostryukova E (2017) Analysis of gut microbiota in patients with Parkinson's disease. Bull Exp Biol Med 162(6):734–737 [DOI] [PubMed] [Google Scholar]
Pietrucci D, Cerroni R, Unida V, Farcomeni A, Pierantozzi M, Mercuri NB, Biocca S, Stefani A, Desideri A (2019) Dysbiosis of gut microbiota in a selected population of Parkinson's patients. Parkinsonism Relat Disord 65:124–130 [DOI] [PubMed] [Google Scholar]
Rahimlou M, Hosseini SA, Majdinasab N, Haghighizadeh MH, Husain D (2020) Effects of long-term administration of Multi-Strain Probiotic on circulating levels of BDNF, NGF, IL-6 and mental health in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. Nutr Neurosci. 10.1080/1028415X.2020.1758887 [DOI] [PubMed] [Google Scholar]
Ramirez AI, de Hoz R, Salobrar-Garcia E, Salazar JJ, Rojas B, Ajoy D, López-Cuenca I, Rojas P, Triviño A, Ramírez JM (2017) The role of microglia in retinal neurodegeneration: Alzheimer's disease, Parkinson, and glaucoma. Front Aging Neurosci 9:214. [DOI] [PMC free article] [PubMed] [Google Scholar]
Ren J, Yuan L, Wang W, Zhang M, Wang Q, Li S, Zhang L, Hu K (2019) Tricetin protects against 6-OHDA-induced neurotoxicity in Parkinson's disease model by activating Nrf2/HO-1 signaling pathway and preventing mitochondria-dependent apoptosis pathway. Toxicol Appl Pharmacol 378:114617. [DOI] [PubMed] [Google Scholar]
Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A (2021) Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Parkinson's Dis 7(1):27. 10.1038/s41531-021-00156-z [DOI] [PMC free article] [PubMed] [Google Scholar]
Sanders LH, Greenamyre JT (2013) Oxidative damage to macromolecules in human Parkinson disease and the rotenone model. Free Radical Biol Med 62:111–120 [DOI] [PMC free article] [PubMed] [Google Scholar]
Sarkar SR, Banerjee S (2019) Gut microbiota in neurodegenerative disorders. J Neuroimmunol 328:98–104 [DOI] [PubMed] [Google Scholar]
Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, Haapaniemi E, Kaakkola S, Eerola-Rautio J, Pohja M (2015) Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 30(3):350–358 [DOI] [PubMed] [Google Scholar]
Scudamore O, Ciossek T (2018) Increased oxidative stress exacerbates α-synuclein aggregation in vivo. J Neuropathol Exp Neurol 77(6):443–453 [DOI] [PubMed] [Google Scholar]
Sidorova YA, Saarma M (2020) Can growth factors cure Parkinson's disease? Trends Pharmacol Sci 41(12):909–922. 10.1016/j.tips.2020.09.010 [DOI] [PubMed] [Google Scholar]
Souza JM, Giasson BI, Chen Q, Lee VM-Y, Ischiropoulos H (2000) Dityrosine cross-linking promotes formation of stable α-synuclein polymers: implication of nitrative and oxidative stress in the pathogenesis of neurodegenerative synucleinopathies. J Biol Chem 275(24):18344–18349 [DOI] [PubMed] [Google Scholar]

Su CM, Kung CT, Chen FC, Cheng HH, Hsiao SY, Lai YR, Huang CC, Tsai NW, Lu CH (2018) Manifestations and outcomes of patients with Parkinson's disease and serious infection in the emergency department. Biomed Res Int 2018:6014896. 10.1155/2018/6014896 [DOI] [PMC free article] [PubMed] [Google Scholar]
Sun J, Li H, Jin Y, Yu J, Mao S, Su K-P, Ling Z, Liu J (2021) Probiotic Clostridium butyricum ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. Brain Behav Immun 91:703–715 [DOI] [PubMed] [Google Scholar]
Suzuki M, Yoshioka M, Hashimoto M, Murakami M, Noya M, Takahashi D, Urashima M (2013) Randomized, double-blind, placebo-controlled trial of vitamin D supplementation in Parkinson disease. The American of Clinical Nutrition 97(5):1004–1013 [DOI] [PubMed] [Google Scholar]
Sveinbjornsdottir S (2016) The clinical symptoms of Parkinson's disease. J Neurochem 139:318–324 [DOI] [PubMed] [Google Scholar]
Tamtaji OR, Behnam M, Pourattar MA, Jafarpour H, Asemi Z (2019) Aquaporin 4: a key player in Parkinson's disease. J Cell Physiol 234(12):21471–21478. 10.1002/jcp.28871 [DOI] [PubMed] [Google Scholar]
Tamtaji OR, Hadinezhad T, Fallah M, Shahmirzadi AR, Taghizadeh M, Behnam M, Asemi Z (2020a) The therapeutic potential of quercetin in parkinson's disease: insights into its molecular and cellular regulation. Curr Drug Targets 21(5):509–518 [DOI] [PubMed] [Google Scholar]
Tamtaji OR, Reiter RJ, Alipoor R, Dadgostar E, Kouchaki E, Asemi Z (2020b) Melatonin and Parkinson disease: current status and future perspectives for molecular mechanisms. Cell Mol Neurobiol 40(1):15–23 [DOI] [PMC free article] [PubMed] [Google Scholar]
Tamtaji OR, Taghizadeh M, Aghadavod E, Mafi A, Dadgostar E, Kakhaki RD, Abolhassani J, Asemi Z (2019b) The effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clin Neurol Neurosurg 176:116–121 [DOI] [PubMed] [Google Scholar]
Tamtaji OR, Taghizadeh M, Kakhaki RD, Kouchaki E, Bahmani F, Borzabadi S, Oryan S, Mafi A, Asemi Z (2019c) Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clin Nutr 38(3):1031–1035 [DOI] [PubMed] [Google Scholar]
Tan AH, Lim S-Y, Chong KK, Manap MAAA, Hor JW, Lim JL, Low SC, Chong CW, Mahadeva S, Lang AE (2021) Probiotics for constipation in Parkinson disease: a randomized placebo-controlled study. Neurology 96(5):e772–e782 [DOI] [PubMed] [Google Scholar]
Tan F, Liu G, Lau S-Y, Jaafar M, Park Y-H, Azzam G, Li Y, Liong M-T (2020) Lactobacillus probiotics improved the gut microbiota profile of a Drosophila melanogaster Alzheimer's disease model and alleviated neurodegeneration in the eye. Beneficial Microbes 11(1):79–89 [DOI] [PubMed] [Google Scholar]
Tankou SK, Regev K, Healy BC, Cox LM, Tjon E, Kivisakk P, Vanande IP, Cook S, Gandhi R, Glanz B (2018) Investigation of probiotics in multiple sclerosis. Mult Scler J 24(1):58–63 [DOI] [PubMed] [Google Scholar]
Theodore S, Cao S, McLean PJ, Standaert DG (2008) Targeted overexpression of human α-synuclein triggers microglial activation and an adaptive immune response in a mouse model of Parkinson disease. J Neuropathol Exp Neurol 67(12):1149–1158 [DOI] [PMC free article] [PubMed] [Google Scholar]
van Kessel SP, Frye AK, El-Gendy AO, Castejon M, Keshavarzian A, van Dijk G, El Aidy S (2019) Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease. Nat Commun 10(1):310. 10.1038/s41467-019-08294-y [DOI] [PMC free article] [PubMed] [Google Scholar]
Visñuk DP, de Giori GS, LeBlanc JG, de LeBlanc AM (2020) Neuroprotective effects associated with immune modulation by selected lactic acid bacteria in a Parkinson's disease model. Nutrition 79:110995. [DOI] [PubMed] [Google Scholar]
Wang W, Ma C, Mao Z, Li M (2004) JNK inhibition as a potential strategy in treating Parkinson's disease. Drug News Perspect 17(10):646–654 [DOI] [PubMed] [Google Scholar]
Wei Z, Li X, Li X, Liu Q, Cheng Y (2018) Oxidative stress in Parkinson's disease: a systematic review and meta-analysis. Front Mol Neurosci 11:236. [DOI] [PMC free article] [PubMed] [Google Scholar]
Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S (2017) Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. Cell Mol Life Sci CMLS 74(20):3769–3787. 10.1007/s00018-017-2550-9 [DOI] [PMC free article] [PubMed] [Google Scholar]
Xie C, Prasad AA (2020) Probiotics treatment improves hippocampal dependent cognition in a rodent model of Parkinson's disease. Microorganisms 8(11):1661. [DOI] [PMC free article] [PubMed] [Google Scholar]
Zarkovic K (2003) 4-hydroxynonenal and neurodegenerative diseases. Mol Aspects Med 24(4–5):293–303 [DOI] [PubMed] [Google Scholar]
Zhu Y, Zhang J, Zeng Y (2012) Overview of tyrosine hydroxylase in Parkinson's disease. CNS Neurol DisordDrug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders) 11(4):350–358 [DOI] [PubMed] [Google Scholar]