International Journal of Health Sciences and Research
[Indexed, Peer-Reviewed Journal]
Volume 15; Issue: 9; September 2025
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

Parkinson's Disease and the Gut Microbiota: Mechanistic Insights and Emerging Therapeutic Approaches

Afra Wasama Islam[1], Anusaya Sadanand Gawai[1], Arifa Akthar Niha[1], Johora Akter[1]

[1]Faculty of Medicine, Tbilisi State Medical University, Georgia

Corresponding Author: Afra Wasama Islam
https://orcid.org/0009-0007-4855-6226

DOI: https://doi.org/10.52403/ijhsr.20250918

ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disorder that affects around 14 per 100,000 people each year, making it the second most frequent disease among the elderly behind Alzheimer's. It primarily affects males aged 55 to 65 and is projected to double in prevalence by 2050. The disease causes the loss of dopaminergic neurons in the substantia nigra and the formation of α-synuclein aggregates, including Lewy bodies, in the central and enteric nervous systems. It causes both motor and non-motor symptoms, including rigidity, bradykinesia, and tremors. Environmental pollutants, genetic predispositions, and dietary factors all play a role in the disease's onset and course. Emerging studies focus on the role of gut microbiota imbalances and dysbiosis in Parkinson's disease progression, with data suggesting that changes in gut-brain axis communication may worsen disease symptoms. This review analyses the relationship between gut microbiota, gastrointestinal dysfunction, and Parkinson's disease, with a focus on the effects of reduced short-chain fatty acids and increased intestinal permeability on disease pathology. It also explores the possibilities of dietary therapies, such as ketogenic diets, in controlling Parkinson's symptoms. Recent therapeutic innovations, such as omega-3 fatty acids, vitamins, fecal microbiota transplantation, gene therapy, and probiotics, present intriguing treatment options. This review emphasizes the significance of a comprehensive approach to management, which includes innovative medications, lifestyle intervention, and nutritional measures to enhance prognosis and perhaps alter disease progression.

Keywords: Parkinson's Disease, gut microbiota, gut microbiome therapy, alpha-synuclein, treatment, fecal microbiota transplantation

1. INTRODUCTION

Nearly affecting more than 14 per 100,000 persons per year, an advancing neurodegenerative disease, Parkinson's Disease (PD) stands the second most prevalent only after Alzheimer's Disease among the elderly aged 60-80 years old.[1,2] Data has shown that the usual age of onset is 55-65 years old in nearly 1% of the population and 75-89 years and above in 2% of the population, commonly occurring in males predominantly and is expected to increase twofold by the year 2050.[1,3] This complex disease is driven by both

environmental and genetic factors, with its pathogenesis primarily marked by the loss of dopaminergic neurons in the substantia nigra and the buildup of α-synuclein in the CNS, ANS, brainstem, cerebral cortex, and other areas, including the olfactory bulb and glands.[2,4]

Patients with PD have reported several hallmark symptoms which primarily involve the motor system. These symptoms are characterized by rigidity, bradykinesia, resting tremors, and impaired balance.[1,2,5] However, recent studies have revealed that non-motor system malfunctions also play a role, including olfactory dysfunction like anosmia, gastrointestinal issues like vomiting, dysphagia, weight loss, and constipation, cardiovascular disturbances like cardiac dysautonomia, and urogenital problems such as polyuria, nocturia, and urge incontinence.[1,4,5] In addition to this, patients have also been shown to be affected with mental health disorders such as depression, anxiety, cognitive impairments, and sleep disorders such as insomnia.[1] The development of PD is influenced by various factors that can be either protective or damaging. Studies reported that oxidative stress and mucosal irritation, triggered by environmental toxins, gut dysbiosis, and certain health conditions, are major factors. These factors initiate the formation of α-synuclein, which eventually accumulates in the enteric nervous system in PD. [6] This could be prevented by consuming uric acid metabolites, antioxidants that reduce oxidative stress through chelation and can henceforth, provide protection against neuronal degeneration. Other triggers include alcohol, milk, and yogurt consumption.[7] Some neuroprotective foods include cigarette smoking, vitamin E supplements, and consumption of tea and coffee. [7-9]

2. Pathophysiology

Degeneration of dopaminergic neurons occurs gradually and is the hallmark of PD. [16] When these neurons die off, the neurotransmitter dopamine is reduced. This affects feedback loops in the basal ganglia and causes clinical symptoms such as bradykinesia, tremor, and rigidity.[20] Research on PD has identified key molecular indicators in its pathogenesis, including α-synuclein buildup, neuroinflammation, mitochondrial dysfunction, oxidative damage, autophagy failure, iron deposition, synaptic dysfunction, endoplasmic reticulum stress, and insulin resistance.[10] This complex disease is affected by both genetic and environmental factors. While only 10% of cases are familial, some are associated with several gene variants.[13] Moreover, several studies demonstrated notable differences in the composition of the gut microbiome between PD patients and healthy controls, which may affect the pathophysiology and clinical phenomenology.[10] Although, PD has usually been defined with movement symptoms, however, the symptoms of the disease are known to be varied, involving non-motor features of pathology impacting several nervous system regions, neurotransmitters, and protein aggregates.[15] Pathophysiologic factors contributing to disease progression and development are illustrated in Figure 1.

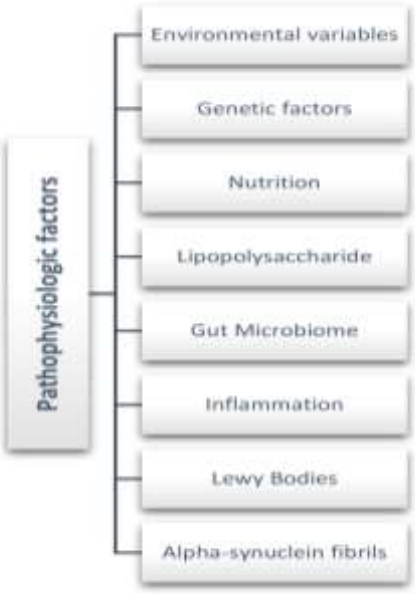

Figure 1. Pathophysiologic factors contributing to the development and progression of Parkinson's disease

2.1. Environmental variables

Before the 1918 influenza pandemic, it was believed that environmental factors mostly caused PD. [13] Recently, the discovery of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) led to the theory that infections might cause Parkinson's. MPTP specifically degenerates the nigrostriatal pathway, causing parkinsonism in humans and animals. Since then, various substances and environmental factors have been studied, but no links have been established.[16]

2.2. Genetic factors

In recent decades, the understanding of PD's etiology has evolved, with family history now linked to a higher risk of the disease. [16] Both autosomal dominant and recessive monogenic variants of PD are caused by mutations in several genes. Numerous genetic variations have been found to influence the likelihood of idiopathic disease. These variants include genes like LRRK2, SNCA, GBA, PRKN, and PINK1. These genes also encode proteins that influence immune function. [11]

2.3. Nutrition

Studies have suggested that Western diets raise risk and aggravate the progression of PD and these food habits may also change the gut microbiota, which could impact the symptoms of PD. [10]

2.4. Lipopolysaccharides

Lipids play a significant role in PD pathogenesis, affecting its progression through oxidative stress, organelle dysfunction, and immune responses. Additionally, SNPs in lipid metabolism genes, including a familial mutation in the glucocerebrosidase (GBA) enzyme, are strongly linked to PD's etiology. [13]

2.5. Inflammation

Intestinal inflammation has also been linked to modifications in the makeup of gut bacteria. Several inflammatory mediators, such as IL-1α, IL-1β, CXCL8, CRP, and calprotectin, have been found in the stool of PD patients compared to controls. The levels of some of these molecules are inversely correlated with the age at which PD symptoms first appear, indicating that they may play a role in the disorder's development.[11]

2.6. Alpha-synuclein fibrils and Lewy body formation

A hallmark of PD is the pathological accumulation of misfolded α-synuclein protein, encoded by the SNCA gene, which forms toxic amyloid fibrils leading to dopaminergic neuronal loss. [17,20] The aSyn protein, due to its disordered structure, can self-assemble into cross-β fibrillar aggregates, contributing to insoluble plaque formation. [13] These aggregates are detected in both central and enteric nervous systems and are particularly prominent in colon biopsies, suggesting early involvement of the gut in PD pathogenesis. [20,22] Their prion-like behavior allows spread from the vagus nerve to the substantia nigra, aligning with Braak's hypothesis that non-motor symptoms such as constipation and depression often precede motor signs by years. [11,12,14]

Lewy bodies and Lewy neurites are intracellular inclusions composed primarily of aggregated α-synuclein are the defining features of PD pathology. Their formation is influenced by lipid interactions and cellular membranes. [14] The presence of α-synuclein aggregates in the gut further supports the gut-brain axis involvement in PD. [20] Animal models have replicated this sequence, where gut-originating α-synuclein aggregates precede CNS involvement and motor impairment. Notably, mice raised in germ-free environments showed reduced α-synuclein pathology, highlighting the role of gut microbiota in disease progression. Aggregated α-synuclein may also function as a neo-antigen, activating adaptive immunity via TLRs 2 and 4, and leading to glial cell activation, T-cell recruitment, and local inflammation in both enteric and central systems.[21] Pathogenesis for PD has been summarized in Table 1.

Table 1. Mechanisms Linking Gut Dysbiosis to Parkinson's Disease Pathogenesis

Mechanism	Description	Evidence Type
α-Synuclein aggregation	Triggered by microbial metabolites & LPS	Human & animal studies
Increased intestinal permeability	"Leaky gut" allows endotoxins into bloodstream	Biomarker studies (zonulin, sucralase)
SCFA reduction	Low butyrate impairs anti-inflammatory signaling	Stool metabolomics
Neuroinflammation	Activated microglia from peripheral immune signaling	CSF cytokine elevation
Microbial LPS production	Triggers TLR4 → dopaminergic neuron loss	Rodent & postmortem human studies

3. Gut microbiota

Microorganisms that reside in the GIT are known as the gut microbiota.[24] With a genome of over 3 million and a population of 100 trillion, the human gut microbiome is the biggest in the body and is often referred to as the "second genome". These microbes share a symbiotic and mutualistic relationship with the host.[31] These symbionts, along with aiding in digestion, perform a variety of functions which include creating and modulating the immune system, generating vital metabolites, breaking down medications, maintaining the gut barrier, supporting CNS development, and protecting against infections.[24, 27] Metabolites from a diverse and stable gut flora are essential for maintaining health and supporting physiological functions. A healthy gut environment is crucial for a disease-free body. The gut microbiome is primarily composed of four bacterial phyla: *Firmicutes* (over two-thirds), followed by *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria*.[31] Animal models have shown compositional disruptions in gut microbiome brought on by the use of antibiotics, absence of breastfeeding, infections, stress, and environmental factors that can have long-term impacts.[27]

The host and the gut microbiota are generally in a balanced state under normal conditions, but when the gut microbiota is out of balance, it can cause gut dysfunction, which can lead to several disorders.[31] Increased abundance of pro-inflammatory bacteria has been seen in the gut microbiota of patients with PD, yet the precise nature of these changes is still unknown. [27,28]

3.1. Role of gut microbiome in PD

According to a meta-analysis, the gut microbiota compositions of PD patients and controls varied significantly.[12] Even after adjusting for gastrointestinal function, another cohort found significant differences in the microbiome of Parkinson's patients. PD-associated microbiota showed reduced carbohydrate fermentation and butyrate production, with increased proteolytic fermentation and generation of harmful metabolites like p-cresol and phenylacetylglutamine. These findings suggest that microbiota dysbiosis may contribute to the development and progression of PD through elevated levels of harmful microbial metabolites in the serum.[23]

Following a review of several studies, it has been discovered that PD is linked to an increase in intestinal species like *Akkermansia*, *Lactobacillus*, *Hungatella*, and *Bifidobacterium*. [12,30] There was a decreased abundance of *Roseburia*, *Faecalibacterium*, *Blautia*, *Anaerostipes*, and *Fusicatenibacter*. Fewer microbes produced SCFA, which influences inflammation in CNS, an attribute of neuroinflammatory and neurodegenerative diseases. [12,30] Patients with PD have also been found to have lower levels of *Prevotella copri* and this imbalance may promote inflammation, Lewy body formation, and α-synuclein aggregation in nerve cells. In early-stage PD patients not treated with levodopa, *Prevotella copri* levels were significantly lower compared to age-matched healthy controls.[22]

Studies have also found an increased abundance of *Akkermansia* and higher

intestinal permeability in PD patients. *A. muciniphila* breaks down the gut mucus layer, raising the risk of intestinal permeability, oxidative stress, and pesticide exposure. Additionally, colonic biopsies in PD patients showed reduced expression of occludin, which may expose the intestinal neural plexus to oxidative stress and toxins, potentially leading to abnormal α-synuclein aggregation in the intestine.[12,25] Research also demonstrated that patients with PD have been found to have significantly lower levels of metabolic products secreted by their gut bacteria, which may lead to constipation.[19] While animal studies indicate that this genus may contribute to an increased transit time, the increase in *Akkermansia* may be a result of constipation, a non-motor PD symptom. The two most highly enriched species in PD were *Lactobacillus* and *Bifidobacterium*, whose abundance varies widely between human diseases and chronic states along with *Akkermansia*.[30]

Reduced *Faecalibacterium* and *Roseburia* genus are related to PD. This imbalance can cause an intestinal pathology similar to inflammatory bowel illness, which in turn causes PD. [12] This is supported by the finding that patients with IBD had a noticeably greater chance of getting PD (28%-30%).[30] *Faecalibacterium* and *Roseburia* produce butyrate, which has anti-inflammatory properties. Most intestinal SCFAs, including propionate, promote anti-inflammatory cytokines while suppressing pro-inflammatory ones. A German cohort study found that SCFA levels in the fecal samples of PD patients were low.[12]

The cognitive deficits associated with PD have also been related to modifications in the metabolites' composition, such as the reduction of SCFAs. [19,26] Reduced butyrate levels have been linked to increased gait abnormalities and postural instability. Several gut microorganisms were also found to correlate with disease duration, motor symptom severity, and non-motor symptoms. In both progressing and stable PD groups, overall gut microbiota numbers decreased as the disease advanced. [11] Either patients with greater alterations in these taxa may have more rapidly progressing PD, or changes in these taxa were probably going to occur more quickly as PD progressed. [12] The variations in the levels of different bacterial species in PD has been summarized in Table 2.

Table 2. Key Changes in Gut Microbiota Composition in Parkinson's Disease

Bacterial Taxa	Observed Change in PD	Functional Implication
Akkermansia muciniphila	↑ Increased	Mucus degradation → leaky gut, inflammation
Lactobacillus spp.	↑ Increased	Variable effects; may reflect disease state
Faecalibacterium prausnitzii	↓ Decreased	Anti-inflammatory SCFA producer
Roseburia spp.	↓ Decreased	Butyrate production, gut barrier maintenance
Prevotella copri	↓ Decreased	Immune modulation, mucin synthesis
Desulfovibrio spp.	↑ Increased	Produces LPS and H_2S → pro-inflammatory

3.2. GI Dysfunction

The primary early non-motor symptom of PD, which affects up to 80% of patients, is intestinal dysbiosis and severe GI dysfunction. [32] GI dysfunction manifests as dysphagia, constipation, abdominal bloating, early satiety, inappropriate salivation, and fecal incontinence. Among this constipation is the most common of all. [4,36] The International Movement Disorders Society lists it as a clinical biomarker and notes that it raises the risk of dementia. [32] In PD, 61-73% of patients experience esophageal dysfunction, with up to 50% having difficulty swallowing, leading to hypersalivation. Over 65% suffer from defecatory dysfunction, marked by excessive straining and incomplete excretion. Impaired gastric emptying is another major symptom, causing postprandial bloating, nausea, early satiety, and abdominal pain. The gastrointestinal dysfunction in PD may result from lesions in the basal ganglia, swallowing centers, DMVN, and the median raphe nucleus, as well as abnormalities in the ANS.

Medication side effects, such as those from anticholinergic and dopaminergic drugs, can also contribute to GI issues. [4]

A breach in the intestinal barrier can cause gut bacteria and their metabolites to translocate into the system, impacting the homeostatic machinery. [5,12] A leaky gut is caused by a loss of intestinal barrier integrity, which gives bacteria and their antigens, such as LPS, access to the body. [29] In an animal study performed in rodents, LPS administered intraperitoneally to a mouse resulted in increased intestinal permeability and phosphorylated α-synuclein buildup in the dorsal vagal nucleus and intestinal mucosa. [12] Another study found that PD participants excreted more sucrase than controls, suggesting increased intestinal permeability. Mucosal biopsies linked this permeability to inflammation and *E. coli* antigens. Enzymes like alpha-1-antitrypsin, zonulin, and calprotectin were used to measure intestinal leakage. [29] Thus, proving that PD and increased intestinal permeability which causes leaky gut. [12]

3.3. Gut-Brain-Axis

A bidirectional communication network between the gut and the brain is known as the gut-brain axis (GBA). [14] A critical modulatory communication link between the stomach and brain is shown by research on probiotic therapies, which reveals that some bacterial species can enhance anxiety and mood. [27] Like PD, gut microbiota changes have been linked to GBA malfunction, neuroinflammation, and dopaminergic degeneration. [14] Studies have shown that PD patients have Lewy bodies in enteric nervous system cells, resulting from pathological α-synuclein inclusions. [21] Rodent research indicates that stress worsens rotenone's effects on the brain, reducing striatal dopamine and DA metabolites, increasing lipopolysaccharide responsiveness, and decreasing resting microglia. [25] The bidirectional model explains how enteric glial cells initiate and spread inflammation, disrupt the epithelial barrier, and misfold α-synuclein, ultimately affecting the central nervous system and contributing to early non-motor symptoms of PD. [14] Experimental findings in rodents support the idea that these α-synuclein inclusions are conveyed via axonal retrograde movements from the peripheral nervous system to the brain. [21] Studies have also shown that almost 2 decades before the manifestation of classic PD-like symptoms, gastrointestinal problems have been linked to clinical courses of people with PD. [13]

4. Risk Factors and Risk Assessment

One of the key risk factors for PD is growing old. Research has shown that older people have larger amounts of mitochondrial DNA deletions in their nigral neurons, with significant peaks starting shortly before age 70, affecting mostly males. [3,34] Studies have shown a higher incidence of Parkinson's disease among white individuals, possibly due to a Western diet high in saturated fats and processed foods. This diet may increase LPS-containing bacteria in the gut, compromising the gut barrier and leading to endotoxemia, insulin resistance, mitochondrial damage, and gluconeogenesis. This diet can also cause gut dysbiosis, increasing the risk of PD. Conversely, a healthy gut microbiota is linked to a lower risk of neurological disorders, particularly PD. [35]

About 5% to 10% of PD cases are linked to mutations in specific genes, such as PARK. These mutations increase ROS production in neurons, disrupt antioxidant mechanisms, and lead to the accumulation of abnormal α-synuclein protein, causing neuronal damage and apoptosis through mitochondrial pathways. The protein parkin, encoded by the PARK2 gene, maintains mitochondrial quality control; mutations in this gene often result in early-onset PD, particularly in patients under 30. Several other genetic factors are also involved. [36]

Various studies emphasize the importance of vitamins in reducing PD risk, particularly vitamin E, which offers protective

antioxidant effects. Carotenoids and vitamin C also play a crucial role by neutralizing ROS damage, reducing ROS production, enhancing defense mechanisms, and preventing LDL oxidation. [37,38] Other important antioxidants include selenium, essential for selenoproteins that regulate the intracellular redox state, and glutathione, which converts ROS to glutathione disulfide. However, an excess of these processes can lead to oxidative stress. [36]

Studies have suggested that the human appendix may contain strains of α-synuclein which can later cause PD, thereby suggesting that appendectomy may prevent the pathogenesis. [20] Patients with type 2 diabetes also have a higher risk of PD due to shared mechanisms like insulin dysregulation, oxidative stress, mitochondrial damage, and inflammation. This suggests that GLP-1R agonists might benefit both the gut-brain axis, offering protection to neurons and beta cells. [34]

Research has also suggested that the use of certain antibiotics and medications can contribute to the development of PD. [39]

Caffeine intake and cigarette smoking are linked to a lower risk of Parkinson's disease. Caffeine's metabolites block adenosine receptors, protecting dopaminergic neurons. Studies show that high caffeine consumers are often smokers, and smoking speeds up caffeine metabolism, affecting the central nervous system. [9,37] Certain drugs decrease the risk for PD like NSAIDs, ibuprofen, β-adrenoceptor agonists, and calcium channel blockers, especially in older patients. Occupational workers are particularly vulnerable to pesticide exposure, and milk and dairy products are likely to be a risk factor for PD. [37]

Early gastrointestinal symptoms like hypersalivation, constipation, dysphagia, and stomach irregularities can signal worsening cognitive function and help identify early PD. [40]

5. Therapeutic Modulation for PD

Over a decade, numerous treatments for PD have been proposed, including medications, dietary strategies, supplements, fecal transplants, gene therapy, prebiotics, probiotics, synbiotics, and exercise-based rehabilitation as mentioned in Table 3.

Table 3. Management approaches for Parkinson's Disease.

Approach	Details
Diet and Nutrition	Mediterranean diet reduces inflammation, promotes cognitive function, and lowers PD risk. DASH diet Improves cognitive abilities. Whereas, the ketogenic diet improves non-motor symptoms and reduces neuroinflammation.
Omega-3 Supplementation	Contains DHA, EPA, and ALA; has neuroprotective, antioxidant, and anti-inflammatory properties; reduces oxidative stress and α-synuclein accumulation.
Vitamins	Low levels of vitamin D are linked to PD development and neuroinflammation. Whereas vitamin B12 is correlated with motor dysfunction.
Fecal Microbiota Transplantation (FMT)	Alters gut microbiota to improve gut function, reduce inflammation, and alleviate PD symptoms.
Gene Therapy	Experimental therapies with GBA1 gene and α-synuclein mutation reduction. Seen to have improved motor and cognitive functions in trials
Pharmacological Intervention	Dopamine replacement like Carbidopa/Levodopa, MAO-B inhibitors like Selegiline, Rasagiline, SSRIs/SNRIs for depression, and Botulinum toxin for sialorrhea.
Probiotics, Prebiotics and Synbiotics	Probiotics, such as *Lactobacillus acidophilus* and *Bifidobacterium infantis*, help improve gastrointestinal (GI) symptoms and motor function and reduce neuroinflammation in Parkinson's disease (PD) patients. Prebiotics promote the growth of beneficial bacteria in the gut, which leads to reduced motor symptoms, improved GI function, and decreased inflammation. Synbiotics, a combination of probiotics and prebiotics, further enhance gut health and help alleviate constipation in PD patients.

[PD= Parkinson's Disease, DASH= Dietary Approaches to Stop Hypertension, DHA= Docosahexaenoic acid, EPA = Eicosapentaenoic acid, ALA= α-linolenic acid, SSRIs= Selective serotonin reuptake inhibitors MAO B= monoamine oxidase B]

5.1 Diet, Nutrition, and Gut Microbiome

Diet and nutrition have always played a critical role in the pathogenesis of various diseases, and have been one of the most important modifiable factors. As mentioned earlier, diet often influences the immune system by regulating the gut microbiota, which can also affect the CNS through the GBA. [41,42,44] A good nutritious diet can change the pro-inflammatory bacteria into anti-inflammatory bacteria which not only helps the GI function but also aids in the treatment processes of various neuropsychiatric diseases such as PD. [41,43] Consisting of fruits, vegetables, grains, legumes, nuts, olive oil, and healthy fats, the Mediterranean diet has been shown to have the highest nutritional content among the numerous well-known dietary regimens that are used worldwide. [41] This food pattern has a lot of bacteria that break down polysaccharides, and ferment dietary fiber and polysaccharides to create SFCAs, which in turn reduces inflammation and prevents obesity.[40,42,45] A couple of studies have demonstrated that following the Mediterranean diet in the age groups of 45-60, lowered the risk of PD. [46] Similarly, a different study demonstrated that adopting a Mediterranean diet lowered the risk of getting PD early symptoms. [47] Likewise, a case-control study conducted suggested that the higher the adherence to the Mediterranean diet the lower the risk of developing PD and vice versa. [48] Another randomized clinical trial found that this diet improved cognitive function, including language, attention, and memory. [49] In addition to fiber, Mediterranean diet staples like olive oil, grains, and vegetables are packed with polyphenols, flavonoids linked to a lower risk of PD.[40] Recent research found that these compounds have higher levels of antioxidant activity and anti-inflammatory, neuroprotective, and immunomodulatory properties. These actions promote the elimination of alpha-synuclein. [40,42]

Furthermore, another type of dietary pattern, the DASH diet also shares nutritional similarities with the Mediterranean diet. An array of studies has suggested that the DASH and Mediterranean diets, combined to form the MIND diet, may stimulate cognitive abilities in people with PD. [40]

In addition to this, scientists have also found that a ketogenic diet which has high fat content with an adequate amount of protein, is receiving acceptance as a potential therapy for PD. [40,86] This diet leads to a state known as ketosis, which facilitates the replacement of glucose with ketone molecules such as acetone, β-hydroxybutyrate, and acetoacetic acid. Although limited evidence, several clinical trials conducted in humans showed that ketone bodies have reduced UPDRS scores, indicating considerable improvements in non-motor symptoms. [40] Studies show that ketone bodies can reduce neuroinflammation by crossing the blood-brain barrier and modulating gene expression. They upregulate anti-inflammatory genes like MAP3K8 and TLR5 while down-regulating pro-inflammatory ones like TNF-α and NF-κB, leading to lower levels of inflammatory factors (IL-1β, IL-6) and reduced microglia activation in animal and in vitro models. [87,88]

5.2. Supplementation

5.2.1 Omega 3 Supplementation

Found in several food sources, omega-3 (ω3) are polyunsaturated fatty acids (PUFAs), examples of which include docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and α-linolenic acid (ALA). There is an array of health benefits linked to these, including antioxidant, anti-inflammatory, and neuroprotective properties. [40] Out of the 3 main types, DHA is the most important ω3 in the brain which can reduce oxidative stress and α-syn accumulation. [41] Additionally, research has indicated a correlation between it and decreased astrocyte and microglia proliferation. [50] In a translational study conducted, it has been suggested that combining uridine and DHA

in a diet can protect from GI dysfunction, α-syn accumulation, colon shortening, and T cell infiltration. [51] Furthermore, a rat-based trial has demonstrated that ω-3 PUFA can stop microglial activity and dopaminergic damage by blocking LPS-induced NF-κb activation. [52] Moreover, numerous clinical research studies and epidemiological trials have indicated a relationship between ω3 PUFA consumption and depression, frequently alleviating its symptoms. [40,41] In addition to its positive benefits on the brain, ω-3 has been shown to significantly reduce C-reactive protein (CRP), and NOS, and promote BDNF levels in the central nervous system. [53,54]

5.2.2. Vitamins

Various studies have discovered a connection of sorts between PD and vitamins. Given the significant roles that oxidative stress and neuroinflammation play in neurodegeneration and pathogenesis of PD vitamins may be a useful adjuvant therapy for the disease due to their antioxidant qualities and biological ability to regulate gene expression. [55] Researchers have identified an odd correlation between low levels of vitamin B12 and motor dysfunction. [41] They have also discovered a strong correlation between decreased levels of 25-OH vitamin D and less exposure to sunlight and an elevated risk of developing PD. Lower 25(OH)D levels might be responsible for dopaminergic neuronal death contributing to PD development, due to the lack of its protective function. [56] Additionally, a lower concentration of vitamin D correlates with high levels of C-reactive protein (CRP), a marker of inflammation. [57]

5.3. Fecal Microbiota Transplantation

Fecal microbiota transplantation or fecal bacteriotherapy involves the process of transferring filtered stool from a healthy donor to a patient's gut for the treatment of certain pathologies. This process can change the microbial environment of the gut and restore abnormal intestinal microbiota and is primarily done via colonoscopy. [40] Preserved intestinal barrier function, enhanced intestinal motility, SCFA generation, or fewer pro-inflammatory bacterial strains in the gut are among the advantageous outcomes of FMT. Currently, this therapeutic strategy has been used to treat diseases like recurrent *Clostridium difficile* infection, IBD, metabolic syndrome, and obesity. Researchers are also exploring this therapeutic option to treat several neurological disorders such as multiple sclerosis, ASD, Tourette syndrome, diabetic neuropathy, and PD. [40] A 2016 study by Sampson and colleagues found that transferring stool from Parkinson's patients to mice with excess α-synuclein worsened their symptoms compared to mice given stool from healthy individuals. The study also showed significant changes in SCFAs, highlighting the critical role of the microbial community in PD. [58]

Furthermore, administering *Faecalibacterium prausnitzii* to mice has been shown to alleviate colitis symptoms, suggesting its anti-inflammatory potential for treating IBD. These bacteria can also lower intestinal inflammation by improving cellular permeability and enhancing barrier function. [59] Studies also provided evidence that FMT balances the gut by reducing the growth of *Desulfovibrio*, *Akkermansia,* and *Proteobacteria*, and simultaneously increasing the *Bacteroidetes* and *Actinobacteria* species. [60] A study found that a single FMT session significantly relieved constipation and movement symptoms in a Parkinson's patient. Within a week after FMT treatment, the patient's leg tremor nearly disappeared. [61] When FMT was administered, 11 PD patients in a distinct small experimental study demonstrated improvements in both motor and non-motor abilities. [62]

5.4. Gene Therapy

Recent studies have highlighted the potential of gene therapy in altering the course of PD. In a randomized, double-blind

trial, patients receiving AAV2-GAD gene delivery to the subthalamic nucleus showed significant improvement in UPDRS motor scores after six months, indicating symptom relief. [63] Mutations in the GBA1 gene, present in 5–25% of PD patients, can increase disease risk up to twentyfold. Delivering functional GBA1 via AAV9 in rodent models improved motor and cognitive function.[64] Additionally, CRISPR-Cas9 targeting of the A53T-mutated SNCA gene in transgenic mice reduced α-synuclein aggregates and protected dopaminergic neurons.[65] While not yet standard therapy, these approaches show promise for disease modification. [63–65]

5.5 Pharmacological intervention

Pharmacological management of PD primarily targets dopamine deficiency. First-line therapies include carbidopa/levodopa and dopamine agonists, often supplemented by complementary approaches to support cognitive health. [66–69] Exercise also offers neuroprotective benefits and enhances quality of life. [70–72] Monoamine oxidase B (MAO-B) inhibitors such as Selegiline, Safinamide, and Rasagiline prolong dopamine availability. Selegiline and Safinamide are used adjunctively with levodopa, while Rasagiline may be used alone or in combination. The SELEDO trial demonstrated that Selegiline combined with levodopa was more effective than levodopa alone. [66,67,73]

For non-motor symptoms, SSRIs and SNRIs are used for depression, while sialorrhea is managed with atropine or botulinum toxins. Psychosis may be treated with clozapine or quetiapine, and sleep disturbances with agents like amitriptyline or clonazepam. [66] NSAIDs, particularly aspirin, have been associated with a lower PD risk due to possible neuroprotective effects. [74]

Animal studies suggest that ceftriaxone, a β-lactam antibiotic, may reduce oxidative stress and neuroinflammation, enhance astrocyte survival, and promote beneficial gut bacteria like *Akkermansia*. It also downregulates pro-inflammatory mediators such as TLR-4, IL-1β, and TNF-α. [40]

5.6 Probiotics

Probiotics are defined as live microorganisms that, in the right amounts, benefit the host's health.[5] According to countless studies, *lactobacilli, bifidobacteria,* and *enterococci* are the most frequently used bacteria in probiotic supplements. [35] These bacteria can restore the gut environment, reduce intestinal permeability, and alleviate GI symptoms like bloating, constipation, and abdominal pain. They may also help prevent conditions like urogenital infections, obesity, diabetes, and liver diseases. [66,75] A clinical study conducted in 40 individuals showed that *L. acidophilus* and *B. infantis* together can help PD patients with their bloating and stomach discomfort symptoms; on the other hand, a probiotic mix containing four strains, *B. bifidum, L. reuteri, L. acidophilus,* and *L. fermentum*, can relieve movement abnormalities. [76,77] Moreover, a pilot study performed by Lu et al, revealed that PD patients' UPDRS motor score and quality of life were enhanced by using *L. plantarum* PS128 supplement for 12 weeks together with standard anti-parkinsonian medicine. [78] Another study performed in animals with MPTP-induced parkinsonism, demonstrated that *L. plantarum* DP189 serves as an efficient psychobiotic to reduce α-synuclein aggravation by controlling inflammation, oxidative damage, and dysbiosis of the gut microbiota. [79] In addition, several animal studies showed that the stain PS 128 of *L.plantarum* can change the gut microbial environment, increase levels of dopamine and serotonin, and reduce neurodegenerative processes, thereby decreasing the progression of PD. [80] A 12-week randomized trial with 82 PD participants found that those treated with *Probio M8*, compared to a placebo, showed improvements in defecation, cognitive function, sleep quality, and reductions in gastrointestinal, depressive, and anxiety

symptoms. The study also noted changes in serum neurotransmitters, SCFAs, lipid metabolism, and gut microbiota. [81] A 12-week randomized controlled trial with 50 PD patients found that probiotic supplementation *(B. bifidum, L. acidophilus, L. casei, L. fermentum)* reduced the gene expression of pro-inflammatory cytokines IL-1, IL-8, and TNF-α in PBMCs while increasing TGF-β and PPAR-γ levels. [82]

5.7 Prebiotics

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines prebiotics as substrates selectively used by host microorganisms to provide health benefits while preserving the benefits of microflora. [40] Dietary fibers derived from raw oats, wheat, soybeans, non-digestible carbohydrates, and oligosaccharides, such as lactulose, polyphenols like galacto-oligosaccharides (GOS), and fructo-oligosaccharides (FOS), are known as prebiotics. [32,42] They positively impact lipid metabolism, reduce the risk of Clostridium difficile infections, and alleviate GI symptoms such as constipation. They also alter microbial composition in the bloodstream by promoting beneficial bacteria and reducing pathogens in the GI tract. [40] An animal study showed that prebiotic supplementation can reduce motor symptoms, lower α-synuclein levels, restore GI function, reduce inflammation, and increase dopamine transporter expression. It also found that polymannuronic acid can prevent dopaminergic neuronal loss. [83] Certain studies have also indicated that prebiotics can increase the levels of BDNF, which provides neuroprotection, in the hippocampus. [42]

5.8 Synbiotics

Probiotic and prebiotic compositions that function well together are called synbiotics. The prebiotic components of synbiotics specifically aid in the growth or metabolism of probiotics, which in turn improves host health. [32] This formulation together has the potential to be more beneficial than either one alone. According to a clinical trial, probiotic *Lactobacillus salivarius* reduced inflammatory markers in healthy individuals, and the benefit was more noticeable when prebiotics were added. [84] A double-blind, four-week randomized clinical trial by Cassani et al. on 120 PD patients with constipation found that fermented milk increased weekly complete bowel movements, reducing constipation compared to a placebo.[85] Constipation negatively impacts PD patients' overall quality of life, and efficient treatment approaches can provide significant benefits in the clinic. [32]

All in all, prebiotics and probiotics, or combined, together have the potential to effectively reset the eubiosis of the gut microbiota and enhance gastrointestinal processes, both of which may be advantageous for the treatment of PD.

CONCLUSION

Parkinson's Disease is a neurodegenerative disorder that primarily affects men between the ages of 60-80. It is marked by the loss of dopaminergic neurons in the brain, leading to symptoms such as movement and balance difficulties, dementia, insomnia, and mental health issues. Both genetic and environmental factors, including α-synuclein buildup, Lewy body formation, neuroinflammation, and gut microbiome changes, contribute to the development of PD. Dysbiosis in the gut, caused by bacteria like *Faecalibacterium* and *Roseburia*, worsens inflammation, reduces cognitive function, and triggers neurodegeneration. The accumulation of α-synuclein, which behaves similarly to prions, and the formation of Lewy bodies are linked to gut flora that exerts neurotoxic effects on the central, autonomic, and enteric nervous systems. The gut-brain axis plays a key role in α-synuclein misfolding through the vagus nerve. Risk factors for PD include aging, genetic mutations, microbiota imbalances, mitochondrial dysfunction, and oxidative stress. Certain food products, such as

caffeine, have been shown to increase risk. Beyond medications, PD management may include supplements like omega-3, probiotics, vitamins, gene therapy, and more recently, fecal microbiota transplantation. In severe cases, surgery is an option. PD is also associated with numerous comorbid conditions, affecting the skeletal, cardiovascular, renal, and hormonal systems in many patients. Future research should explore how various factors contribute to PD and interact, given the range of symptoms. Treatment and care must address both central and peripheral aspects of the disease.

Declaration by Authors

Ethical Approval: This research does not require approval from approval or Institutional Review Board approval.

Acknowledgement: None

Author Contributions

Conceptualization and Supervision: Afra Wasama Islam. Writing-original draft: Afra Wasama Islam, Anusaya Sadanand Gawai, Arifa Akthar Niha, Johora Akter. Writing-review & editing: All authors

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Cheng Y, Tan G, Zhu Q, Wang C, Ruan G, Ying S, et al. Efficacy of fecal microbiota transplantation in patients with Parkinson's disease: clinical trial results from a randomized, placebo-controlled design. Gut Microbes. 2023; 15:2284247.
2. Gazerani P. Probiotics for Parkinson's Disease. Int J Mol Sci. 2019; 20:4121.
3. Kaur G, Behl T, Bungau S, Kumar A, Uddin MS, Mehta V, et al. Dysregulation of the gut-brain axis, dysbiosis and influence of numerous factors on gut microbiota associated Parkinson's disease. Curr Neuropharmacol. 2021; 19:233–47.
4. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol. 2015; 21:10609–20.
5. Zhao Z, Ning J, Bao X, Shang M, Ma J, Li G, et al. Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis. Microbiome. 2021; 9:226.
6. Metta V, Leta V, Mrudula KR, Prashanth LK, Goyal V, Borgohain R, et al. Gastrointestinal dysfunction in Parkinson's disease: molecular pathology and implications of gut microbiome, probiotics, and fecal microbiota transplantation. J Neurol. 2022; 269:1154–63.
7. Belvisi D, Pellicciari R, Fabbrini G, Tinazzi M, Berardelli A, Defazio G. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: What do prospective studies suggest? Neurobiol Dis. 2020; 134:104671.
8. Kyrozis A, Ghika A, Stathopoulos P, Vassilopoulos D, Trichopoulos D, Trichopoulou A. Dietary and lifestyle variables in relation to incidence of Parkinson's disease in Greece. Eur J Epidemiol. 2013; 28:67–77.
9. Liu R, Guo X, Park Y, Huang X, Sinha R, Freedman ND, et al. Caffeine intake, smoking, and risk of Parkinson disease in men and women. Am J Epidemiol. 2012; 175:1200–7.
10. Chu C-Q, Yu L, Chen W, Tian F-W, Zhai Q-X. Dietary patterns affect Parkinson's disease via the microbiota-gut-brain axis. Trends Food Sci Technol. 2021; 116:90–101.
11. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol. 2022; 22:657–73.
12. Nishiwaki H, Ito M, Ishida T, Hamaguchi T, Maeda T, Kashihara K, et al. Meta-analysis of gut dysbiosis in Parkinson's disease. Mov Disord. 2020; 35:1626–35.
13. Bhattacharyya D, Bhunia A. Gut-brain axis in Parkinson's disease etiology: the role of lipopolysaccharide. Chem Phys Lipids. 2021; 235:105029.
14. Claudino Dos Santos JC, Lima MPP, Brito GA de C, Viana GS de B. Role of enteric glia and microbiota-gut-brain axis in Parkinson disease pathogenesis. Ageing Res Rev. 2023; 84:101812.
15. Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015; 386:896–912.

16. Corti O, Lesage S, Brice A. What genetics tells us about the causes and mechanisms of Parkinson's disease. Physiol Rev. 2011; 91:1161–218.
17. Exploring the disease-modifying potential of the probiotic Bacillus subtilis in Parkinson disease. Cochrane Library.
18. Liddle RA. Parkinson's disease from the gut. Brain Res. 2018; 1693:201–6.
19. Zhou S, Li B, Deng Y, Yi J, Mao G, Wang R, et al. Meta-analysis of the relations between gut microbiota and pathogens and Parkinson's disease. Adv Clin Exp Med. 2023; 32:613–21.
20. Schaeffer E, Kluge A, Böttner M, Zunke F, Cossais F, Berg D, et al. Alpha synuclein connects the gut-brain axis in Parkinson's disease patients – a view on clinical aspects, cellular pathology and analytical methodology. Front Cell Dev Biol. 2020; 8:573696.
21. Campos-Acuña J, Elgueta D, Pacheco R. T-cell-driven inflammation as a mediator of the gut-brain axis involved in Parkinson's disease. Front Immunol. 2019; 10:239.
22. Abdelsalam NA, Hegazy SM, Aziz RK. The curious case of Prevotella copri. Gut Microbes. 2023; 15:2249152.
23. Cirstea MS, Yu AC, Golz E, Sundvick K, Kliger D, Radisavljevic N, et al. Microbiota composition and metabolism are associated with gut function in Parkinson's disease. Mov Disord. 2020; 35:1208–17.
24. Barrio C, Arias-Sánchez S, Martín-Monzón I. The gut microbiota-brain axis, psychobiotics and its influence on brain and behaviour: a systematic review. Psychoneuroendocrinology. 2022; 137:105640.
25. Dodiya HB, Forsyth CB, Voigt RM, Engen PA, Patel J, Shaikh M, et al. Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease. Neurobiol Dis. 2020; 135:104352.
26. Grant H, Anderton R, Gasson N, Lawrence BJ. The gut microbiome and cognition in Parkinson's disease: a systematic review. Nutr Neurosci. 2023; 26:932–41.
27. Nielsen SD, Pearson NM, Seidler K. The link between the gut microbiota and Parkinson's disease: a systematic mechanism review with focus on α-synuclein transport. Brain Res. 2021; 1769:147609.
28. Zheng S-Y, Li H-X, Xu R-C, Miao W-T, Dai M-Y, Ding S-T, et al. Potential roles of gut microbiota and microbial metabolites in Parkinson's disease. Ageing Res Rev. 2021; 69:101347.
29. Shannon KM. Gut-derived sterile inflammation and Parkinson's disease. Front Neurol. 2022; 13:831090.
30. Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Parkinsons Dis. 2021; 7:1–13.
31. Zhang Z, Liu Z, Lv A, Fan C. How Toll-like receptors influence Parkinson's disease in the microbiome-gut-brain axis. Front Immunol. 2023; 14:1154626.
32. Zhang X, Tang B, Guo J. Parkinson's disease and gut microbiota: from clinical to mechanistic and therapeutic studies. Transl Neurodegener. 2023; 12:59.
33. Yemula N, Dietrich C, Dostal V, Hornberger M. Parkinson's disease and the gut: symptoms, nutrition, and microbiota. J Parkinsons Dis. 2021; 11:1491–505.
34. Kim DS, Choi H-I, Wang Y, Luo Y, Hoffer BJ, Greig NH. A new treatment strategy for Parkinson's disease through the gut-brain axis: the glucagon-like peptide-1 receptor pathway. Cell Transplant. 2017; 26:1560–71.
35. Alfonsetti M, Castelli V, d'Angelo M. Are we what we eat? Impact of diet on the gut–brain axis in Parkinson's disease. Nutrients. 2022; 14:380.
36. Park H-A, Ellis AC. Dietary antioxidants and Parkinson's disease. Antioxidants. 2020; 9:570.
37. Belvisi D, Pellicciari R, Fabbrini G, Tinazzi M, Berardelli A, Defazio G. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: what do prospective studies suggest? Neurobiol Dis. 2020; 134:104671.
38. Lee D, Jo MG, Kim SY, Chung CG, Lee SB. Dietary antioxidants and the mitochondrial quality control: their potential roles in Parkinson's disease treatment. Antioxidants. 2020; 9:1056.
39. Kim C-H, Jung J, Lee Y, Kim K, Kang S, Kang G, et al. Comparison of metabolites

and gut microbes between patients with Parkinson's disease and healthy individuals—A pilot clinical observational study (STROBE compliant). Healthcare. 2022; 10:302.
40. Varesi A, Campagnoli LIM, Fahmideh F, Pierella E, Romeo M, Ricevuti G, et al. The interplay between gut microbiota and Parkinson's disease: implications on diagnosis and treatment. Int J Mol Sci. 2022; 23:12289.
41. Sun X, Xue L, Wang Z, Xie A. Update to the treatment of Parkinson's disease based on the gut-brain axis mechanism. Front Neurosci. 2022; 16:878239.
42. Wang Q, Luo Y, Ray Chaudhuri K, Reynolds R, Tan E-K, Pettersson S. The role of gut dysbiosis in Parkinson's disease: mechanistic insights and therapeutic options. Brain. 2021; 144:2571–93.
43. Larroya-García A, Navas-Carrillo D, Orenes-Piñero E. Impact of gut microbiota on neurological diseases: diet composition and novel treatments. Crit Rev Food Sci Nutr. 2019; 59:3102–16.
44. Wastyk HC, Fragiadakis GK, Perelman D, Dahan D, Merrill BD, Yu FB, et al. Gut microbiota-targeted diets modulate human immune status. Cell. 2021; 184:4137–53. e14.
45. Shankar V, Gouda M, Moncivaiz J, Gordon A, Reo NV, Hussein L, et al. Differences in gut metabolites and microbial composition and functions between Egyptian and U.S. children are consistent with their diets. mSystems. 2017;2:e00169-16.
46. Yin W, Löf M, Pedersen NL, Sandin S, Fang F. Mediterranean dietary pattern at middle age and risk of Parkinson's disease: a Swedish cohort study. Mov Disord. 2021; 36:255–60.
47. Maraki MI, Yannakoulia M, Stamelou M, Stefanis L, Xiromerisiou G, Kosmidis MH, et al. Mediterranean diet adherence is related to reduced probability of prodromal Parkinson's disease. Mov Disord. 2019; 34:48–57.
48. Alcalay RN, Gu Y, Mejia-Santana H, Cote L, Marder KS, Scarmeas N. The association between Mediterranean diet adherence and Parkinson's disease. Mov Disord. 2012; 27:771–4.
49. Paknahad Z, Sheklabadi E, Derakhshan Y, Bagherniya M, Chitsaz A. The effect of the Mediterranean diet on cognitive function in patients with Parkinson's disease: a randomized clinical controlled trial. Complement Ther Med. 2020; 50:102366.
50. Mori MA, Delattre AM, Carabelli B, Pudell C, Bortolanza M, Staziaki PV, et al. Neuroprotective effect of omega-3 polyunsaturated fatty acids in the 6-OHDA model of Parkinson's disease is mediated by a reduction of inducible nitric oxide synthase. Nutr Neurosci. 2018; 21:341–51.
51. Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Huschens AM, Shaikh M, et al. Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. Gut. 2019; 68:829–43.
52. Ji A, Diao H, Wang X, Yang R, Zhang J, Luo W, et al. n-3 polyunsaturated fatty acids inhibit lipopolysaccharide-induced microglial activation and dopaminergic injury in rats. Neurotoxicology. 2012; 33:780–8.
53. Cardoso HD, dos Santos Junior EF, de Santana DF, Gonçalves-Pimentel C, Angelim MK, Isaac AR, et al. Omega-3 deficiency and neurodegeneration in the substantia nigra: involvement of increased nitric oxide production and reduced BDNF expression. Biochim Biophys Acta. 2014; 1840:1902–12.
54. Taghizadeh M, Tamtaji OR, Dadgostar E, Daneshvar Kakhaki R, Bahmani F, Abolhassani J, et al. The effects of omega-3 fatty acids and vitamin E co-supplementation on clinical and metabolic status in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Neurochem Int. 2017; 108:183–9.
55. Zhao X, Zhang M, Li C, Jiang X, Su Y, Zhang Y. Benefits of vitamins in the treatment of Parkinson's disease. Oxid Med Cell Longev. 2019; 2019:9426867.
56. Rimmelzwaan LM, van Schoor NM, Lips P, Berendse HW, Eekhoff EMW. Systematic review of the relationship between vitamin D and Parkinson's disease. J Parkinsons Dis. 2016; 6:29–37.
57. Detopoulou P, Voulgaridou G, Saridaki A, Pylarinou I, Argyris EM, Dedes V, et al. Vitamin D in Parkinson's disease: a systematic review of randomized controlled trials. Clin Nutr Open Sci. 2023; 52:1–13.
58. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut microbiota regulates motor deficits and

neuroinflammation in a model of Parkinson's disease. Cell. 2016; 167:1469–80. e12.
59. Martín R, Chain F, Miquel S, Lu J, Gratadoux JJ, Sokol H, et al. The commensal bacterium Faecalibacterium prausnitzii is protective in DNBS-induced chronic moderate and severe colitis models. Inflamm Bowel Dis. 2014; 20:417–30.
60. Sun MF, Zhu YL, Zhou ZL, Jia XB, Xu YD, Yang Q, et al. Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: gut microbiota, glial reaction and TLR4/TNF-α signaling pathway. Brain Behav Immun. 2018; 70:48–60.
61. Huang H, Xu H, Luo Q, He J, Li M, Chen H, et al. Fecal microbiota transplantation to treat Parkinson's disease with constipation. Medicine (Baltimore). 2019;98: e16163.
62. Kuai X, Yao X, Xu L, Zhou Y, Zhang L, Liu Y, et al. Evaluation of fecal microbiota transplantation in Parkinson's disease patients with constipation. Microb Cell Fact. 2021; 20:98.
63. LeWitt PA, Rezai AR, Leehey MA, Ojemann SG, Flaherty AW, Eskandar EN, et al. AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomised trial. Lancet Neurol. 2011; 10:309–19.
64. Abeliovich A, Hefti F, Sevigny J. Gene therapy for Parkinson's disease associated with GBA1 mutations. J Parkinsons Dis. 2021;11: S183–8.
65. Yoon HH, Ye S, Lim S, Jo A, Lee H, Hong F, et al. CRISPR-Cas9 gene editing protects from the A53T-SNCA overexpression-induced pathology of Parkinson's disease in vivo. CRISPR J. 2022; 5:95–108.
66. Church FC. Treatment options for motor and non-motor symptoms of Parkinson's disease. Biomolecules. 2021; 11:612.
67. Ahlskog JE. The Parkinson's disease treatment book: partnering with your doctor to get the most from your medications. New York: Oxford University Press; 2005.
68. Hall MFE, Church FC. Integrative medicine and health therapy for Parkinson disease. Top Geriatr Rehabil. 2020; 36:176.
69. Kim SN, Wang X, Park HJ. Editorial: integrative approach to Parkinson's disease. Front Aging Neurosci. 2019; 11:339.
70. Crowley EK, Nolan YM, Sullivan AM. Exercise as a therapeutic intervention for motor and non-motor symptoms in Parkinson's disease: evidence from rodent models. Prog Neurobiol. 2019; 172:2–22.
71. Amara AW, Memon AA. Effects of exercise on non-motor symptoms in Parkinson's disease. Clin Ther. 2018; 40:8–15.
72. Crowley EK, Nolan YM, Sullivan AM. Exercise as therapy for Parkinson's? Aging (Albany NY). 2018; 10:1536–7.
73. Przuntek H, Conrad B, Dichgans J, Kraus PH, Krauseneck P, Pergande G, et al. SELEDO: a 5-year long-term trial on the effect of selegiline in early Parkinsonian patients treated with levodopa. Eur J Neurol. 1999; 6:141–50.
74. Sarkar S, Raymick J, Imam S. Neuroprotective and therapeutic strategies against Parkinson's disease: recent perspectives. Int J Mol Sci. 2016; 17:904.
75. Cristofori F, Dargenio VN, Dargenio C, Miniello VL, Barone M, Francavilla R. Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body. Front Immunol. 2021; 12:578386.
76. Georgescu D, Ancusa OE, Georgescu LA, Ionita I, Reisz D. Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: is there hope? Clin Interv Aging. 2016; 11:1601–8.
77. Tamtaji OR, Taghizadeh M, Daneshvar Kakhaki R, Kouchaki E, Bahmani F, Borzabadi S, et al. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Clin Nutr. 2019; 38:1031–5.
78. Lu CS, Chang HC, Weng YH, Chen CC, Kuo YS, Tsai YC. The add-on effect of Lactobacillus plantarum PS128 in patients with Parkinson's disease: a pilot study. Front Nutr. 2021; 8:650053.
79. Wang L, Zhao Z, Zhao L, Zhao Y, Yang G, Wang C, et al. Lactobacillus plantarum DP189 reduces α-syn aggravation in MPTP-induced Parkinson's disease mice via regulating oxidative damage, inflammation, and gut microbiota disorder. J Agric Food Chem. 2022; 70:1163–73.
80. Liao JF, Cheng YF, You ST, Kuo WC, Huang CW, Chiou JJ, et al. Lactobacillus plantarum PS128 alleviates neurodegenerative progression in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse models of Parkinson's

disease. Brain Behav Immun. 2020; 90:26–46.
81. Sun H, Zhao F, Liu Y, Ma T, Jin H, Quan K, et al. Probiotics synergized with conventional regimen in managing Parkinson's disease. NPJ Parkinsons Dis. 2022; 8:62.
82. Borzabadi S, Oryan S, Eidi A, Aghadavod E, Daneshvar Kakhaki R, Tamtaji OR, et al. The effects of probiotic supplementation on gene expression related to inflammation, insulin and lipid in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Arch Iran Med. 2018; 21:289–95.
83. Perez-Pardo P, de Jong EM, Broersen LM, van Wijk N, Attali A, Garssen J, et al. Promising effects of neurorestorative diets on motor, cognitive, and gastrointestinal dysfunction after symptom development in a mouse model of Parkinson's disease. Front Aging Neurosci. 2017; 9:57.
84. Rajkumar H, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R. Effect of probiotic Lactobacillus salivarius UBL S22 and prebiotic fructo-oligosaccharide on serum lipids, inflammatory markers, insulin sensitivity, and gut bacteria in healthy young volunteers: a randomized controlled single-blind pilot study. J Cardiovasc Pharmacol Ther. 2015; 20:289–98.
85. Cassani E, Privitera G, Pezzoli G, Pusani C, Madio C, Iorio L, et al. Use of probiotics for the treatment of constipation in Parkinson's disease patients. Minerva Gastroenterol Dietol. 2011; 57:117–21.
86. Zhu M, Liu X, Ye Y, Yan X, Cheng Y, Zhao L, et al. Gut microbiota: a novel therapeutic target for Parkinson's disease. Front Immunol. 2022; 13:937555.
87. Huang C, Wang P, Xu X, Zhang Y, Gong Y, Hu W, et al. The ketone body metabolite β-hydroxybutyrate induces an antidepression-associated ramification of microglia via HDACs inhibition-triggered Akt-small RhoGTPase activation. Glia. 2018; 66:256–78.
88. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, et al. Ketone body β-hydroxybutyrate blocks the NLRP3 inflammasome-mediated inflammatory disease. Nat Med. 2015; 21:263–9.
89. Fu SP, Wang JF, Xue WJ, Liu HM, Liu B, Zeng YL, et al. Anti-inflammatory effects of BHBA in both in vivo and in vitro Parkinson's disease models are mediated by GPR109A-dependent mechanisms. J Neuroinflammation. 2015; 12:9.

How to cite this article: Afra Wasama Islam, Anusaya Sadanand Gawai, Arifa Akthar Niha, Johora Akter. Parkinson's disease and the gut microbiota: mechanistic insights and emerging therapeutic approaches. *Int J Health Sci Res.* 2025; 15(9):140-155. DOI: *https://doi.org/10.52403/ijhsr.20250918*

*****