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Gut microbiota and Parkinson's disease

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Abstract

Emerging evidence suggests that dysbiosis of the gut microbiota is associated with the pathogenesis of Parkinson's disease (PD), a prevalent neurodegenerative disorder. The microbiota–gut–brain axis plays a crucial role in the development and progression of PD, and numerous studies have demonstrated the potential therapeutic benefits of modulations in the intestinal microbiota. This review provides insights into the characterization of the gut microbiota in patients with PD and highlights associations with clinical symptoms and underlying mechanisms. The discussion underscores the increased influence of the gut microbiota in the pathogenesis of PD. While the relationship is not fully elucidated, existing research demonstrates a strong correlation between changes in the composition of gut microbiota and disease development, and further investigation is warranted to explain the specific underlying mechanisms.

Keywords: Parkinson's disease; Microbiota–gut–brain axis; Gut microbiota; Neuroinflammation; Metabolism

Introduction

Parkinson's disease (PD) is a highly prevalent neurodegenerative disease, second only to Alzheimer's disease, and primarily affects individuals older than 60 years.[1] Epidemiological findings indicate that approximately 200 per 100,000 individuals worldwide are diagnosed with PD, with an average of one new diagnosis every hour. The global prevalence of PD is expected to double by 2040.[2] PD is characterized by motor symptoms such as resting tremor, bradykinesia, rigidity, and impaired balance. In addition to typical motor impairments, patients often experience non-motor symptoms, including constipation, hyposmia, and rapid eye movement sleep behavior disorder (RBD),[3,4] which severely impact the quality of life. The pathological hallmarks of PD are the loss of dopaminergic neurons in the substantia nigra and the abnormal aggregation of α-synuclein (α-syn). Braak's hypothesis postulates that pathological α-syn may initially aggregate in the enteric nervous system before spreading to the brain via the vagus nerve.[5] Emerging clinical and experimental evidence indicates dysbiosis of the gut microbiota in patients with PD and in animal models,[6] suggesting that the microbiota–gut–brain axis plays a crucial role in the pathogenesis of the disease. Alterations in the composition of the gut microbiota may represent a risk factor for PD development. This review focuses on the impact of gut microbiota on PD progression and highlights the promising role of gut microbiota-targeted interventions for disease management.

Microbiota–Gut–Brain Axis

The gut is often referred to as the "second brain" due to the influence of the gut microbiota on brain health. The gut microbiota comprises commensal intestinal bacteria and transient pathogenic bacteria, and its composition is influenced by various factors such as diet and environmental exposure. The intestinal microbiota maintains a dynamic homeostatic balance; disruptions in this equilibrium, termed dysbiosis, have been implicated in PD pathogenesis.[7]

A meta-analysis of the gut microbiome in PD utilizing 16S rRNA gene sequencing and shotgun metagenomics revealed increased abundances of *Streptococcus*, *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, and *Desulfovibrio*, while the abundance of *Roseburia*, *Faecalibacterium*, *Blautia*, *Lachnospira*, and *Prevotella* decreased in patients with PD. These alterations may promote PD pathogenesis by reducing the levels of anti-inflammatory short-chain fatty acids (SCFAs) and increasing those of proinflammatory

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substances such as lipopolysaccharides (LPS), hydrogen sulfide, and glutamate.[8] Tamtaji *et al*[9] conducted a randomized, double-blind, placebo-controlled trial and found that 12 weeks of probiotic supplementation with *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *L. reuteri*, and *L. fermentum* improved the scores in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in patients with PD. This observation suggests that clinical symptoms can be alleviated by increasing the content of beneficial gut microbiota. Interestingly, Hill-Burns *et al*[10] indicated that *Bifidobacterium* and *Lactobacillus* were in higher concentrations in patients with PD than in healthy controls, potentially reflecting a compensatory regulatory response,[11] but the specific underlying mechanism remains unclear.

Several studies have investigated the composition of the gut microbiome in patients with PD. Hill-Burns *et al*[10] conducted a 16S rRNA gene sequencing analysis of fecal samples from 197 patients and 130 healthy controls and found increased abundances of *Akkermansia*, *Lactobacillus*, and *Bifidobacterium*, but decreased abundance of *Lachnospiraceae*, in patients with PD. A meta-analysis of 15 case–control studies reported low levels of *Prevotellaceae*, *Faecalibacterium*, and *Lachnospiraceae* in patients with PD compared to those in healthy controls, but enrichment in *Bifidobacteriaceae*, *Ruminococcaceae*, *Verrucomicrobiaceae*, and *Christensenellaceae*; moreover, shared alterations in the gut microbiota were observed across patients with PD from different geographical regions.[12] Additionally, specific gut microbiota taxa may be associated with PD, including *Enterococcus faecalis*, *Helicobacter pylori*, and *Desulfovibrio* species.[13]

Bacteria of the genus *Faecalibacterium* were detected in significantly decreased concentrations in the sigmoid mucosa of patients with PD.[14] Wang *et al*[15] found that transplanting *E. faecalis* and *E. faecium* into PD mouse models significantly increased dopamine levels in the brain and improved motor deficits. *H. pylori* resides in the human stomach, which is the only known reservoir host, is a common cause of gastritis, peptic ulcers, and other digestive diseases.[16] A large meta-analysis that included data from 33,215 patients with PD found that the risk of PD increased 1.5-fold to 2-fold after *H. pylori* infection.[17] Eradication of *H. pylori* has been reported to improve levodopa absorption and motor function,[18] but clinical improvement is not observed in all patients with PD. Tan *et al*[19] conducted a randomized, double-blind, placebo-controlled, single-center trial, with 32 patients in the *H. pylori* eradication group and 35 in the placebo group; the authors found no significant differences in motor, non-motor, or quality of life outcomes at weeks 12 and 52. While *H. pylori* infection exhibits a familial pattern, PD is predominantly sporadic, suggesting that dysbiosis of the gut microbiota is not the sole factor in disease pathogenesis, but may act in combination with genetic susceptibility. Whether PD progression can be attributed to combinatorial alterations in distinct gut microbiota or if individual taxa contribute independently remains unclear and warrants further in-depth investigation.

Gut Microbiota and Clinical Phenotypes of PD

The gut microbiota composition of patients with PD differs significantly from that of healthy individuals, with correlations identified between clinical phenotypes and specific signatures of intestinal microbiota. In 2014, Scheperjans *et al*[20] utilized 16S rRNA gene sequencing to compare the fecal microbiomes of 72 patients with PD and 72 healthy controls and revealed a 77.6% reduction in the abundance of *Prevotellaceae* in the former group. A higher relative abundance of *Enterobacteriaceae* was positively associated with increased severity of postural instability and gait difficulty. Barichella *et al*[21] reported that elevated *Lachnospiraceae* abundance correlated with milder postural instability and gait disturbances. Mehanna *et al*[22] compared the composition of the gut microbiome across PD clinical phenotypes, and found lower levels of *bifidobacteria* in the postural instability/gait difficulty and tremor-predominant phenotypes. Non-tremor-predominant phenotypes exhibited a significantly reduced abundance of *lactobacilli*, while the mixed phenotype displayed a significant increase in Bacteroides. Notably, patients with the tremor-predominant phenotype were characterized by lower abundances of *Firmicutes* and a reduced *Firmicutes/Bacteroidetes* ratio.

In addition to the motor symptoms, non-motor symptoms in PD, such as constipation, cognitive impairment, and mood disorders, have also been linked to variations in the gut microbiota composition. Du *et al*[23] used V3–V4 region 16S rRNA gene sequencing to compare fresh fecal samples from 20 PD patients with constipation and 17 healthy controls and revealed higher abundances of *Bifidobacteriales*, *Coriobacteriales*, *Desulfovibrionales*, *Bacillales*, *Lactobacillales*, and *Peptostreptococcales_Tissierellales* in the former. Vandeputte *et al*[24] found that stool consistency positively correlated with the *Bacteroidetes/Firmicutes* ratio and abundances of *Akkermansia* and *Methanobrevibacter*. In a three-year follow-up study of 25 patients with PD, Cilia *et al*[25] reported that low baseline abundances of *Roseburia* were associated with a worse evolution of non-motor and cognitive functions, while reduced *Ruminococcaceae* and *Actinobacteria* levels correlated with a faster decline in overall cognitive performance. A low abundance of *Bifidobacterium* has been linked to worsening hallucinations.[26] Sun *et al*[27] conducted a metagenomic analysis of fecal samples from 45 patients with PD and found that the abundance of *L. fermentum* negatively correlated with the scores in the Mini-Mental State Examination (MMSE) and positively correlated with measures in the Hamilton Anxiety (HAMA) and Depression (HAMD) scales. Through 16S rDNA sequencing of feces from 76 patients with PD, Heintz-Buschart *et al*[28] identified significant associations between MDS-UPDRS Part I scores and *Anaerotruncus/Akkermansia* abundance, as well as correlations between depressive symptoms and the abundance of *Anaerotruncus* spp.

RBD is considered the most specific prodromal marker of PD and a strong clinical predictor for future risk, with approximately half of the patients experiencing RBD symptoms.[29] Schenck *et al*[30] reported that after a mean 3.7-year follow-up of 29 male patients with RBD, 11

(37.9%) developed PD, and over 80.8% developed PD or dementia with Lewy bodies after 16 years. Several studies have demonstrated alterations in the gut microbiota in RBD that resemble those observed in early stage PD. Zhang *et al*[31] identified *Aerococcus*, *Eubacterium*, *Butyricicoccus*, and *Faecalibacterium* as differentially abundant genera among PD patients with and without RBD, with the levels of *Butyricicoccus* and *Faecalibacterium* negatively correlating with RBD severity. Through 16S rRNA amplicon sequencing of fecal samples from 76 patients with PD, 21 with idiopathic RBD (iRBD), and 78 healthy controls, Heintz-Buschart *et al*[28] found that over 75% of the differential gut microbiota between PD and controls exhibited similar trends in iRBD. Huang *et al*[32] conducted a cross-sectional study that involved 36 patients with early PD, 170 with RBD, 127 first-degree RBD relatives (RBD-FDRs), and 108 healthy controls; they demonstrated that alterations in the gut microbiota in the RBD and RBD-FDR groups were comparable to those in early PD, and characterized by reduced abundances of butyrate-producing bacteria and increased levels of the proinflammatory genus *Collinsella*.

Mechanisms Underlying Gut Dysbiosis and PD

The specific mechanisms linking the gut microbiota to PD are yet to be fully elucidated, implicating multiple pathways may connect the gut and the brain, as illustrated in Figure 1.

Neuroinflammation

Patients with inflammatory bowel disease have a 22% increased risk of developing PD,[33] whereas treatment with agents against tumor necrosis factor-α (TNF-α) was associated with a 78% reduced risk.[34] The levels of intestinal inflammatory marker calreticulin were found to be significantly elevated in intestinal mucosal tissues and fecal samples from patients with PD,[35] along with increased abundances of the proinflammatory bacterial genera *Ralstonia*, *Akkermansia*, *Oscillospira*, and *Bacteroides*.[14] Colon biopsies from patients with PD displayed higher $CD3^+$ T cell infiltration and upregulated expression of the proinflammatory cytokines interleukin-1β (IL-1β) and interferon-gamma.[36] In a 6-hydroxydopamine-induced rat model of PD, eosinophil infiltration was observed in the mucosal and submucosal layers of colonic tissues using hematoxylin and eosin staining.[37] Collectively, these findings substantiate the important role of intestinal inflammation in PD pathogenesis.

The intestinal barrier comprises the intestinal microbiota, mucosal layer, intestinal epithelium, and lamina propria. Intestinal epithelial cells and their intercellular tight

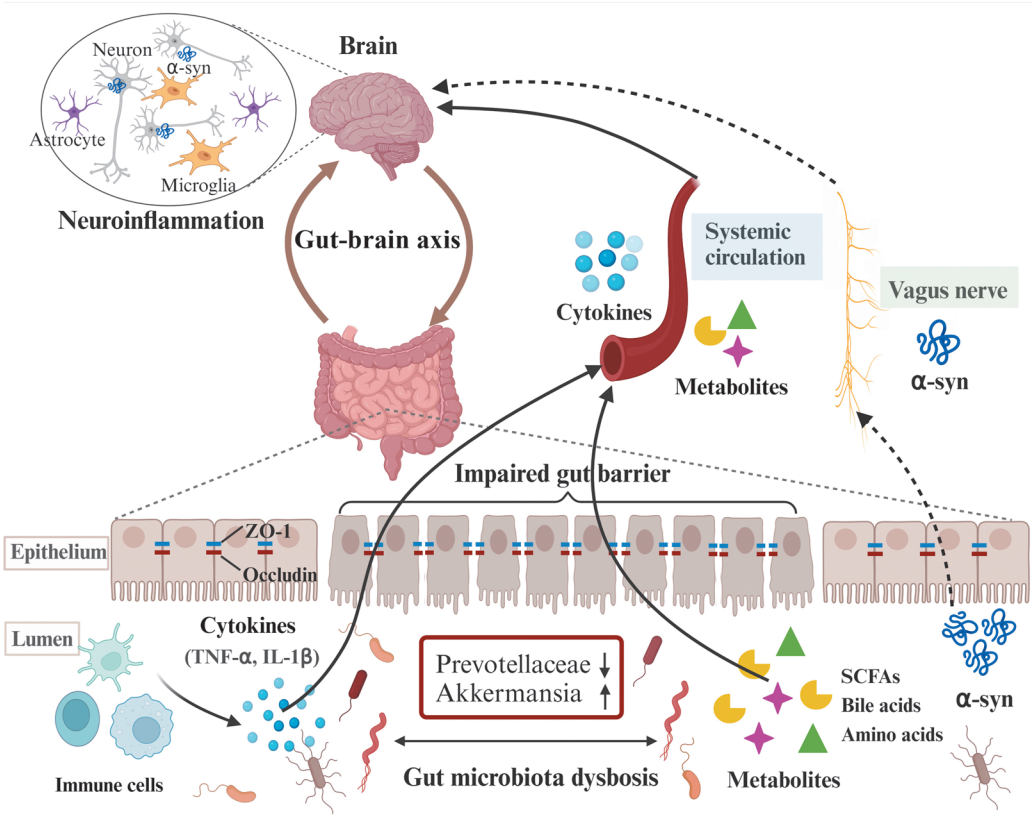

Figure 1: Underlying mechanisms of microbiota-gut-brain in Parkinson's disease. Dysbiosis of the gut microbiota, characterized by reduced levels of Prevotellaceae and increased abundance of Akkermansia in PD patients, leads to decreased expression of tight junction proteins such as ZO-1 and occludin, thereby impairing intestinal barrier function. Consequently, pro-inflammatory cytokines, including TNF-α and IL-1β, traverse from the gut to the brain via systemic circulation, promoting neuroinflammation and subsequent damage to dopaminergic neurons. Additionally, the gut microbiota regulates the release of metabolites such as SCFAs, bile acids, and amino acids, modulating the communication between the gut and the brain. Dysregulation of pro-inflammatory cytokine release and alterations in metabolite profiles are implicated in the misfolding and aggregation of α-synuclein in the gut, which is then transmitted to the brain via the vagus nerve. IL-1β: Interleukin-1 beta; PD: Parkinson's disease; SCFAs: Short-chain fatty acids; TNF-α: Tumor necrosis factor-alpha; ZO-1: Zonula Occludens-1.

junction proteins not only facilitate nutrient absorption but also serve as a crucial physical barrier against pathogenic invasion, with a vital role in maintaining intestinal homeostasis. Dysbiosis of the gut microbiota can lead to changes in the permeability of the intestinal barrier. The reduced levels of *Prevotellaceae* in PD have been associated with improvements in barrier integrity through the production of mucins.[20] Conversely, the increased abundance of *Akkermansia*[38] is related to barrier degradation, as the bacterium utilizes the mucus layer as an energy source.[28] The combined effect promotes the degradation of intestinal mucins and compromises the function of the intestinal barrier. Clairembault *et al*[39] demonstrated a significant decrease in the expression levels of the tight junction proteins Zonula Occludens-1 (ZO-1) and occludin in colonic mucosal samples from patients with PD, providing more direct evidence for the impaired intestinal barrier function in PD.

Substantial activation of microglia and astrocytes has been noted in patients with PD.[40] The gut microbiota plays a crucial role in maintaining microglial homeostasis. Erny *et al*[41] reported defects in the maturation, differentiation, and function of microglia in germ-free mice, whereas microglial characteristics were partially restored when the host gut was re-colonized with complex microbiota. Physiologically, M1 proinflammatory and M2 anti-inflammatory microglia are in a dynamic equilibrium. In the progression of PD, M1 microglia are stimulated and release proinflammatory cytokines that exacerbate disease development.[42] Activated astrocytes can release a variety of neurotoxic cytokines, such as TNF-α and IL-1β, leading to damage to dopaminergic neurons.[43]

Patients with PD show increased relative abundances of *Gammaproteobacteria* and *Enterobacteriaceae*,[20] which produce LPS phosphate, leading to elevated levels in the intestinal tract. Due to the disrupted function of the intestinal barrier and increased permeability in PD, gut-derived LPS is more likely to enter the bloodstream and cause systemic inflammation.[44] LPS can cross the compromised blood–brain barrier and bind to toll-like receptor 4 on microglial cells, promoting the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6; these events induce local neuroinflammation and damage to dopaminergic neurons.[45] Sampson *et al*[46] found that when healthy human gut microbiota was transplanted into PD mice, neuroinflammation was suppressed and motor deficits were improved. Gut dysbiosis can precipitate neuroinflammation via the gut–microbiota–brain axis.

Microbial metabolites

Gut microbiota can regulate the production of metabolites and may influence gut–brain communication. In recent years, the widespread application of metabolomics technology has indicated that SCFAs, bile acids, and disruptions in amino acid metabolism are implicated in the pathogenesis of PD.

Patients with PD harbor a significantly reduced abundance of the SCFA-producing colonic bacteria *Lachnospiraceae* and *Ruminococcaceae*, with a concomitant reduction in the levels of SCFAs.[11] SCFAs, including acetic acid, propionic acid, and butyric acid, are produced by intestinal bacteria through the fermentation of carbohydrates and proteins and play critical roles in maintaining intestinal homeostasis and supporting energy metabolism. SCFAs improve the integrity of the intestinal barrier by stimulating the expression of tight junction proteins.[47] Kim *et al*[48] found that SCFAs activate G protein-coupled receptors 41 and 43 on intestinal epithelial cells, leading to the production of chemokines and cytokines; these mechanisms mediate protective immunity and tissue inflammation. Additionally, SCFAs regulate gut immune responses by inhibiting histone deacetylases, with a subsequent decrease in the expression of proinflammatory cytokines (TNF-α, IL-6, and IL-12) and an increase in the expression of the anti-inflammatory cytokine IL-10.[49]

The appendix is a lymphoid tissue in the cecum associated with the storage and regulation of the gut microbiota. An increased abundance of bacteria responsible for the synthesis of bile acids has been observed in the appendix tissues of patients with PD.[50] The duodenal mucosa of patients with PD harbors an abundance of Burkholderiales, which encode the rate-limiting enzyme for secondary bile acid synthesis.[51] Microbiota-mediated alterations in bile acid metabolism may represent another pathway that contributes to the pathogenesis of PD. Zhao *et al*[52] first reported that bile acid metabolites are potential biomarkers for PD in 2018. Tauroursodeoxycholic acid (TUDCA) is an endogenous bile acid that exerts neuroprotective effects on dopaminergic neurons by modulating mitochondrial autophagy and cellular redox reactions.[53,54] In addition to its neuroprotective effects, TUDCA is also effective in alleviating motor symptoms in PD mice.[55]

Amino acid metabolism by the gut microbiota plays an important role in the pathogenesis of PD. Tyrosine is a conditionally essential amino acid involved in PD development as a precursor for dopamine synthesis. Tyrosine is metabolized by gut microbes to indoles and phenolic compounds,[56] which are known to reduce inflammation. Serum tryptophan levels are decreased in patients with PD, and tryptophan metabolism is associated with symptom severity and nigral pathology.[57] *Clostridium* and *Lactobacillus* are involved in tryptophan metabolism.[58] Tryptophan is metabolized to kynurenine (the major metabolite), 5-hydroxytryptamine, and indoles; kynurenine is the major metabolite and has been implicated in PD development. Kynurenine is further metabolized to quinolinic acid and kynurenic acid; the former reduces the activity of tyrosine hydroxylase, resulting in decreased dopamine production.[59] Kynurenic acid exerts neuroprotective effects by scavenging reactive oxygen species and extracellular glutamate.[60] Its concentration in cortical areas, the caudate nucleus, and the cerebellum decreases significantly in patients with PD.[61] High levels of endogenous kynurenic acid prevent the effects of quinolinic acid on tyrosine hydroxylase and ameliorate motor deficits in PD.[62] Dysbiosis of gut microbiota has been associated with decreased levels of branched-chain amino acids (BCAAs) in the plasma and cerebrospinal fluid of patients with PD.[63] Yan *et al*[64] found that in

rotenone-induced PD mice, changes in the gut microbiota led to reduced plasma BCAA (leucine, isoleucine, and valine) levels, and motor symptoms were significantly improved by BCAA supplementation. BCAAs can swiftly cross the blood–brain barrier, leading to improved PD symptoms by inhibiting neuroinflammation and reducing oxidative stress.[65]

Vagus nerve

In 2003, Braak *et al*[66] examined autopsy brains from 110 individuals with PD and found that α-syn aggregates from peripheral nerves accumulated progressively in the medulla oblongata, pons, thalamus, and cortex. Subsequently, the "dual-hit hypothesis", proposed in 2007, suggested the gut as the origin of α-syn aggregation.[5] In 2015, Svensson *et al*[67] provided new evidence supporting the Braak hypothesis. The study included 15,000 patients who had undergone vagotomy and reported that none developed PD within five years after truncal vagotomy. After 20 years of follow-up, the risk of PD was reduced by 50% in this population. In 2019, Kim *et al*[68] provided more direct evidence in support of the Braak hypothesis. Pathological α-syn preformed fibrils were injected into the duodenal and pyloric muscularis layers; one month post-injection, α-syn was detected in the dorsal motor nucleus of the vagus and the locus coeruleus. Within 3 months, α-syn had disseminated to the amygdala, ventral midbrain, hypothalamus, and the prefrontal cortex. At seven months post-injection, α-syn had spread extensively to brain regions, including the hippocampus, striatum, and olfactory bulb. α-syn aggregates in colonic tissue before the onset of PD[69] and intestinal α-syn aggregation are more pronounced in patients who develop PD than in non-affected subjects.[70] These findings further confirm that PD onset originates in the gut, with the vagus nerve being an important transmission pathway. Pisa *et al*[71] first identified the presence of *Streptococcus* and *Pseudomonas* in postmortem brain tissues from patients with PD. Although the study provided novel insights into the potential existence of multiple microbial infections in the PD brain, the importance of these findings is limited because autopsy specimens rather than biopsy samples were used.

Relationship Between Gut Microbiota and Gene Expression

Unlike the familial clustering observed in *H. pylori*-induced gastric ulcers, only 5–10% of PD cases are familial and associated with mutations in genes such as *SNCA*, *GBA*, *LRRK2*, *PARK2*, *PINK1*, and *DJ-1*.[72] Most PD cases are sporadic, suggesting that the gut microbiota alone does not contribute to PD pathogenesis but likely interacts with factors related to genetic susceptibility. Wallen *et al*[73] conducted a study that involved 511 patients with PD and 291 healthy controls to explore the interactions between *SNCA* gene variants and PD, and revealed that the increased relative abundance of opportunistic pathogens is modulated by the host genotype; this observation suggests an interaction between genetic susceptibility and dysbiosis of the gut microbiome. *LRRK2* is an important risk gene for sporadic PD (sPD). *Escherichia coli* in the gut was present in a significantly higher abundance in patients with sPD carrying with the *LRRK2* risk variant (*R1628P or G2385R*) than in non-carriers. By gavaging *LRRK2 R1628P* mice with *E. coli*, pathological α-syn aggregates in the colon and spreads to the brain via the gut–brain axis.[74] Tyrosine decarboxylase, primarily encoded by the tyrosine decarboxylase gene (*tyrDC*) in *E. faecalis*, is an important microbial metabolic pathway for the conversion of levodopa to dopamine. Zhang *et al*[75] found that *tyrDC* abundance and *E. faecalis* abundance were associated with levodopa responsiveness, suggesting the potential of TyrDC as a predictive marker of drug response. Animal studies have shown that intestinal infections with Gram-negative bacteria in *Pink1*$^{-/-}$ mice induced loss of dopaminergic neurons in the substantia nigra and caused motor impairment.[76] Motor impairment was worsened in α-syn-overexpressing mice colonized with microbiota from PD donors compared to the condition in wild-type mice.[46] These studies suggest that the gut microbiota, combined with genetic susceptibility, contributes to the development of PD. Host genetics and the gut microbiota will be a new direction for future research.

Therapeutic Strategies Targeting Gut Microbiota in PD

Diet

Diet can greatly influence the gut microbiota. Coffee consumption leads to an increase in the levels of intestinal anti-inflammatory bifidobacteria,[77] which improve the function of the intestinal mucosa and reduce gut inflammation, further reducing the risk of developing PD.[78] The Mediterranean diet focuses on consuming vegetables, fruits, fish, whole grains, nuts, and olives. Rusch *et al*[79] found that a Mediterranean dietary intervention in patients with PD resulted in decreased abundances of *Clostridium bolteae*, *Ruminococcous*, *Blautia*, *Dorea*, and *Lachnospiraceae*, as well as improved constipation symptoms. Dietary fiber is an important energy source for the colonic microbiota, and fiber deprivation is associated with disruptions in the intestinal mucus barrier and increased abundance of the mucin-degrading bacterium *Akkermansia muciniphila*.[80] A high-fiber diet can protect against PD by promoting the production of SCFAs.[81] Although dietary changes cannot directly stop PD progression, some beneficial effect on PD is expected by influencing the microbiota–gut–brain axis.

Prebiotics and probiotics

Prebiotics are a group of nutrients that cannot be digested or absorbed by the host but are metabolized by the gut microbiota to influence host health. A prebiotic high-fiber diet leads to an increase in the abundance of *Bacteroidota* and a decrease in the abundance of *Firmicutes* in the gut. By modulating microglial states, a prebiotic diet reduces α-syn aggregation and attenuates motor deficits in α-syn-overexpressing mice.[82] Intervention with a prebiotic fiber mixture (resistant starch, rice bran, resistant maltodextrin, and inulin) effectively modulates the gut microbiota and influences SCFA production, reduces the severity of motor and non-motor symptoms, and improves gastrointestinal

function in patients with PD.[83] Although current research on the effects of prebiotics on PD is relatively limited, it provides a basis for the clinical use of prebiotics in disease management.

Probiotics are a group of live microorganisms capable of colonizing the host intestinal tract and exerting beneficial health effects. They are commonly consumed as supplements, yogurt, or other fermented foods. Probiotic supplementation has been shown to effectively improve constipation symptoms in patients with PD.[23] Tamtaji *et al*[9] conducted a randomized, double-blind, placebo-controlled trial that involved 60 patients with PD. The participants consumed probiotics, including *L. acidophilus*, *B. bifidum*, *Lactobacillus reuteri*, and *L. fermentum*, for 12 weeks, and positive effects on the MDS-UPDRS were noted. Yang *et al*[84] found that a 12-week intervention with the *Lacticaseibacillus paracasei* strain Shirota (LcS) significantly alleviated constipation-related symptoms and non-motor symptoms in patients with PD. *Lactobacillus plantarum* PS128 is known as a psychotropic probiotic due to its ability to effectively improve symptoms in patients with autism spectrum disorder. Lu *et al*[85] found improvements in the UPDRS motor score and quality of life after 12 weeks of supplementation with *L. plantarum* PS128. Sun *et al*[27] found that *Bifidobacterium animalis* subsp. *lactis* Probio-M8 (Probio-M8) acted in synergy with conventional therapy for three months to significantly alter the levels of the host gut microbiota and serum metabolites and improve motor symptoms, constipation, sleep quality, mental status, and cognitive functions. Although the evidence that probiotic supplementation can directly treat PD is insufficient, these studies highlight that probiotics play a role in maintaining homeostasis with the gut microbiota and may improve the gastrointestinal and motor symptoms of PD, thereby influencing the disease process.

Several studies have shown that probiotics can improve PD symptoms, but the mechanisms by which different probiotic strains exert protective effects vary. Treatment with *Clostridium butyricum* reversed dysbiosis of the gut microbiota in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mice and ameliorated motor deficits via the gut microbiota–glucagon-like peptide-1 (GLP-1) pathway.[86] The engineered *C. butyricum*-pMTL007-GLP-1 improved the microbiome imbalance in PD mice by reducing the abundance of *Bifidobacterium*; it exerted its neuroprotective effects by promoting mitophagy and attenuating oxidative stress.[87] Treatment with *Pediococcus pentosaceus* improved the gut microbial dysbiosis and increased the level of gamma-aminobutyric acid.[88] *L. plantarum* DP189 reversed alterations in the gut microbiota in PD mice by decreasing the content of pathogenic bacteria (*Proteobacteria* and *Actinobacteria*) while increasing that of beneficial bacteria (*Lactobacillus* and *Prevotella*); the treatment resulted in delayed α-syn aggregation in the substantia nigra by inhibiting oxidative stress and proinflammatory responses.[89] The next-generation probiotic strain *Lactococcus lactis* MG1363-pMG36e-GLP-1 reshaped intestinal dysbiosis in PD mice by increasing the abundance of *Akkermansia*, *Oscillospira*, and *Sutterella* and exerted neuroprotective effects by modulating oxidative stress and inhibiting the ferroptosis pathway.[90]

The findings of these studies provide a theoretical basis for the use of probiotics in treating PD. The selection of specific probiotic strains, optimal combinations, therapeutic doses, and treatment duration have not been fully established. In addition, interindividual variability and different disease stages may affect the efficacy of probiotic treatments. Therefore, extensive clinical research is needed to explore and validate the role of probiotics in PD treatment.

Fecal microbiota transplantation (FMT)

FMT is an effective procedure to reconstitute the gut microbiome and is increasingly used to manage neurodegenerative diseases.[91]Animal studies have shown that FMT can effectively alleviate microbiome dysbiosis in the gut, reduce inflammatory responses, and increase the levels of striatal dopamine and the neurotransmitter 5-hydroxytryptamine.[45,92] Although applications of FMT in PD are currently limited, Kuai *et al*[93] have suggested therapeutic potential for improving motor and non-motor symptoms in patients with PD, with minimal adverse reactions and good safety profiles. Cheng *et al*[94] found that oral FMT capsules can restore the gut microecology in patients with PD, improving gastrointestinal symptoms and quality of life; notably, severe side effects were not observed throughout the entire follow-up period. Bruggeman *et al*[95] conducted the first randomized, double-blind, placebo-controlled trial involving 46 PD patients who received nasojejunal FMT therapy. The results showed that a single FMT session improves motor symptoms in early stage patients. This study demonstrates the efficacy of modulations in the gut microbiota as a potential treatment strategy for PD and provides valuable insights for the future clinical use of the procedure in patients with PD.

FMT for PD is still in its early stages, and evidence from large-scale, long-term randomized controlled clinical trials is lacking. Further clinical trials are needed to verify its safety, efficacy, and durability. Additionally, investigations are required regarding its effects on motor function, neuroimaging parameters, and serum metabolites. Lastly, issues related to technical standardization, procedural norms, and donor screening need to be addressed to ensure the safety and efficacy of the technique in clinical practice.

Conclusions

The microbiota–gut–brain axis plays a critical role in the pathogenesis of PD, with correlations observed between the gut microbiota composition and clinical phenotypes. The gut microbiota can influence the development of PD through pathways related to neuroinflammation, metabolism, and the vagus nerve. Extensive research has confirmed changes in the gut microbiota of patients with PD. Despite these advancements, current clinical studies on the gut microbiome and PD have certain limitations, such as relatively small sample sizes and a lack of long-term

follow-up clinical studies. Furthermore, it remains unclear which specific bacterial taxa play critical roles and how these microbial changes relate to the underlying pathogenic mechanisms of PD. Notably, translating findings from animal models to humans is challenging. Future long-term follow-up cohort studies and larger sample sizes are needed, as well as exploration of specific bacterial taxa to further elucidate the complex relationship between PD and the gut microbiota.

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Conflicts of interest

None.

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