Translational Neurodegeneration

REVIEW

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Parkinson's disease and gut microbiota: from clinical to mechanistic and therapeutic studies

Xuxiang Zhang[1], Beisha Tang[1,2,3,4,5,6] and Jifeng Guo[1,2,3,4,5,6*]

Abstract

Parkinson's disease (PD) is one of the most prevalent neurodegenerative diseases. The typical symptomatology of PD includes motor symptoms; however, a range of nonmotor symptoms, such as intestinal issues, usually occur before the motor symptoms. Various microorganisms inhabiting the gastrointestinal tract can profoundly influence the physiopathology of the central nervous system through neurological, endocrine, and immune system pathways involved in the microbiota–gut–brain axis. In addition, extensive evidence suggests that the gut microbiota is strongly associated with PD. This review summarizes the latest findings on microbial changes in PD and their clinical relevance, describes the underlying mechanisms through which intestinal bacteria may mediate PD, and discusses the correlations between gut microbes and anti-PD drugs. In addition, this review outlines the status of research on microbial therapies for PD and the future directions of PD–gut microbiota research.

Keywords Gut microbiota, Microbiota–gut–brain axis, Mechanisms, Alpha-synuclein, Microbial therapy

Introduction

Parkinson's disease (PD) is a relatively common neurodegenerative disease in the elderly population. The exact factor that triggers PD is still unclear; however, its development is driven by a mixture of genetic and environmental variables. Given that fewer than 10% of cases are attributable to certain genetic factors, determining the environmental risk factors for PD is important [1, 2].

The intestine serves as a gateway to the environment, through which environmental variables can influence the pathogenesis and evolution of PD. Although the gut has immune and physical barrier functions [3, 4] that can protect it from environmental damage, these functions deteriorate with age [5, 6], resulting in increased opportunities for the body to be exposed to potentially harmful environmental elements [7]. Braak et al. [8] have proposed an "ascending anatomical theory", which implies that PD evolves from the gut toward the brain. Several studies have accumulated considerable evidence both for and against this theory (Table 1).

Borghammer and colleagues [9–14] recently proposed the body-first and brain-first hypotheses of PD, in which autonomic damage and dopaminergic dysfunction are proposed to appear in different

*Correspondence:
Jifeng Guo
guojifeng@csu.edu.cn
[1] Department of Neurology, Xiangya Hospital, Central South University, Changsha 410008, China
[2] Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha 410008, China
[3] Hunan International Scientific and Technological Cooperation Base of Neurodegenerative and Neurogenetic Diseases, Changsha 410008, China
[4] Center for Medical Genetics and Hunan Key Laboratory of Medical Genetics, School of Life Sciences, Central South University, Changsha 410008, China
[5] Engineering Research Center of Hunan Province in Cognitive Impairment Disorders, Central South University, Changsha 410008, China
[6] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, China

Table 1 Evidence for and against the gut origin of PD

Evidence for	Evidence against
Epidemiological studies	
Gastrointestinal symptoms usually precede the motor symptoms of PD [18].	CNS and PNS are simultaneously involved in PD, with peripheral symptoms appearing first owing to poorer compensatory mechanisms [19].
IBD increases the incidence of PD [20–24]. Effective treatment can reduce the risk of PD [23, 25].	A retrospective study did not confirm that IBD increases the risk for PD [26]. The results of a Mendelian randomization study did not support that treating IBD could prevent PD [27].
Vagotomy and appendectomy can lower the risk of PD [28, 29].	A long-term follow-up study did not confirm that vagotomy reduces the risk of PD [30]. In most studies, appendectomy is not correlated with PD; rather it even slightly increases the risk of PD in some studies [31–33].
Neuropathological studies	
Pathological changes in PD may first occur in the ENS [34].	Results of several clinicopathological studies do not support the peripheral origin of PD. The studies showed that α-syn histopathology of the PNS rarely precedes the CNS [35–37].
Increased intestinal permeability and decreased level of the tight junction protein occludin in PD [38–40].	
Clinical studies	
Intestinal flora dysbiosis can occur in the prodromal phase of PD [41].	
Gut microbes are associated with motor and nonmotor PD phenotypes [42].	
Microbial therapy can improve the clinical manifestations of PD [43].	
Animal studies	
Changes in intestinal flora produce abnormal metabolites and structural proteins, which may trigger α-syn accumulation [44, 45].	The origin of PD may be multifocal [19].
α-Syn originates in the gut and spreads to the CNS through a transsynaptic intercellular approach [46].	PD pathologies, such as α-syn overexpression, can also propagate from the CNS to the intestine [47–51].
Fecal microbiome transplantation can exacerbate or improve PD-like symptoms in animal models [45].	

PD: Parkinson's disease, CNS: central nervous systems, PNS: peripheral nervous systems, IBD: inflammatory bowel disease, ENS: enteric nervous system, α-syn: alpha-synuclein

chronological sequences. In the body-first subtype, the pathology originates in the gut or the peripheral autonomic nervous system. It is accompanied by more common prodromal autonomic symptoms, such as rapid eye movement sleep behavior disorder. In contrast, the brain-first subtype has pathology that initially appears in the midbrain or olfactory bulb, has a shorter prodromal period, and has fewer nonmotor symptoms before diagnosis. A large body of evidence has accumulated in recent years regarding the peripheral origin of PD. Gastrointestinal dysfunction has been detected in patients prior to the diagnosis of PD, and intestinal neuronal innervation may have been affected in the early stage of PD [15]. Imaging data have shown significant dysfunction of the parasympathetic and sympathetic nervous systems in patients with idiopathic rapid eye movement sleep behavior disorder, similar to patients with PD [16]. Pathological investigations have also indicated that α-syn misfolding and aggregation in idiopathic rapid eye movement sleep behavior disorder occurs in the peripheral nervous system and then travels rostrally to the brainstem [15, 17].

Gastrointestinal dysfunction and PD

Gastrointestinal dysfunction is the main early nonmotor symptom of PD. Up to 80% of patients with PD may experience gastrointestinal problems [52, 53]. Constipation is particularly common in PD [54] and occurs years or even decades before the motor symptoms of PD [18, 55]. Some epidemiological studies have demonstrated that constipation increases the risk of PD to some extent [56]. In addition, constipation indicates a worse disease course in PD; for example, constipation in the early stages of PD increases the risk of dementia [57]. The considerable evidence from previous studies has led the International Movement Disorders Society (MDS) to include constipation as a clinical biomarker of PD in its diagnostic criteria for the prodromal phase of PD [58].

PD may originate in the intestine

Alpha-synuclein (α-syn) inclusions were first discovered in the 1980s in the enteric tissues of patients with PD, leading researchers to speculate that the gastrointestinal system may be implicated in the pathogenesis of PD [59–61]. Subsequently, Braak et al. [8, 62] proposed that

pathogenic α-syn inclusions may begin in the gastrointestinal system [63, 64]. Epidemiological studies have shown that vagotomy and appendectomy may reduce the risk of developing PD [28, 29]. Results of some animal studies also support this hypothesis. In a rat model, Kim et al. [65] demonstrated that truncal vagotomy prevents transneuronal transmission of α-syn from the gut to the central nervous systems (CNS). In addition, it has been proven that α-syn spreads to the CNS and higher cortical regions through transsynaptic cell-to-cell transmission [46]. However, reliable evidence that supports the current view on the gut origin of α-syn is still lacking. In addition, some studies have shown contradictory results. For example, some studies proposed that α-syn transmission along the gut–brain axis may be bidirectional [48, 66, 67]. Furthermore, evidence from autopsies does not support the peripheral origin of PD. Notably, in a previous study, analysis of whole-body autopsy data from the Arizona Study of Aging and Neurodegenerative Disorders revealed few autopsy cases of peripheral α-syn pathology without CNS involvement [36]. However, this study does not serve as compelling evidence against the body-first hypothesis of PD, as clarifying the α-syn pathology of the gut is extremely challenging because of factors such as the scope, the time, and the methodology of the assay, and the high probability of test misses [13, 68].

Gut microbes and the microbiota–gut–brain axis

Gut microbes help regulate gastrointestinal and immune functions. They also affect the digestion and metabolism of several foods, nutrients, metabolites, and drugs [69–74]. The balance of gut microbes and its impact on human health have received great attention. Disruption of the gut microbiota balance has been linked to many human disorders, including gastrointestinal, neurological, metabolic, respiratory, and cardiovascular diseases [75]. Gut microbes are the pivotal hub of the gut–brain link and have been called the body's second brain [76]. The term "microbiota–gut–brain" was coined to characterize this complex mechanism [77].

It is well known that PD affects not only the CNS but also the digestive system and the enteric nervous system (ENS). Pathologic changes in the ENS occur early in PD, even before pathologic changes in the CNS [78]. Research conducted on PD patients and animal models indicates the presence of neuronal and glial injury within the ENS [79]. Several research groups have reported Lewy-type pathology in biopsied enteric neurons from PD patients. Atrophic degeneration of neurons in the myenteric plexus and submucosal plexus with colocalized α-syn deposits has been reported in PD patients [80]. Constipation symptoms in patients may result from the dysfunction of vasoactive intestinal peptide secretomotor neurons in the submucosal plexus [81]. In addition, glial markers such as glial fibrillary acidic protein (GFAP) and Sox-10 are increased and associated with pro-inflammatory cytokines in the gastrointestinal tract of PD patients [82]. Animal studies have found that aged rats exhibit neuronal loss and changes of the ENS neurochemical phenotypes, accompanied by dystrophic enteric neurons which contain α-syn aggregates, and that pathologic α-syn can, in turn, affect the cytoskeleton of ENS neurons [78, 83]. In A30P transgenic mice overexpressing α-syn, the ENS is more sensitive to A30P α-syn than the CNS, and similarly, mice overexpressing wild-type human α-syn under the Thy1 promoter show alterations in the colonic myenteric ganglion several months prior to striatal dopamine loss [83, 84].

The gut–brain axis is involved in PD; thus, gut-related dysbiosis and alterations in microbial-derived components are risk factors and important determinants of PD [85]. Studying the mechanism by which the microbiota–gut–brain axis affects the neurological system can help clarify the etiology of PD.

Gut microbiota in PD

Dysbiosis in PD

Since the first gut dysbiosis-PD study [86] published in 2015, dozens of human case–control studies have been published to date (Table 2 and Additional file 1: Table S1). The sample sizes of these studies varied from tens to hundreds, although the inclusion and exclusion criteria may differ. For example, some studies included only drug-naïve PD or early PD, while some included only late-onset PD, or included only male patients to exclude the influence of gender. Consistently, however, most of these studies excluded subjects with concomitant intestinal diseases and recent use of antibiotics, as these factors significantly interfere with the detection of gut microbes. Similarly, some studies have matched the PD and the control groups regarding diet, medications, environmental factors, and other factors that may influence the gut microbiota. Further, a considerable number of studies have included spouses as the control group to eliminate the interference of confounding factors as much as possible.

Results regarding microbial alterations in the gut of PD patients vary; however, some findings have been robustly replicated (Fig. 1). For example, it has been consistently demonstrated that patients with PD show decreased *Lachnospiraceae* and *Prevotellaceae* abundances and increased *Verrucomicrobiaceae* and *Lactobacillaceae* abundances. It is also important to note that alterations in gut microbiology may vary across race/ethnicity, which may be related to factors such as genetic background, diet, environment, and the testing method

Table 2 Microbiome alterations in clinical cohorts of PD

Ref.	Sample size	Control factors	Method	Microbiota alterations	Alpha diversity	Beta diversity
[86]	PD: 72 non-PD: 72	Onset age > 50 years; age- and sex-matched; no endocrine diseases	16S rRNA V1-3	Family increased: Lactobacillaceae, Verrucomicrobiaceae, Bradyrhizobiaceae, Clostridiales Incertae Sedis IV, Ruminococcaceae; family decreased: Prevotellaceae	nd	sd
[87]	PD: 31 non-PD: 28	Early, L-DOPA-naïve PD; only male; age-matched; diet and smoking habits considered	shotgun metagenomic	Family/genus increased: Verrucomicrobiaceae (genus *Akkermansia*); family/genus decreased: Prevotellaceae (genus *Prevotella*), Erysipelotrichaceae (genus *Eubacterium*); species increased: *Akkermansia muciniphila, Alistipes shahii;* species decreased: *Prevotella copri, Eubacterium bioforme, Clostridium saccharolyticum*	nd	sd
[88]	PD: 24 healthy: 14	Age-, sex-, BMI-matched; no diabetes, infectious diseases or special diets	16S rRNA V3-5	Family increased: Enterobacteriaceae, Veillonellaceae, Erysipelotrichaceae, Coriobacteriaceae, Streptococcaceae, Moraxellaceae, Enterococcaceae; genus increased: *Acidaminococcus, Acinetobacter, Enterococcus, Escherichia-Shigella, Megamonas, Megasphaera, Proteus, Streptococcus;* genus decreased: *Blautia, Faecalibacterium, Ruminococcus*	nd	sd
[89]	PD: 76 RBD: 21 healthy: 78	Comorbidities and comedication were documented	16S/18S rRNA V4	Family increased: Verrucomicrobiaceae; genus increased: *Akkermansia*	nd	sd
[90]	PD: 45 healthy: 45	Spouses as control; no serious chronic illnesses (e.g., diabetes); IBS excluded	16S rRNA V3-4	Genus increased: *Clostridium IV, Holdemania, Clostridium XVIII, Butyricicoccus, Anaerotruncus, Aquabacterium, Sphingomonas*	sd (>)	sd
[91]	PD: 64 Control: 64	Age- and sex-matched; dietary habits and medications assessed	16S rRNA V3-4	Family decreased: Prevotellaceae; genus increased: *Bifidobacterium;* genus decreased: *Roseburia*	nd	sd
[92]	PD: 193 PSP: 22 MSA: 22 non-PD: 113	39 drug-naïve PD; age-, BMI-, region-matched; spouses as control; dietary habits assessed; autoimmune disease and advanced-stage PD excluded	16S rRNA V3-4	Family increased: Verrucomicrobiaceae, Enterobacteriaceae, Christensenellaceae, Lactobacillaceae, Coriobacteriaceae, Bifidobacteriaceae; family decreased: Lachnospiraceae; genus increased: *Akkermansia, Parabacteroides;* genus decreased: *Roseburia*	sd (>)	sd
[93]	PD: 197 healthy: 103	Age 40–85 years, onset age 40–80 years, disease duration ≤ 12 years; age-matched; medications, diet, and demographics collected	16S rRNA V4	Family increased: Christensenellaceae, Desulfovibrionaceae; family decreased: Lachnospiraceae; genus increased: *Bilophila, Akkermansia;* genus decreased: *Roseburia, Faecalibacterium*	nd	sd
[94]	Training set PD: 40 healthy: 40 Validation set PD: 78 healthy: 75 MSA: 40 AD: 25	Spouses as partial control; no serious illness (e.g. heart failure); no chronic disease (e.g., diabetes); lifestyle factors and medications considered	shotgun metagenomic	Family increased: Carnobacteriaceae, Lactobacillaceae, Rikenellaceae, Streptococcaceae, Synergistaceae Genus increased: *Alistipes, Enterobacter, Gordonibacter, Granulicatella, Holdemania, Lactobacillus, Streptococcus* Species increased: *Clostridium_asparagiforme, Clostridium_leptum, Enterobacter_cloacae, Gordonibacter_pamelaeae, Granulicatella_unclassified, Holdemania_filiformis, Lachnospiraceae_bacterium 1_1_57FAA, Lachnospiraceae_bacterium 3_1_57FAA_CT1, Lactobacillus_salivarius, Paraprevotella_clara, Streptococcus_anginosus, Streptococcus_salivarius, Streptococcus_thermophilus*	sd (>)	sd

Table 2 (continued)

Ref.	Sample size	Control factors	Method	Microbiota alterations	Alpha diversity	Beta diversity
[95]	PD: 26 Control: 25	Early, L-DOPA-naïve PD; only male; 11 healthy controls, 14 diseased controls had cardiovascular risk factors	shotgun metagenomic	Species increased: *Akkermansia muciniphila, Alistipes shahii, Alistipes obesi, Alistipes ihumii;* species decreased: *Prevotella copri, Clostridium saccharolyticum, Desulfibrio piger*	na	na
[96]	PD: 104 non-PD: 96	91 spouses, 5 siblings as control; diet, lifestyle and housing condition considered	16S rRNA V3-4	Family increased: Christensenellaceae, Verrucomicrobiaceae, Synergistaceae, Catabacteriaceae, Lactobacillaceae; genus increased: *Cloacibacillus, Catabacter, Christensenella, Butyrivibrio, Bifidobacterium, Megasphaera;* species increased: *Bacteroides fragilis, Lactobacillus acidophilus*	nd	na
[97]	PD: 490 healthy: 234	Region-matched; 55% controls were spouses	shotgun metagenomic	Genus: 23 ↑, 11 ↓; species: 55 ↑, 29 ↓	na	sd
[98]	PD: 96 non-PD: 74	Newly diagnosed PD; environmental factors considered; no immunocompromised	16S rRNA V4	Phylum increased: Proteobacteria, Verrucomicrobiota, Actinobacteria; genus increased: *Akkermansia, Enterococcus, Hungatella*	sd (<)	sd

<, ↓: a lower abundance in patients with PD compared to controls; >, ↑: a higher abundance in patients with PD compared to controls

PD: Parkinson's disease, nd: no difference, sd: significant difference, L-DOPA: Levodopa, BMI: body mass index, IBS: irritable bowel syndrome, RBD: rapid eye movement sleep behavior disorder, PSP: progressive supranuclear palsy, MSA: multiple system atrophy, AD: Alzheimer's disease, na: not available

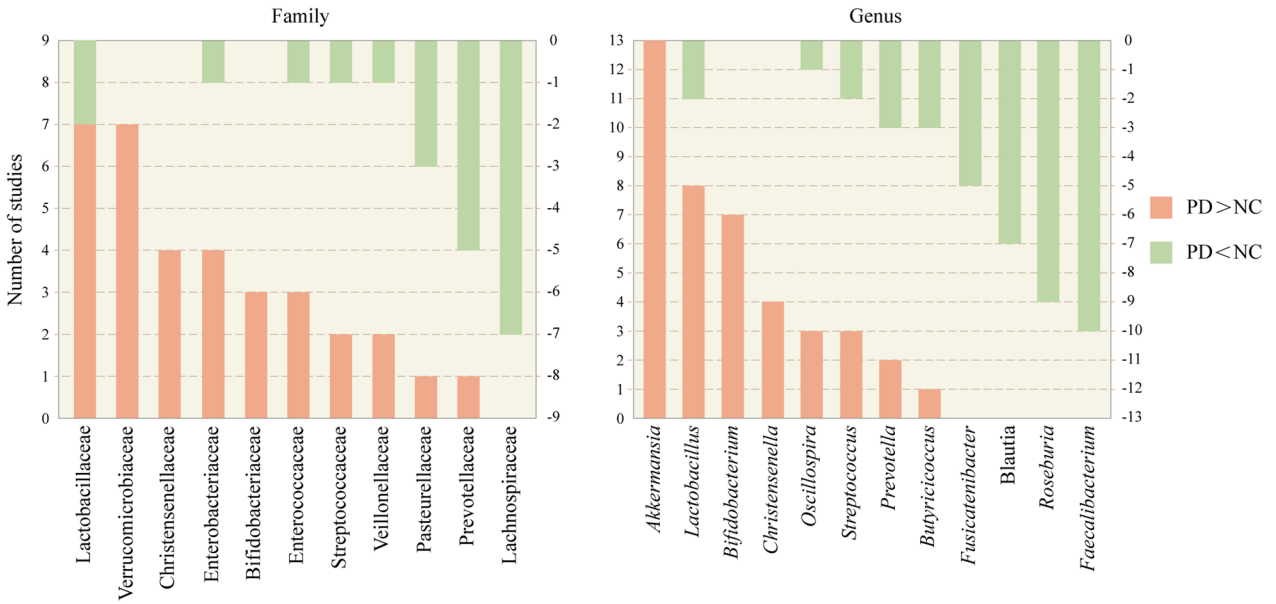

Fig. 1 The most commonly reported 11 families and 12 genera of gut microbiota that are different between the PD and the NC groups. Orange bars represent the number of studies in which PD had a higher abundance than NC. Cyan bars represent the number of studies in which PD had a lower abundance than NC. PD, Parkinson's disease, NC, normal control

used (Fig. 2) [86, 87, 89, 91, 92, 99–103]. Alterations in microbiota (e.g., increased abundance of *Christensenellaceae* or *Oscillospira*) are associated with an increased risk of developing PD, indicating that specific changes in the microbiome can be used to diagnose the disease at an early stage. Dysbiosis is already present in untreated patients with early-onset and treatment-naïve PD [100]. Surprisingly, the gut microbiota is altered in patients with idiopathic rapid eye movement sleep behavior disorder and this alteration has a similar trend to that of patients with PD, and is even already present in their first-degree relatives. This suggests that changes in gut microbiota have already occurred in the prodromal phase of PD [89, 104, 105]. The findings on gut microbes in the differential diagnosis of PD are inconsistent [92, 94, 106]. Therefore, using gut microbes as a biomarker for differential diagnosis of PD is premature.

Gut microbiota and PD symptoms

The results of recent clinical studies indicate that gut microbes are associated with PD phenotypes, such as onset time [107], duration [100], disease stage [108], and clinical symptoms (both motor and nonmotor) [86, 89, 90, 92, 109]. Gut microbes may also help predict those who may be at risk for PD; for example, reduced abundance of short-chain fatty acid (SCFA)-producing microbes could predict the likelihood of future transition to PD in patients with idiopathic rapid eye movement sleep behavior disorder [105].

Regarding motor symptoms, abundance of *Lactobacillus* is correlated with the degree of impaired motor function [92], whereas abundance of the Enterobacteriaceae family is correlated with postural instability, walking difficulties, and akinetic-rigid subscores [86, 91]. Enterobacteriaceae, *Clostridium*, Verrucomicrobia, and *Akkermansia* levels help to distinguish whether PD is dominantly the tremor type [107, 110–112]. Besides motor symptoms, gut microbes may also be associated with nonmotor symptoms. Low counts of *Bacteroides fragilis* are associated with deterioration of motivation/activeness, whereas *Bifidobacterium* is correlated with hallucinations/delusions [113]. Based on data from a study of 423 patients with new-onset PD, gastrointestinal symptoms associated with gut microbiota dysregulation could predict cognitive function [114].

Despite advances in research on gut microbes and PD, there is poor consistency among the existing studies, most likely because gut microbes are influenced by numerous factors. Variations in experimental design (e.g., fecal collection methods, DNA extraction procedures, sequencing techniques, depth heterogeneity, and statistical methods), as well as different individual patient-related factors (e.g., geography, age, ethnicity, host genetics, diet, medications, lifestyle habits, disease severity, and other confounding factors) can affect the results. Therefore, reliable PD microbiome characteristics can only be obtained by adopting a rigorous study design, using standardized processes and methods, and

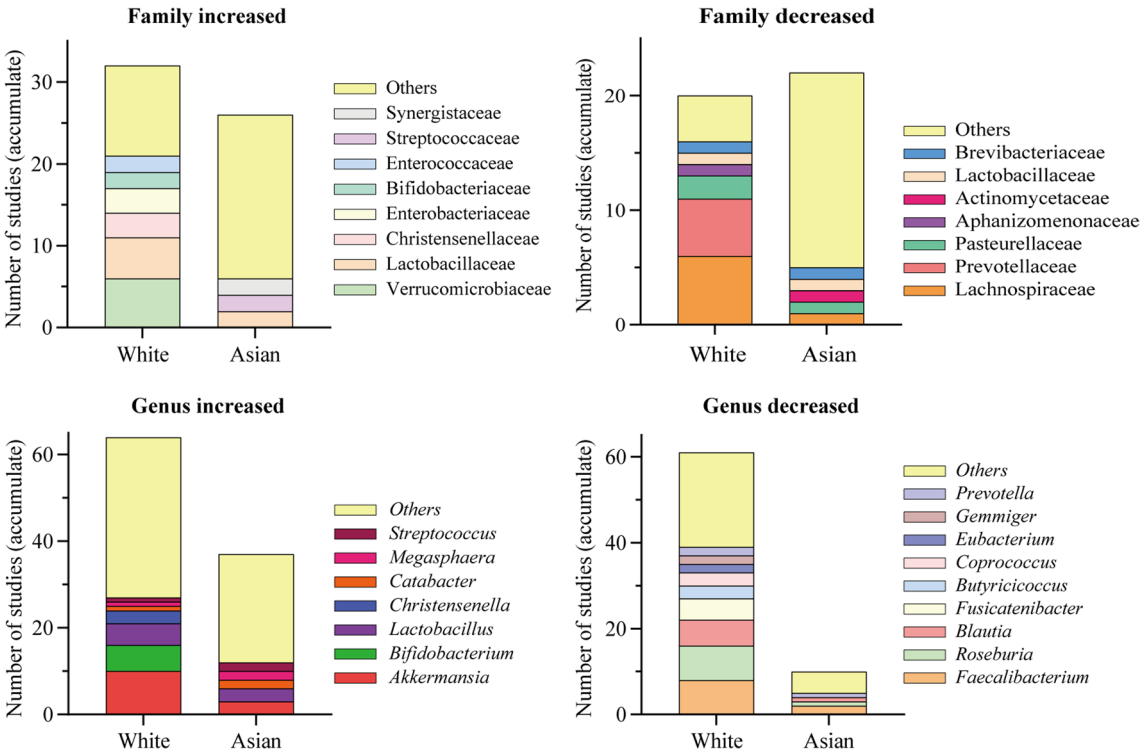

Fig. 2 Alterations in intestinal flora in White and Asian populations with PD. The figure illustrates the number of times the intestinal flora at the family and genus levels have been cumulatively reported in the literature

using appropriate sample sizes. At the outset of the study, in addition to excluding subjects with acute and chronic gastrointestinal diseases and those who have recently taken antibiotics and probiotics that have a significant impact on intestinal microbiology, it is also necessary to consider the patient's genetic background, disease stage, and severity of the condition, and match them with a control group by age, gender, geographical location, diet, underlying diseases, lifestyle, and environmental exposure. The interference of confounding factors such as comorbidities and medications should also be considered simultaneously [115–117].

Gut microbial mechanisms in PD

The specific mechanisms underlying the relationship between gut microbiota and PD have not been fully elucidated, implicating multiple pathways that indirectly lead to dopaminergic neurodegeneration and various CNS dysfunction or impairment (Fig. 3) [118].

Gut microbiota and α-syn

Gut microbes may lead to α-syn misfolding and PD pathology [100, 119]. Like prion disease, molecular mimicry-induced template cross-seeding may cause neuronal protein misfolding in PD [120]. The molecular mimicry of PD may be caused by an extracellular amyloid generated by gut bacteria [121–123]. For example, curli, an extracellular amyloid protein with structural and biophysical properties similar to human pathological amyloids, is secreted by *Escherichia coli* via coordinated biosynthetic processes. Curli may activate the innate immune system and facilitate α-syn aggregation and neuroinflammation [44, 124]. In animal experiments, addition of curli-producing bacteria to old Fischer 344 rats or α-syn-overexpressing *Caenorhabditis elegans* or mice induced accumulation of α-syn in intestinal and brain tissues, and this process could be reversed by depletion of curli through genetic or pharmacological approaches [44, 121, 125]. In another study, intraperitoneal injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in a mouse model increased α-syn expression in the ileal and affected gut microbiota composition [126]. In another mouse model overexpressing human α-syn, the absence of certain gut microorganisms reduced α-syn neuropathology, whereas the presence of the gut microbiota resulted in higher α-syn aggregation. Thus, genetically mediated α-syn overexpression and gut microbiota components have a combined impact on α-syn aggregation in the brain [45].

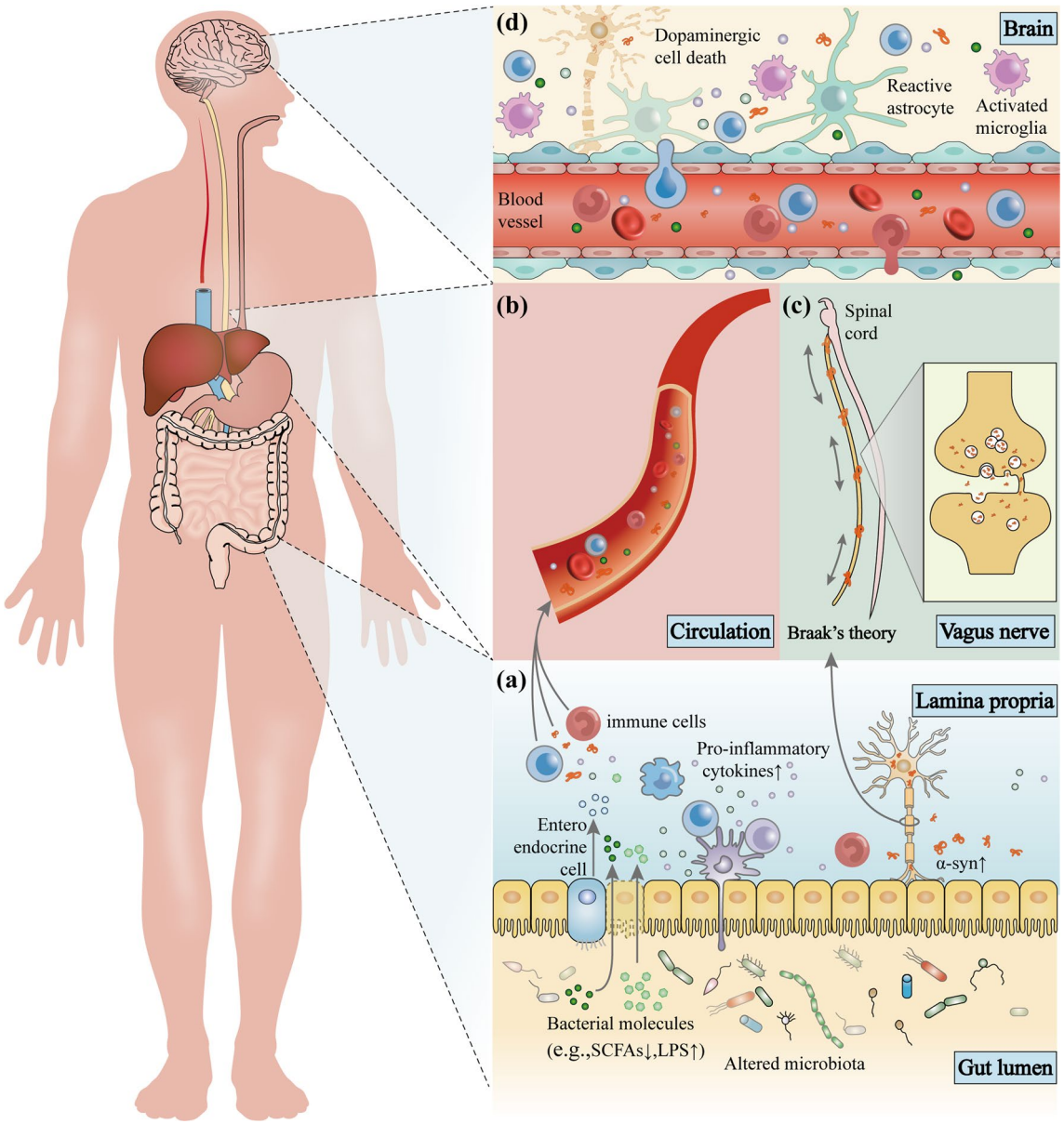

Fig. 3 The microbiota–gut–brain axis in Parkinson's disease (PD). Disordered gut microbes, through the microbiota–gut–brain axis, play a role in the pathogenesis of PD via the immune, endocrine, and nervous systems. **a** Alterations in intestinal microbes and their metabolites can leave the gut in an inflammatory state. These substances can cross the damaged intestinal barrier, activate mucosal immune cells, induce the release of pro-inflammatory cytokines, and promote misfolding and aggregation of α-syn. **b** Increased intestinal permeability allows release of signaling molecules by intestinal microbes and activated immune cells as well as through metabolic secretion to enter the circulation and cause systemic inflammation. **c** Misfolded α-syn in the gut can be transferred to the brain through intercellular transmission via the vagus nerve, and this transmission may be bidirectional. **d** The damaged blood–brain barrier and vagal pathways allow pathological products and α-syn to enter the brain, promoting the activation of immune cells in the brain, including microglia and astrocytes, causing neuroinflammation, and ultimately leading to the loss of dopaminergic neurons and the development of PD

Immunity and inflammation

Progressive dopaminergic neurodegeneration and substantial neuroinflammation in the striatal pathway of the substantia nigra (SN) are two signs of PD [64, 127]. Numerous findings suggest that the inflammation-induced oxidative stress and cytokine toxicity play important roles in PD [128–130]. Gut microbiota may regulate the inflammatory signals and interact with other organs, making it a key player in "inflammaging" [131].

Intestinal infection-related inflammation in PD

The elevated expression of inflammatory cytokine and chemokine genes in the intestinal tissues of patients with PD indicates that PD is closely associated with inflammation in the intestine [100, 132, 133]. Moreover, increased levels of glial cell markers (GFAP and Sox-10) and several pro-inflammatory cytokines are detected in colon biopsy tissues of patients with PD [133]. Similarly, increased amounts of various inflammatory mediators (e.g., interleukin [IL]-1β, IL-6, interferon gamma [IFN-γ], and tumor necrosis factor alpha [TNF-α]) in the stool samples of patients with PD indicate the presence of gastrointestinal inflammation [64, 119, 134–136]. These inflammatory changes increase the susceptibility of the host to immune dysfunction and autoimmunity [137].

Gut microbiota and intestinal inflammation

Gut microbial dysbiosis can result in peripheral and central immune activation and inflammation [138, 139], causing persistent intestinal epithelial inflammation and neuroinflammation via the microbiota–gut–brain axis [140, 141]. The blood–brain barrier (BBB) can be damaged by pro-inflammatory molecules in the systemic circulation, allowing inflammatory cytokines to enter the SN, leading to neuroinflammation and death of dopaminergic neurons [141–144].

Changes of anti-inflammatory bacteria have been detected in patients with PD. A study in PD patients revealed a considerable drop in *Blautia*, *Coprococcus*, and *Roseburia* genera in stool samples; a decrease of *Faecalibacterium* and increase of *Ralstonia* in the gastrointestinal mucosa; and a shift to a more inflammatory state of microorganisms in the colon [100]. The relative abundances of Verrucomicrobia and *Bacteroides* have been revealed in PD, which are associated with elevated plasma TNF-α and IFN-γ levels. This suggests that the gut flora is changed in a systemic sub-inflammatory condition in PD [109]. Notably, young *Pink1* knockout mice may develop severe dyskinesia and striatal dopaminergic axon loss later in life when exposed to Gram-negative bacteria that induce moderate intestinal symptoms, suggesting an interaction between a genetic predisposition to PD and intestinal microbes, as well as intestinal inflammation [145].

PD and inflammatory bowel disease (IBD)

Several systematic reviews and meta-analyses showed that individuals with IBD have a 20%–90% increased chance of developing PD [20–24]. In addition, individuals with IBD have fewer Firmicutes and more Enterobacteriaceae than healthy individuals [146]. These microbial characteristics of IBD are consistent with some microbial abnormalities identified in PD [101]. Research on IBD and PD has focused on numerous shared genetic risk factors [147], as the two diseases share several loci that influence the risks of both diseases in similar directions. IBD and PD are both associated with mutations of leucine-rich repeat kinase 2 (*LRRK2*), a gene that mediates microbial immunological signaling [25]. Substantial evidence supports the role of *LRRK2* in immune cells and inflammatory diseases [148, 149]. Recent animal studies have shown that colitis in *Lrrk2* p.G2019S mice is more severe than that in littermate controls or *Lrrk2* wild-type mice. The *Lrrk2* p.G2019S mice with colitis show reduced motor function and increased loss of dopaminergic neurons. *LRRK2* mutations significantly enhance inflammation in the colon and the brain and impact neuronal survival. This response is associated with immunomodulation by *LRRK2* [150, 151]. Similarly, increased *LRRK2* expression was observed in colon biopsies from patients with PD, and the expression levels correlated with disease severity, even in the prodromal phase of the disease, when colon *LRRK2* expression was dramatically increased [152]. *NOD2* is the most closely correlated gene for Crohn's disease (CD) and has the most frequently replicated associations with CD. A meta-analysis showed that intronic single nucleotide polymorphisms (SNPs) of *NOD2* (rs6500328) are also related to the susceptibility to PD [153, 154]. In addition, patients with PD show an overexpression of the *CARD15* gene SNP, which is linked to CD [155]. There are also other reported risk loci for PD and IBD. These loci are involved in immune response and microbial induction (e.g., *HLA* locus) as well as in lysosomal dysfunction (e.g., *GALC* and *GPR65*), and are shared by PD and IBD with similar mechanisms [24, 49, 156]. The association between PD and IBD has also been confirmed therapeutically. A previous study showed that patients with IBD who received anti-TNF biologics as part of chronic anti-inflammatory treatment are 78% less likely to develop PD compared to those who did not, indicating that inhibiting peripheral inflammation may prevent PD [23, 25]. However, a subsequent Mendelian randomization research did not yield consistent results with those studies [27].

Toll-like receptors (TLRs)

TLRs are transmembrane pattern recognition receptor proteins that initiate the innate immune response by detecting foreign microbial and viral molecules and maintaining intestinal homeostasis [157]. Several studies have shown that PD is closely associated with TLRs. Patients with PD show elevated blood and brain levels of TLR2 and TLR4 [158]. Gut microbes influence TLR2 expression, and TLR2 recognizes bacterial products such as lipoteichoic acid, lipoproteins, peptidoglycans, and bacterial amyloid (e.g., curli protein) [159]. By binding

and activating TLR2, curli increases intracellular α-syn, triggering a neuroinflammatory response via the TLR2/MyD88/NF-κB pathway [160, 161]. Similarly, activation of TLR2 in the brains of PD patients increases proinflammatory cytokine levels and microglial recruitment and amplifies neuroinflammation and α-syn expression. Most α-syn-positive Lewy bodies also exhibit high TLR2 immunoreactivity, indicating a strong relationship between these pathologies [162, 163]. Similarly, more TLR4-expressing cells are observed in the colonic tissues of PD patients than in healthy controls [164]. The TLR4 signaling system, which recognizes Gram-negative bacterial lipopolysaccharides (LPS) and endogenous chemicals, plays a significant role in the inflammation observed in the intestines and brains of patients with PD [132]. TLR4 is crucial for clearing α-syn; in addition, it interacts with α-syn to initiate PD-associated microglial cell responses [165, 166]. TLR4 deficiency significantly attenuates the effects of rotenone on intestinal barrier integrity, GFAP expression in myenteric plexuses, colonic α-syn, nigrostriatal microglial activation, dopaminergic neuron loss, and motor dysfunction [132]. Considering the crucial role of TLR4 in PD, studies on the treatment of PD by targeting and modulating this pathway have been conducted, and the results imply that the microbiota–gut–brain axis is involved [167].

Microbial toxins: LPS

Gram-negative bacteria produce the endotoxin LPS in their cell walls. PD-associated intestinal dysbiosis results in LPS-mediated intestinal inflammation and weakens the intestinal barrier by activating the TLR4/MyD88/NF-κB signaling cascade [109].

Peripheral injection of LPS in C57BL/6J mice increases pro-inflammatory cytokine levels and activates microglia in the SN via the NOD-like receptor protein 3 (NLRP3)–IL-1β signaling pathway, leading to brain neurodegeneration [168]. In CNS disorders, the NLRP3 inflammasome is essential for the intestinal/peripheral inflammation caused by microbiota and neuroinflammation [169]. Moreover, another study showed that repeated administration of *Proteus mirabilis* or LPS to young wild-type or MPTP-treated mice is sufficient to cause symptoms similar to PD [170, 171]. In addition, LPS can facilitate the transfer of α-syn to the CNS by binding to it and initiating intestinal fibrosis [172, 173]. This finding supports the hypothesis that the gut microbial pro-inflammatory environment is a major factor in the pathogenesis of PD.

Gut microbiota-derived metabolites and PD

Changes in microbial metabolites can modulate CNS pathophysiology. Gut microbes produce approximately 40% of human metabolites, including SCFAs, trimethylamine N-oxide (TMAO) and amino acids, which have several physiological functions [174]. Metabolic condition appears to be more important than species balance in terms of microbiome function [175]. Alterations in the composition of the microbiota may lead to metabolic changes in PD, which may play an important role in the onset and progression of PD, with SCFAs being particularly important (Table 3) [176].

Two sides of SCFAs

SCFAs are significant byproducts of intestinal microorganisms and mainly include formic, acetic, propionic, and butyric acids. Patients with PD show significantly decreased levels of acetate, propionate, and butyrate in stool samples [177]. Butyrate can provide energy to the intestinal epithelial cells. In addition, it suppresses the activity of the transcription factor NF-κB and decreases intestinal mucosal inflammation, which modulates the action of pro-inflammatory cytokines [178, 179]. Moreover, butyrate may activate autophagy via the Atg5 and PI3K-Akt-mTOR pathways, leading to degradation of α-syn in rat models of pesticide-induced PD. Animal studies have demonstrated that some SCFAs have significant protective effects on striatal dopaminergic and tyrosine hydroxylase-positive neurons [180–182]. Changes in the gut microbiota-mediated SCFAs may be a driving force for dopaminergic neuronal degeneration. Reduction of several SCFA-producing bacteria, such as *Roseburia*, *Eubacterium*, *Ruminococcus*, *Blautia*, *Faecalibacterium prausnitzii*, and *Coprococcus*, many of which are also butyric acid-producing bacteria, has been observed in PD [97, 100, 101]. Reduction of gut microbiota-derived SCFAs leads to decreased colonic motility and mucin synthesis as well as increased intestinal mucosal inflammation and permeability [38, 183–185]. This exposes the internal environment to bacterial antigens and endotoxins, causing systemic inflammation, neuroinflammation and neurodegeneration, and leading to overexpression, misfolding, and reduced clearance of α-syn, thus promoting PD dyskinesia [45, 186]. Conversely, increasing the gut bacteria that produce butyric acid can protect the damaged intestinal barrier and increase the striatal dopamine level [187]. Butyric acid, produced by the gut microbiota when prebiotic fiber is fermented, is regarded as a promising treatment option for PD [188, 189]. In an animal study, sodium butyrate, an HDAC inhibitor, ameliorated dyskinesia in a *Drosophila* PD model [182]. In another study, long-term administration of phenylbutyrate increased DJ-1 activity, decreased α-syn aggregation, and prevented age-related motor deterioration and cognitive impairment in a transgenic mouse model of diffuse Lewy body disease [190]. Recent studies have found that fermentation of feces from PD

Table 3 Altered gut microbial metabolites in patients with PD

Ref.	Sample size	Sample	Control factors	Dietary instruments	Technique	Findings
[101]	PD: 34 Healthy: 34	Fecal	Age-matched; no special dietary habits	Dietary habits were interviewed	Gas chromatography	PD is associated with certain gut microbiota and reduced fecal SCFAs
[93]	PD: 75 Healthy: 50	Serum	Aged 40–85 years, onset age 40–80 years, disease duration ≤ 12 years; age-matched; medications, diet, and demographics collected	FFQ	UPLC-MS; HILIC-MS	The microbiota of PD had decreased carbohydrate fermentation and butyrate synthesis and enhanced proteolytic fermentation and p-cresol and phenylacetylglutamine production. Patients with constipation and stool consistency had more proteolytic metabolites and taxonomic changes
[206]	PD-MCI: 13 PD-NC: 14 Healthy: 13	Fecal	Spouses as control; age-matched; BMI-matched; no serious chronic illnesses (e.g., hyperlipidemia, diabetes); no fat-rich diet	Questionnaire including caffeine and alcohol intake	GC–MS	SCFAs were similar in PD-MCI, PD-NC, and healthy, however, the isovaleric and isobutyric levels negatively correlated with the MMSE scores
[194]	PD: 64 Healthy: 51	Fecal	Spouses or family members as control; internal medicine, neurological, or unstable psychiatric illness excluded	N.A	GC–MS	Lipids, vitamins, amino acids, and other organic compounds changed. Most modified metabolites closely associated with *Lachnospiraceae* abundance
[95]	PD: 8 Control: 10	Serum	Early, L-DOPA-naïve PD; only male; 5 healthy controls, 5 diseased controls having cardiovascular risk factors	Omnivorous vegetarian probiotics	Targeted metabolomics	Disease severity is linked to mucin and host glycans breakdown by microbes. Gut-community metabolic modeling shows that PD bacteria cause folic acid deficiency and hyperhomocysteinemia
[96]	PD: 104 Non-PD: 96	Fecal	91 spouses, 5 siblings as control; diet, lifestyle and housing condition considered	FFQ	NMR; LC–MS	Neuroprotective chemicals such as SCFAs, ubiquinones, and salicylate, as well as ceramides, sphingosine, and TMAO, are linked to PD metabolite features and functional changes. Clinical signs include cognitive impairment, BMI, frailty, constipation, and physical activity are also linked to it

PD: Parkinson's disease, SCFAs: short chain fatty acids, FFQ: Food Frequency Questionnaire, UPLC-MS: ultraperformance liquid chromatography-mass spectrometry, HILIC-MS: hydrophilic metabolites for hydrophilic interaction liquid chromatography-mass spectrometry, MCI: mild cognitive impairment, N.A.: non-available, NC: normal cognition, BMI: body mass index, GC–MS: gas chromatography-mass spectrometry, MMSE: Mini-Mental State Examination, na: not available, L-DOPA: Levodopa, NMR: nuclear magnetic resonance, LC–MS: liquid chromatography-mass spectrometry, TMAO: trimethylamine N-oxide

patients with prebiotic fibers can alter the microbiota and promote production of SCFAs that may exert effects on microglia indirectly [191, 192].

Despite the reported benefits, the position of SCFAs in PD is debated. Recent studies have shown no change or even an increase in SCFAs in patients with PD [193, 194]. Interestingly, systemic SCFAs levels are raised even when the fecal levels decrease in patients with PD, possibly due to the impaired gut-blood barrier permeability that may allow SCFAs to enter the systemic circulation [195]. Animal studies similarly found that the increased SCFAs in the feces of mice treated with MPTP were associated with increases of activated striatal glial cells, including microglia and astrocytes [196]. Sampson et al. [45] showed that supplementing SCFAs to germ-free (GF) mice promotes α-syn-mediated neuroinflammation and motor deficits. It is important to note that providing SCFAs to GF animals (which produce little to no SCFAs) results in an acute inoculation state that dramatically alters host physiology and matures immune function [197, 198]. Similarly, pathology has been observed in other neurodegenerative GF model mice and microbe-free human cell culture systems [199–201]. In other research, sodium butyrate accelerates motor dysfunction and dopaminergic neuron death in PD mice. It downregulates the dopamine level and increases the numbers of activated microglia and astrocytes, increasing the glial cell-mediated neuroinflammation [202].

The SCFAs and SCFA-producing bacteria are not disease-specific, and the causal link between SCFAs and various PD pathologies is currently unclear. Further evidence is needed to determine whether SCFAs modulate specific neurons directly [25]. SCFAs may have both positive and negative influence on the autoimmune CNS inflammation [203], and depending on the dose and type, different SCFA concentrations and ratios may result in different health outcomes [204]. The inconsistency of results among the SCFA studies calls for the need to consider possible influences from environment (GF vs. SPF), diet, genetic background, disease stage, form of intervention, and assay methods in animal and clinical studies in the future [192, 201, 205].

TMAO

TMAO is a metabolite derived from intestinal microorganisms and synthesized from dietary elements such as *L*-carnitine and choline [207]. TMAO disrupts the BBB and alters the NLRP3 inflammasome, which may contribute to neuroinflammation and PD. Additionally, TMAO may stimulate human α-syn folding in a dose-dependent manner [208]. In mice, TMAO may cause oxidative stress, neuronal senescence and synaptic impairment, leading to brain aging [209]. However, there is also evidence that TMAO may be neuroprotective by facilitating proper protein folding and reducing endoplasmic reticulum stress and α-syn formation [210]. Clinical findings on TMAO are also inconsistent. One study found elevated TMAO to be associated with worsening of motor symptoms and dementia transformation in PD; conversely, decreased TMAO has also been reported to be associated with PD progression and dementia transformation [96, 210, 211]. The contradictory results may be attributed to the confounding bias or reverse causality. Recent research has shown a high link between cerebrospinal fluid and plasma TMAO levels, supporting that peripheral TMAO may enter the CNS [212].

Amino acids

The gut microbiota is critical for amino acid metabolism and cycling, and amino acid-fermenting bacteria can regulate amino acid distribution in the gastrointestinal tract [194]. Branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs) in the body are mainly derived from dietary nutrients; therefore, gastrointestinal dysfunction in PD may impair their absorption [213]. It has been reported that the disturbances in plasma BCAAs and AAAs in PD patients may be related to the gut microbiota [214]. BCAAs regulate brain function. Tyrosine and phenylalanine produced during AAA metabolism are key substrates for the production of dopamine. Tryptophan is processed by host cells and some intestinal bacteria to serotonin, kynurenine, and indole derivatives that act as neurotransmitters and metabolic regulators [215, 216]. Tryptophan and kynurenine levels are considerably lower in PD patients, suggesting the involvement of this pathway in PD etiology [217]. Notably, the findings of various research on BCAA and AAA alterations in PD have been conflicting [214, 218–220]. Therapeutically, a high-BCAA diet inhibits the pro-inflammatory state in the gut and the brain of mice, restores gut and motor function, and attenuates the loss of dopaminergic neurons [221]. Similarly, tryptophan supplementation prevents the rotenone-induced neurotoxicity and improves motor impairments, perhaps via the aromatic hydrocarbon receptor pathway [222]. Thus, amino acid supplementation may be a promising therapeutic target for PD.

Neuroprotective factors and gut microbiota: ghrelin

Ghrelin is a signaling peptide involved in the gut–brain axis. It interacts with the CNS indirectly via the vagus nerve or directly across the BBB, triggering its target receptor GHSR-1a, which is present in various peripheral and brain areas. Interestingly, the ghrelinergic system and the gut microbiota have synergistic effects in controlling metabolic and central homeostatic functions [223, 224]. Increasing evidence supports the association between

ghrelin disturbance and PD, and gut microbe may mediate this disturbance. Ghrelin and ghrelin receptors have significant neuroprotective effects in PD [225–231], and a dramatic decrease of their concentrations may be involved in the pathogenesis of PD [232]. Injection of the GHSR-1a antagonist [D-Lys3]-GHRP6 into the SN zone of normal mice triggers PD-like dyskinesia [232]. Patients with PD exhibit reduced plasma ghrelin levels [233], which are linked to increased Lactobacillaceae and decreased Prevotellaceae levels [234]. Ghrelin protects dopaminergic neurons by decreasing α-syn accumulation and phosphorylation, increasing autophagy, and blocking the endoplasmic reticulum-mediated apoptosis [235]. *GHSR* gene deletion dramatically enhances the degeneration of dopaminergic neurons, leading to an abrupt decrease in dopamine concentration in the striatal region [225].

Ghrelin may be a novel and efficient therapeutic option for PD [236–238]. Ghrelin-assisted treatments can significantly increase the number of midbrain neural stem cells that promote dopaminergic nerve cell differentiation through the Wnt/β-catenin pathway [239]. In addition, ghrelin and its agonists promote gastric emptying and increase plasma levels of levodopa (*L*-dopa) and dopamine, which may be utilized for alleviating gastrointestinal problems that appear after PD and *L*-dopa treatment [237].

Reflections on animal models of gut microbes in PD

Animal model experiments allow for control over several parameters such as host genetics, ambient circumstances, nutrition, chronobiological measures, gut microbiota, and regional/mucosal sampling [240]. Mechanistic investigations of the gut microbiota in PD have made some headway with the use of animal models (Table 4). However, to date, there is no animal model that can comprehensively encompass all the pathogenic features of PD.

The animal models of PD are primarily divided into neurotoxic and genetic models. Neurotoxin-based models display degeneration of dopaminergic neurons in the substantia nigra pars compacta, but this model lacks the formation of Lewy bodies, the primary pathological hallmark of PD. In contrast, genetic animal models are typically dissimilar to the human condition and rarely reproduce the general traits of the disease [248]. Furthermore, the aging process differs significantly amongst various species of animals. Rodents may lack normal neurodegeneration due to their short lifetime [249]. Although mouse models may replicate the protein misfolding and aggregation found in human brains, most mouse models fail to fully recapitulate the symptoms and pathology of neurodegenerative disorders. The human gut microbiota, on the other hand, is complicated, with high inter-individual variations and numerous confounding factors. Animal models have severe limitations in terms of experimental control, scalability, and recapitulation of human gut interactions with host-specific symbionts and pathogens [250, 251]. Experimental microbial communities may not accurately match the human microbiome, and the gut microbiota of animal models may differ between laboratories [252]. Animal models have substantially improved our knowledge of the molecular involvement of gut microbiome in many illnesses, but their experimental findings are still far from clinically applicable.

Gut microbes and PD drugs

PD medication therapies may be affected by gut bacteria [253–255]. The trillions of microorganisms comprising the gut bacteria produce various enzymes that can directly alter and metabolize drugs, affecting their bioavailability and efficacy [256, 257].

Levodopa

L-dopa is the most clinically used anti-PD drug [258]; however, its bioavailability varies greatly among patients. Given that *L*-dopa is usually administered orally or enterally, scientists believe that gut bacteria may impact its efficacy [87, 259, 260]. van Kessel et al. [255] and Maini Rekdal et al. [253] proved that gut microbiota can regulate *L*-dopa metabolism and they identified a two-step enzymatic pathway for *L*-dopa metabolism by intestinal microbes. First, a pyridoxal phosphate-dependent tyrosine decarboxylase (tyrDC) from the gut microbiota transforms *L*-dopa into dopamine, which is then changed into *m*-tyrosine by a molybdenum-dependent dehydroxylase from *Eggerthella lenta*. Analyses of established human microbiome datasets revealed that the *tyrDC* gene is mostly present in the *Enterococcus* and *Lactobacillus* genera, particularly in *Enterococcus*. The relative abundance of *tyrDC* gene in the fecal microbiota of PD patients was positively associated with higher daily levodopa/carbidopa dosage requirement and disease duration, suggesting that gut microbes can influence the efficacy of PD medications. Further studies in rats that received oral levodopa/carbidopa revealed that the plasma *L*-dopa levels are negatively correlated with jejunum bacterial *tyrDC* gene abundance, suggesting that overexpression of the bacterial *tyrDC* gene leads to detrimental *L*-dopa metabolism in the intestine [255]. In addition, researchers also discovered a small-molecule inhibitor, (S)-α-fluoromethyltyrosine (AFMT), that specifically inhibits *L*-dopa decarboxylation by tyrDC, *Enterococcus faecalis*, and gut microbiota samples from patients with PD, indicating that AFMT may boost *L*-dopa serum

Table 4 Mechanistic studies of microbiota in animal models of PD

Ref.	Animal model	Perturbation	Control factors	Test (phenotype and pathology)	Outcomes	Summarize
[45]	Thy1-α-syn mice	GF versus SPF	Housed in sterile or autoclaved caging, receiving autoclaved food	Beam traversal, pole descent, nasal adhesive removal, hindlimb clasping reflex, α-syn inclusions, microglia morphology	Gut microbiota promotes α-syn-mediated motor impairments and brain damage; depletion of gut bacteria reduces microglial activation; SCFAs regulate microglia and exacerbate PD pathophysiology; in mice, gut microbiota from PD patients enhances motor impairment	Gut microbes may play a key functional role in the pathogenesis of PD
[145]	*Pink1*$^{-/-}$ mice	Administration of *Citrobacter rodentium*	Littermate mice, kept in pathogen-free conditions	Behavioural tests, grip strength test, basal locomotor activity, pole test, histology for dopaminergic neurons	*Pink1*$^{-/-}$ mice with intestinal infection exhibited dyskinesia; significant reduction in dopaminergic axonal varicosities; mitochondria-specific $CD8^+$ T cells in the brains of infected *Pink1*$^{-/-}$ mice killed dopaminergic neurons in vitro	Supports PINK1 as an immune system suppressor and implies that intestinal infections may induce PD
[241]	*Caenorhabditis elegans*	*Bacillus subtilis* probiotic strain PXN21 feeding	All strains were grown at 20 °C, bacteria were grown in SSM medium at 37 °C for 48 h	Locomotion analysis, lifespan assays, quantification of life-traits, α-syn forms and expression levels, nematode RNA sequencing	*Bacillus subtilis* PXN21 inhibits and reverses α-syn aggregation in a *Caenorhabditis elegans* model; probiotics alter host sphingolipid metabolism, whereas gut biofilm formation and bacterial metabolites diminish α-syn aggregation	A foundation for exploring the disease-modifying potential of *Bacillus subtilis* as a dietary supplement
[242]	Rotenone mouse model	GF versus CR	Age- and weight-matched, under sterile conditions	Grip strength test, rotarod test, intestinal permeability measurement, quantification of TH neurons	Rotenone gavage caused TH neuron loss in GF and CR mice, but only CR mice had impaired motor strength and coordination; rotenone affected intestinal permeability in CR mice but not GF animals	The gut microbiota has a potential role in modulating barrier dysfunction and motor deficits in PD
[243]	MPTP- mouse model	Administration of Cb	Animals were kept at 23 ± 2 °C with 12 h light/dark cycles	Pole test, beam walking teat, forced swimming test, open field test, dopaminergic neuron loss, synaptic plasticity, microglial activation	Oral administration of Cb ameliorates MPTP-induced motor deficits, dopaminergic neuron loss, synaptic dysfunction, and microglial activation in mice	Cb exerts neuroprotective effects by modulating the abnormal microbiota-gut-brain axis

Table 4 (continued)

Ref.	Animal model	Perturbation	Control factors	Test (phenotype and pathology)	Outcomes	Summarize
[244]	Rotenone mouse model	Administration of *Lactobacillus plantarum* PS128	Under standard laboratory conditions	Rotarod test, narrow beam test, dopamine level, quantification of TH neurons, microglial activation, neuroinflammation	PS128 dramatically improved motor impairments in PD-like animals by increasing brain dopamine levels, neurotrophic factor expression, decreasing dopaminergic neuron loss, microglial activation, inflammatory factors	By modulating gut microbiota, PS128 improves motor function and neuroprotection in PD
[192]	Thy1-α-syn mice	Feeding a prebiotic high-fiber diet	Housed in sterile, autoclaved cages with sterile water	Beam traversal test, pole test, wire hang, hindlimb score, adhesive removal, fecal output, microglia isolation and sequencing, immunohistochemistry, α-syn aggregation, flow cytometry, gut microbiome profiling	Prebiotic diet improves gut flora, lowers motility abnormalities, and reduces α-syn aggregation in the substantia nigra, mediated by microglia. Prebiotic diet decreases microglial activation and boosts disease resistance. Depletion of microglia reduces prebiotic benefits	Gut microbiome digestion of dietary fiber changes CNS cell physiology and improves behavioural and pathologic outcomes
[44]	Aged male Fischer 344 rats; α-syn-expressing *C. elegans*	Exposed to curli-producing bacteria	Rats: antibiotic treatment; *C. elegans:* standard conditions	Swimming tests, α-syn accumulation and aggregation, inflammation	Exposure to curli-producing bacteria in rats showed increased α-syn deposition in the gut and brain, increased microgliosis and astrogliosis, and elevated brain TLR2, IL-6, and TNF expression. α-syn-expressing *C. elegans* fed with curli-producing bacteria showed increased α-syn aggregation	Amyloid proteins in the microbiota have a role in the onset and progression of neurodegenerative illness
[171]	MPTP/p, MPTP, 6-OHDA-induced mice	Administration of *P. mirabilis*	Conditions: 23 ± 1 °C, relative humidity 60% ± 10%, 12 h light/dark cycle	Pole test, open field test, rotarod test, dopaminergic neuronal damage, activated microglia, LPS levels, colonic pathology, α-syn filament quantitation, α-syn expression	Administration of *P. mirabilis* significantly induced motor impairments, dopaminergic neuron loss, and inflammation in the substantia nigra and striatum and increased α-syn aggregation in the brain and colon	*P. mirabilis* may have a role in the etiology of PD

Table 4 (continued)

Ref.	Animal model	Perturbation	Control factors	Test (phenotype and pathology)	Outcomes	Summarize
[245]	6-OHDA rat model	Antibiotic treatment	Conditions: 22 °C, 12/12 h light/dark cycles	Cylinder test, forepaw stepping test, amphetamine-induced rotation test, quantification of DA, its metabolites, and 5-HT, [^{3}H]-DA uptake, DA neuron depletion, TH immunoreactivity, DAT expression and function, pro-inflammatory markers	Antibiotics decreased motor impairments, TH loss in the striatum and substantia nigra, and pro-inflammatory cytokines	Expands knowledge of gut microbiota's function in DA neuronal vulnerability, motor behavior, and neuroinflammatory responses in PD
[125]	Thy1-α-syn mice	Colonization with curli-producing gut bacteria	Housed in sterile or autoclaved caging, receiving autoclaved food	Beam traversal, pole descent, fecal output, wire hang, adhesive removal and hindlimb scoring, α-syn pathology, inflammatory responses, microglia morphologies	Gut exposure to bacterial amyloid worsens motor impairments and α-syn brain disease via CsgA aggregation	These findings reveal a trans-kingdom link between the gut microbiome and mammalian amyloids, implying that some bacterial taxa may worsen neurologic illness
[242]	Rotenone mouse model	GF versus CR	Age/gender-matched GF mice were treated under sterile conditions	Grip strength test, rotarod test, quantification of TH neurons, intestinal permeability measurement	Chronic rotenone treatment disrupts colonic epithelial permeability and causes motor symptoms exclusively in CR mice with complex microbiota but not in GF mice	Demonstrate that gut microbiota may regulate PD barrier dysfunction and motor impairments
[121]	*C. elegans*	Feeding with *E. coli* knockout mutants	*C. elegans* were maintained at 20 °C	*C. elegans* basal slowing response assays, *C. elegans* butanone associative learning assays, cell viability assay, mitochondrial respiration assay, level of α-syn, the colocalization between CsgA and α-syn	Genetically deleting or pharmacologically suppressing the curli main subunit CsgA in *E. coli* lowered α-syn-induced neuronal mortality, increased mitochondrial health, and enhanced neuronal functioning. Through cross-seeding, CsgA colocalized with α-syn within neurons and enhanced its aggregation	Bacterial components (e.g., curli) can directly affect neurodegenerative lesions
[246]	MPTP- mouse model	FMT from healthy mice	Kept at 22–26 °C, 12 h light/dark cycle	Pole test, traction test, SCFAs analysis, α-syn expression, TH level, microglial marker, neuroinflammation	FMT improved physical function and lowered fecal SCFAs. FMT also reduced the expression of α-syn, prevented microglial activation in the SN, and hindered TLR4/PI3K/AKT/NF-κB signaling in the SN and striatum	FMT may protect mice against PD by reducing α-syn expression and inactivating TLR4/PI3K/AKT/NF-κB signaling

Table 4 (continued)

Ref.	Animal model	Perturbation	Control factors	Test (phenotype and pathology)	Outcomes	Summarize
[247]	MPTP- mouse model	FMT from PD patients or healthy human controls	Conditions: 21 ± 1 °C, humidity 55% ± 5%, 12 h light/dark cycle	Pole test, rotarod test, gut inflammation, phosphorylated AMPK and SOD2 expression, TH expression, glial activation, CD13, PDGFRβ, CD31	FMT derived from healthy human controls may repair gut dysbacteriosis and improve neurodegeneration by suppressing microgliosis and astrogliosis, improving mitochondrial deficits via the AMPK/SOD2 pathway, and restoring nigrostriatal pericytes and BBB integrity	Human gut microbiota changes may be a risk factor for PD, and FMT may be used for preclinical therapy

GF: germ-free, SPF: specific-pathogen-free, α-syn: alpha-synuclein, SCFAs: short chain fatty acids, PD: Parkinson's disease, SSM: Schaeffer's sporulation medium, CR: conventionally raised, TH: tyrosine hydroxylase, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, Cb: Clostridium butyricum, *P. mirabilis*: *Proteus mirabilis*, 6-OHDA: 6-hydroxydopamine, DA: dopamine, DAT: dopamine transporter, 5-HT: 5-hydroxytryptamine, *E. coli*: *Escherichia coli*, FMT: fecal microbiota transplantation, SN: substantia nigra, BBB: the blood–brain-barrier

concentrations and increase the amount of *L*-dopa entering the brain, thereby improving its bioavailability (Fig. 4) [253].

These results imply that gut microbiota species and their enzymes are promising biomarkers for predicting the efficacy of *L*-dopa therapy, as they can affect the bioavailability and efficacy of *L*-dopa in vivo and provide a novel treatment strategy for PD.

Other drugs

Catechol-O-methyl transferase (COMT) inhibitors are often used for the treatment of PD. Studies of gut microbes have revealed an association between COMT inhibitors and alterations in specific taxa; however, the results of these studies are not consistent [91, 101, 102, 108]. Entacapone, a well-established COMT inhibitor, inhibits the growth of *Faecalibacterium prausnitzii* and its potential bioactive metabolite butyrate [101]. Scheperjans et al. [86] discovered a correlation between COMT inhibitors and the abundance of Enterobacteriaceae. Patients treated with COMT inhibitors show a higher abundance of *Bifidobacterium* than those who did not receive the treatment [91]. However, some studies have shown that COMT inhibitors and anticholinergics can also lower the level of *Bifidobacterium* [102]. In addition, the gastrointestinal adverse effects of COMT inhibitors may be associated with microbiota dysbiosis [261].

Dopamine agonists (pramipexole and ropinirole) significantly decrease the small intestinal motility and increase the distal small intestinal bacterial overgrowth in rats. These microbial changes include increases in the abundance of *Lactobacillus* and *Bifidobacterium* and decreases in the abundance of Lachnospiraceae and Prevotellaceae. These findings are consistent with those observed in humans [262].

Microbial therapy

Conversion of the dysfunctional gut flora to health-related gut flora is a major principle of gut microbial therapy. With growing knowledge of gut flora and PD, scientists have investigated therapeutic strategies for PD by modifying gut microbes. Probiotics, prebiotics, synbiotics, fecal microbiome transplantation (FMT), and other microbial therapies have been shown to relieve gastrointestinal symptoms; some can even relieve motor symptoms. These microbial therapies have provided new options for the treatment of PD (Table 5, Fig. 5).

Probiotics

Probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [275]. Typical probiotics consist mainly of bacteria naturally produced in the human intestine, usually *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and combinations of different beneficial bacteria [276]. Probiotics are available from food, supplements, medications, and formula [275]. Increasing evidence has shown that probiotics stimulate intestinal motility and play a protective role as they strengthen the integrity of the intestinal epithelium, prevent disruption of the intestinal barrier, promote a balanced mucosal immune system, and inhibit harmful microorganisms [277, 278].

Probiotics protect against PD; however, clinical and preclinical data supporting this finding are lacking. Probiotics relieve several motor and nonmotor symptoms, particularly the gastrointestinal symptoms. The mechanisms by which probiotics could improve PD symptoms may involve the intestinal environmental change, inhibition of harmful intestinal bacteria, decreased inflammation, prevention of antioxidant stress, and improvement of neuronutrition [243, 279–285]. A study of an established *C. elegans* synucleinopathy model showed that the probiotic *Bacillus subtilis* strain PXN21 suppresses and eliminates α-syn accumulation. The bacteria use metabolites and biofilm development to trigger host defense mechanisms, such as DAF-16/FOXO and sphingolipid metabolism [241]. Surprisingly, since some common probiotics such as *Lactobacillus* and *Bifidobacterium* have been found consistently elevated in patients with PD, the exact role of probiotics in PD is questionable.

Prebiotics

A prebiotic is "a substrate that is selectively utilized by host microorganisms conferring a health benefit" [286]. Generally, prebiotics are regarded as non-digestible dietary components that encourage the development and activity of certain microbial genera to promote the recipient's health [287, 288]. Unlike probiotics, prebiotics do not include living bacteria, but rather consist of dietary fiber. Prebiotics are most frequently found in foods. Some synthetic prebiotics include inulin, galactooligosaccharides, fructo-oligosaccharides, and SCFAs [289].

Prebiotics are becoming more widely used in clinical settings owing to their low risk of side effects, ease of administration, and significant impact on the composition and function of gut microbiota [290]. However, although clinical studies on the correlation between PD and prebiotics are very limited, evidence shows that prebiotics can modulate immune function, improve bowel motility and constipation, and offer other aspects of gastrointestinal health, indicating their potential clinical value [291, 292]. In MPTP-treated mice, polymannuronic acid (PM) reduced inflammation in the intestine, brain and circulation, and enhanced the intestinal barrier and BBB integrity to protect against the development

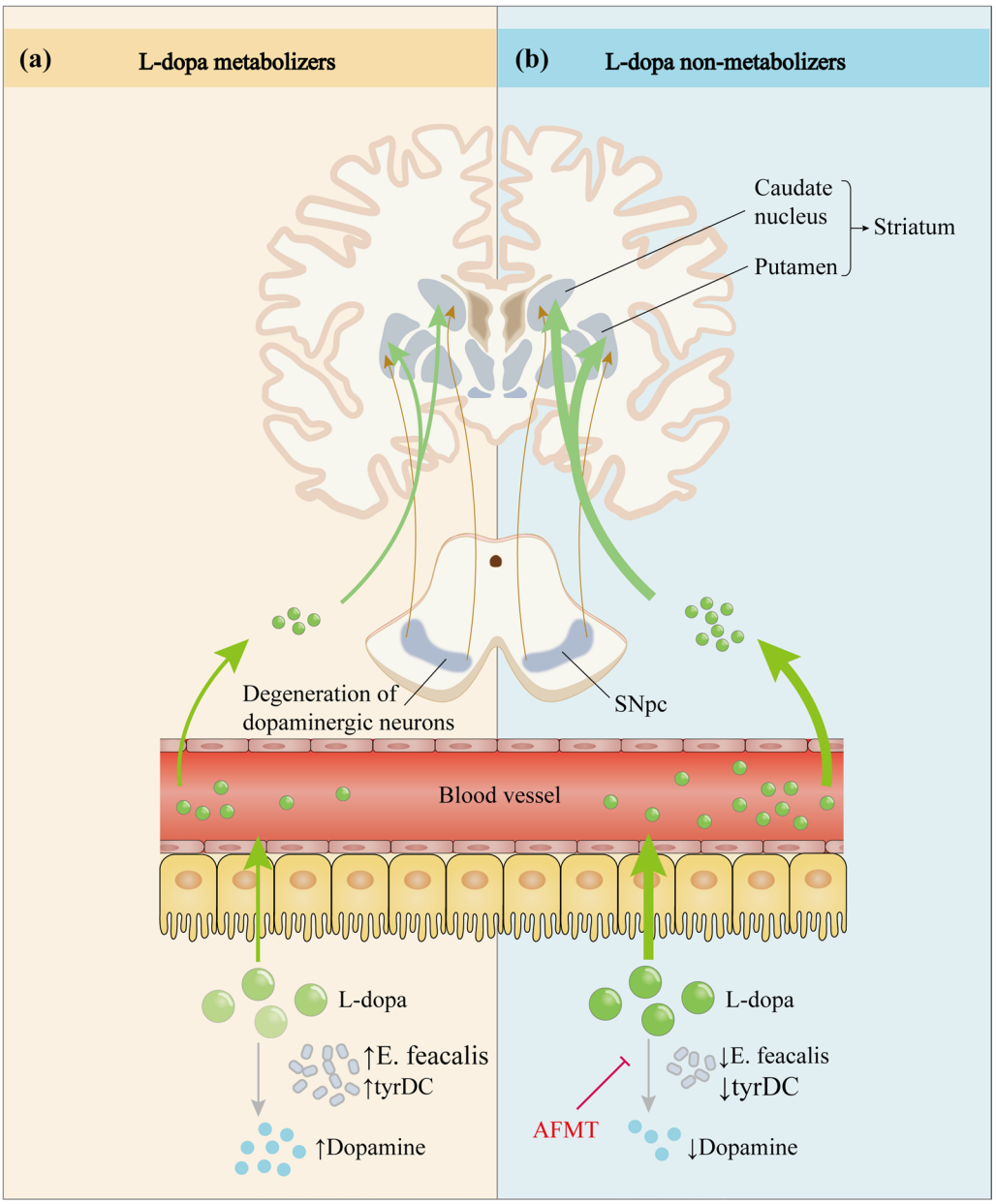

Fig. 4 Effect of intestinal microbes on the metabolic pathway of levodopa. After oral administration, *L*-dopa enters the circulation through active transport in the intestine and crosses the blood–brain barrier into the brain, where it exerts anti-Parkinson's disease effects by restoring striatal dopaminergic neurotransmission. However, only a small fraction of the drug eventually reaches the brain due to interference by various factors. Studies have revealed that tyrDC from *Enterococcus faecalis* can convert *L*-dopa to dopamine in the intestine and affect its absorption. **a** Elevated *E. feacalis* and tyrDC levels enable more *L*-dopa to be metabolized to dopamine in the intestine, resulting in impaired *L*-dopa absorption. **b** Conversely, a decrease in tyrDC allows more *L*-dopa to be absorbed and utilized. In addition, the small molecule inhibitor (S)-α-fluoromethyltyrosine (AFMT) can suppress tyrDC, thereby increasing the bioavailability of *L*-dopa

of PD. PM may affect the brain-gut microbiome axis through gut microbiota-derived SCFAs [293].

Synbiotics

Synbiotics are synergistic mixtures of probiotics and prebiotics, in which the prebiotic ingredients are selectively beneficial to the metabolism or growth of probiotics, resulting in a beneficial effect on host health [294]. The combination of the probiotics and prebiotics can be more effective than each alone [289]. Recently, the use of a new synbiotic consisting of PM and *Lacticaseibacillus rhamnosus* GG (LGG) in a PD animal

Table 5 Microbial therapies for PD

Ref.	Sample size	Type	Treatment duration	Main results
Probiotics				
[263]	Probiotics treatment: 25 Placebo: 25	*Lactobacillus acidophilus, Bifidobacterium bifidum, L. reuteri,* and *L. fermentum*	12 weeks	Downregulated the gene expression of IL-1, IL-8, and TNF-α and upregulated TGF-β and PPAR-γ in PBMC
[264]	Probiotics treatment: 30 Placebo: 30	*L. acidophilus, B. bifidum, L. reuteri,* and *L. fermentum*	12 weeks	Decreased MDS-UPDRS, hs-CRP, and malondialdehyde, enhanced glutathione, and improved insulin sensitivity
[265]	Probiotics treatment: 34 Placebo: 38	*L. acidophilus, L. reuteri, L. gasseri, L. rhamnosus, B. bifidum, B. longum, Enterococcus faecalis, E. faecium*	4 weeks	Improved constipation symptoms
[266]	Probiotics treatment: 23 Placebo: 23	*Bacillus licheniformis, L. acidophilus, B. longum, E. faecalis*	12 weeks	Improved constipation symptoms and positively affected gut microbiota
Prebiotics				
[267]	PD: 19	A diet rich in insoluble fiber	2 months	Improved constipation symptoms and increased plasma levodopa bioavailability and motor function
[268]	Resistant starch: 32 PD, 30 control Solely dietary instructions: 25 PD	Resistant starch	8 weeks	Improved nonmotor symptom scores, increased fecal butyrate, and decreased fecal calprotectin levels
[191]	Newly diagnosed, non-medicated PD: 10 Treated PD: 10	Prebiotic fiber	10 days	Prebiotic intervention was well tolerated and safe, associated with beneficial biological changes in microbiota, SCFA, inflammation, and neurofilament light chain, and may improve clinical symptoms (i.e., gastrointestinal symptoms and UPDRS)
Synbiotics				
[269]	Multiple probiotic strains and prebiotic fiber: 80 Placebo: 40	Multiple probiotic strains: *Streptococcus salivarius* subsp. *thermophilus, E. faecium, L. rhamnosus* GG, *L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii* subsp. *bulgaricus,* and *Bifidobacterium* Prebiotic fiber: fructo-oligosaccharides	4 weeks	Improved constipation symptoms
[270]	Multi-strain probiotic (Hexbio®): 22 Placebo: 26	Multi-strain probiotic (*Lactobacillus* sp. and *Bifidobacterium* sp.) with fructo-oligosaccaride	8 weeks	Improved bowel opening frequency and whole gut transit time
Fecal microbiota transplantation				
[271]	PD: 15	Purified fecal microbiota suspension	Once	Relieved motor and nonmotor symptoms with acceptable safety
[272]	PD: 6	Fecal suspension	Once	Relieved motor and nonmotor symptoms, including constipation
[273]	PD: 11	Frozen fecal microbiota	Once	Reconstructed gut microbiota and improved motor and nonmotor symptoms
[274]	PD: 12	FMT capsules ($n=8$) placebo ($n=4$)	Twice weekly for 12 weeks	Improved subjective motor and non-motor complaints, intestinal microbiota diversity, gut transit, and motility

IL-1: interleukin-1, IL-8: interleukin-8, TNF-α: tumor necrosis factor alpha, TGF-β: transforming growth factor beta, PPAR-γ: peroxisome proliferator-activated receptor gamma, PBMC: peripheral blood mononuclear cell, MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale, hs-CRP: high-sensitivity C-reactive protein, PD: Parkinson's disease, SCFA: short-chain fatty acid

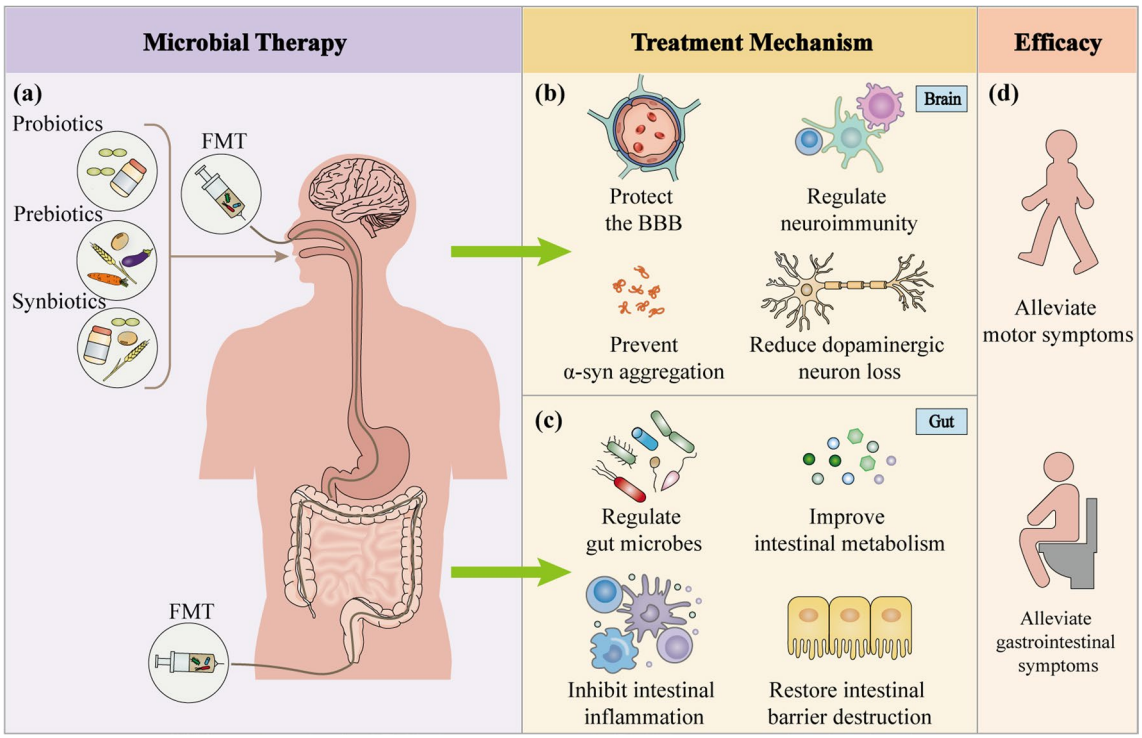

Fig. 5 Microbial therapies for Parkinson's disease. **a** Probiotics, prebiotics, synbiotics, and fecal microbiota transplantation are the most commonly used microbial therapies for PD. These therapies can be administered through oral, nasogastric, rectal, or colonoscopic route. **b** Microbial therapies have neuroprotective effects on the brain by reducing the blood–brain barrier damage, decreasing microglial and astrocytic activation, suppressing neuroinflammation, and inhibiting α-syn aggregation, thereby preventing the death of dopaminergic neurons. **c** In the gut, microbial therapies can regulate gut microbes, improve intestinal metabolism, modulate the intestinal mucosal immune system, inhibit gut inflammation, and restore gut barrier damage, resulting in improved intestinal symptoms. **d** In conclusion, microbial therapies relieve nonmotor symptoms of PD, particularly constipation, as well as the motor symptoms through multiple pathways

model showed neuroprotective effects. The synbiotic can increase the expression of the tyrosine hydroxylase gene and/or protein, prevent the death of dopaminergic neurons, and improve motor function. The mechanisms of action include the anti-inflammatory and anti-apoptotic effects of SCFAs provided by PM, as well as the improved expression of neurotrophic factors by striatal glial cells and increased abundance of Clostridiales offered by LGG [295].

FMT

FMT, also known as fecal transplantation or fecal bacteriotherapy, is a technique that delivers the stool from healthy donors into a patient's gastrointestinal tract [42, 296]. This technique can comprehensively and extensively restore the abnormal gut microbiota and has been approved for clinical use by the WHO and the FDA as a treatment for gastrointestinal infections or other diseases [297]. FMT may regulate the intestinal microbiome through immune, endocrine, metabolic, and neurological mechanisms, thereby affecting the symptoms of neurological disorders. It has been proven that patients with different neurological diseases, including PD, benefit from FMT therapy [298–300].

FMT significantly attenuates intestinal microbial metabolic disorders in PD mice, reduces intestinal inflammation and barrier disruption, attenuates BBB damage, reduces nigrostriatal microglia and astrocyte activation, inhibits neuroinflammation, and reduces gut and brain TLR4/TNF-α signaling pathway components, thereby protecting dopaminergic neurons and increasing striatal dopamine and 5-HT content [142, 196, 301]. FMT improves motor and gastrointestinal dysfunction in PD, leads to healthy intestinal flora diversity in patients, and improves nonmotor symptoms, including sleep, quality of life, anxiety, and depression. A recent study with 12 weeks of continuous treatment and 9 months of follow-up demonstrated that PD FMT was well tolerated and resulted in improvements of subjective symptoms and objective intestinal markers [274].

Despite the positive results obtained after FMT, the treatment is associated with several challenges, such as ethical issues, selection of suitable donors, handling of fecal transplants, the optimal volume and frequency

of transplants, risk and benefit assessment, and long-term safety [302–305]. It is hypothesized that FMT only replaces microorganisms in the intestinal lumen without changing mucosal microorganisms [302]. Notably, clinical trials on FMT treatment for PD have not shown stable long-term efficacy [271, 306].

Conclusions and perspectives

High-throughput sequencing technology has enabled remarkable advancements in gut microbiota research. Although considerable indirect evidence implies that the microbiome may contribute to PD, conclusive evidence is lacking. It is extremely difficult to demonstrate the precise molecular pathways by which the microbiome promotes the pathogenesis of PD. Notably, recent developments in tissue culture technologies, particularly the development of human intestinal organoids and their integration with more elaborate organ-on-a-chip setups, provide excellent model systems for studying host-microbe interactions with a high degree of clinical relevance [250, 252, 307]. Organoids most faithfully recapitulate intestinal cell types, and gut-on-chips are biomimetics recapitulating intestinal physiology, allowing the detection of molecular exchanges between microbes and human cells and their effects, thus providing a reproducible and scalable platform for causal and translational gut microbiome research. Excitingly, advances in organ-on-chip technology have made it possible to utilize multiorgan-on-chip system to mimic the effects of the gut microbiome on extraintestinal organs, which provide technical support for studying CNS disorders, including PD, and for the refinement of the microbiota–gut–brain axis concept [308, 309]. It is believed that in the future, with the deepening of clinical studies, the support of mechanistic modeling approaches and improved in vitro simulation, the specific mechanism of the role of gut microorganisms in the development of PD will be revealed.

Most existing studies on gut microbes in PD are cross-sectional studies, which cannot sufficiently indicate causal relationships between gut microbes and the pathogenesis of PD. Thus, further longitudinal research, especially that of patients with new-onset, unmedicated, or even prodromal PD, is needed to advance our knowledge of the mechanisms underlying the correlation between gut microbes and PD. In addition, further expansion of research subjects, such as the inclusion of patients with atypical PD (e.g., multiple system atrophy and progressive supranuclear palsy), may help elucidate the discriminatory power of gut microbes between PD and similar disorders. Finally, evaluation of extended microbiome data using multiomics, including metagenomics, viral metagenomics, transcriptomics, proteomics, and metabolomics, may provide a multidimensional view of the mechanisms of PD.

Abbreviations

α-syn	Alpha-synuclein
AFMT	(S)-α-fluoromethyltyrosine
BBB	Blood–brain barrier
COMT	Catechol-O-methyl transferase
ENS	Enteric nervous system
FMT	Fecal microbiome transplantation
GFAP	Glial fibrillary acidic protein
IBD	Inflammatory bowel disease
IL	Interleukin
L-DOPA	Levodopa
LPS	Lipopolysaccharide
MDS	Movement Disorders Society
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PD	Parkinson's disease
PM	Polymannuronic acid
PNS	Peripheral nervous system
SCFA	Short-chain fatty acid
SN	Substantia nigra
TLRs	Toll-like receptors
TNF-α	Tumor necrosis factor alpha
tyrDC	Tyrosine decarboxylase

Supplementary Information

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Additional file 1: Table S1. Microbiome alterations in clinical cohorts of Parkinson's disease.

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Author contributions

XZ critically reviewed the literatures and wrote the manuscript. BT edited and revised important points. JG took responsibility for all aspects of the work and ensured that issues related to the accuracy or integrity of any part of the work were properly investigated and resolved. All the authors read and approved the final manuscript.

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Competing interests

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