

Review

Research Progress of Microbiota-Gut-Brain Axis in Parkinson's DiseaseWei Zhang¹, Yalin Ye², Jiayang Song³, Tian Sang¹, Tingting Xia¹, Linhong Xie¹,
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Academic Editors: Rafael Franco and Gernot Riedel

Submitted: 30 May 2023 Revised: 19 June 2023 Accepted: 3 July 2023 Published: 30 October 2023

Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by misfolding of α -synuclein. Clinical manifestations include slowly developing resting tremor, muscle rigidity, bradykinesia and abnormal gait. The pathological mechanisms underlying PD are complex and yet to be fully elucidated. Clinical studies suggest that the onset of gastrointestinal symptoms may precede motor symptoms in PD patients. The microbiota-gut-brain axis plays a bidirectional communication role between the enteric nervous system and the central nervous system. This bidirectional communication between the brain and gut is influenced by the neural, immune and endocrine systems related to the gut microbiome. A growing body of evidence indicates a strong link between dysregulation of the gut microbiota and PD. In this review, we present recent progress in understanding the relationship between the microbiota-gut-brain axis and PD. We focus on the role of the gut microbiota, the unique changes observed in the microbiome of PD patients, and the impact of these changes on the progression of PD. Finally, we evaluate the role of current treatment strategies for PD, including probiotics, fecal microbial transplants, dietary modifications, and related drug therapies.

Keywords: Parkinson's disease; microbiota-gut-brain axis; gut microbiome; gut microbiota intervention**1. Introduction**

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease worldwide. It tends to occur in elderly patients aged >60 years and has recently become the neurological disease with the highest morbidity and mortality [1]. Clinically, PD is characterized by resting tremor, limb stiffness and slow movement. The disease can develop insidiously for decades before the patient is diagnosed with PD due to abnormal motor behaviour. The early symptoms usually manifest as abdominal distention, nausea, constipation, gastroparesis, or weight loss [2]. A meta-analysis showed that patients with Crohn's disease or ulcerative colitis have a higher risk of PD compared to the general population [3].

The most distinctive pathological feature of PD patients is α -synuclein lesions, consisting of aggregated α -synuclein fibrils with an aberrant tertiary structure. This is accompanied by the death of dopaminergic neurons in the substantia nigra pars compacta. The α -synuclein protein misfolds and aggregates into eosinophilic inclusion bodies, also known as Lewy bodies, in which the main component is a cytoplasmic protein consisting of 140 amino acids and encoded by the α -synuclein (*SNCA*) gene. This protein is chemically stable and is not easily hydrolyzed by its own enzymes [4]. Some studies have suggested the structure of this protein is the underlying cause of progressive neurodegeneration in PD patients [5]. After studying the nervous

system of PD patients, Heiko Braak put forward the hypothesis that α -synuclein originating from lesions in the enteric nervous system (ENS) diffuses through the gut-brain axis and into the dorsal motor nucleus of the vagus (DMV). From there, it enters the central nervous system (CNS) via the olfactory bulb, invades the locus coeruleus and substantia nigra, and then spreads to cortical areas, thereby causing the development of PD [6]. Studies have shown that patients are less likely to develop PD if the vagus nerve is removed five years before the onset of the disease, whereas selective removal of the vagus nerve only at the gastric fundus and gastric body results in a near-identical risk of the disease [7]. Follow-up studies found this conclusion was more applicable to early-onset and persistent "body first" PD type, where the pathology originates in the gut or peripheral autonomic nervous system and then spreads to the brain [8].

Bacteria, fungi, archaea, viruses and helminths in the gut comprise a steady-state microbial environment numbering >100 trillion microorganisms. The gut microbiome is first colonized at birth, with maternal obesity and dietary composition affecting the establishment of microbiota homeostasis in infants [9]. The number and diversity of the gut microbiome increase during the first five years of life and then stabilize with age [10]. In addition, factors such as stress, infection, diet, lifestyle and geography can alter gut microbiome homeostasis [11]. There is currently



only limited information on the role played by gut archaea, fungi and viruses in the nervous system. In contrast, numerous studies have investigated the impact of gut bacteria on the progression of inflammatory bowel disease, mood disorders, and neurodegenerative diseases. Metagenomics studies and untargeted sequencing of *16S rRNA* gene amplicons have identified 11 broad phyla of bacteria in the gut [12]. With the exception of a few bacteria that need further identification, >90% of bacteria consist of *Firmicutes*, *Bacteroides*, *Proteus* and *Actinobacteria*, with *Clostridium* and *Verruciformis* being less abundant and *Bacteroides* and *Firmicutes* being the most abundant [13].

2. Microbiota-Gut-Brain Axis

The gut is not merely a simple digestive organ. In addition to the epithelial barrier, endocrine cells, muscle layer, enteric nervous system and immune cells, the gut also includes the dynamic microbial homeostatic system mentioned above. For this reason, the gut is sometimes called the second brain of the body [14]. Indeed, a complex bidirectional communication pathway consisting of multiple mechanisms exists between the brain and the gastrointestinal system and is referred to as the microbiota-gut-brain axis. This system acts bidirectionally through the autonomic nervous system, the enteric nervous system (ENS), the hypothalamic-pituitary-adrenal axis (HPA) and the gut microbes, which is the key area of interaction between microorganisms and brain function [15]. The brain can alter the gut homeostatic environment through the microbiota-gut-brain axis, including the permeability of the gut wall and the abundance of microbiota. Similarly, changes in the gut environment can affect brain activity through the same axis. The microbiota-gut-brain axis has been found to play an important role in the progression of several central nervous system diseases, such as Alzheimer's disease, PD, epilepsy, ischemic cerebrovascular disease, schizophrenia and depression [16].

3. Role of Gut Microbiota

The gut microbiota affects brain function by regulating the neurotransmitters acetylcholine, serotonin, norepinephrine, dopamine, and glutamate. In addition to affecting the synthesis and metabolism of neurotransmitters in humans, microorganisms themselves can also produce neuroactive substances. These include γ -aminobutyric acid by *Bifidobacterium* and *Lactobacillus*, acetylcholine by *Lactobacillus*, and dopamine by *Bacillus* and *Serratia* [17]. Because of the blood-brain barrier, neurotransmitters produced in the gut are unlikely to be transported to the brain but can affect the brain indirectly by acting on the ENS [18]. Gut microbiota also produces enzymes that control the tryptophan metabolic pathway, resulting in the production of serotonin, kynurenine and indole derivatives. By affecting the serotonin precursor tryptophan, the microbiota can thus influence the serotonin content in the brain [19].

Compared to a sterile gut environment, a healthy gut microbiota can reduce the permeability of the blood-brain barrier by upregulating the expression of tight junction proteins, thereby reducing invasion by harmful substances [20]. However, pathological alterations in the gut microbiota lead to chronic gut inflammation and increase gut permeability, thereby promoting the secretion of pro-inflammatory cytokines, including interleukin 1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) into the gut and systemic circulation. These inflammatory cytokines can also cross the blood-brain barrier through the gut-brain axis to cause neuroinflammation [21]. However, if these factors are removed early on, the gut-brain barrier will be repaired, and the risk of PD is reduced [22].

Although the clear mechanism behind the dysregulation of the gut microbiota in PD patients has not been fully elucidated, extensive evidence now supports the Braak theory. *E. coli* has been found to produce an amyloid protein called "curli", which has been shown to hybridize with human amyloid *in vitro* to enhance α -synuclein pathology and induce behavioural abnormalities in mice [23]. The authors of this work hypothesized that changes in gut microbial homeostasis may cause damage to the gut barrier, which on the one hand, stimulates a protective immune response in humans and promotes more pathological α -synuclein expression in the gut nervous system. On the other hand, the systemic inflammatory responses caused by gut inflammation reduce the expression of tight junction proteins and increase gut permeability, resulting in "leaky gut syndrome". This increases the permeability of the blood-brain barrier and facilitates the uploading of pathological α -synuclein along the enteric nerve to the brain, thereby promoting gut-derived α -synuclein-mediated motor dysfunction [24]. Furthermore, it has been demonstrated that transplantation of fecal microbiota from PD patients can promote pathological α -synuclein aggregation, neuroinflammation and Parkinsonian motor symptoms in mice compared to the mice following the transplantation of fecal microbiota from healthy donors the symptoms in mice were alleviated under sterile conditions, thus [25,26], further validating the pathogenic role of amyloid produced by the gut microbiota in the development of PD.

Microbes in the proximal small intestine of PD patients, especially *Enterococcus* and *Lactobacillus*, have been shown to produce more bacterial tyrosine decarboxylase than healthy individuals. This enzyme can decarboxylate levodopa to dopamine even in the presence of tyrosine, competitive substrates, and human decarboxylase inhibitors, thereby greatly reducing the therapeutic effect of levodopa in PD patients and increasing the amount needed to treat PD [27]. However, elevated tyrosine decarboxylase is also accompanied by increased peripheral dopamine production, along with side-effects such as orthostatic hypotension and cardiac arrhythmias.

Table 1. Changes in the gut microbiota of Parkinson's disease (PD) patients compared to healthy individuals.

Microbiota	Classification	Trend 1	Trend 2
<i>Prevotellaceae</i>	<i>Bacteroidota; Bacteroidia; Bacteroidales</i>		↓[28–30]
<i>Faecalibacterium</i>	<i>Clostridia; Eubacteriales; Oscillospiraceae</i>		↓[28,29,31]
<i>Bifidobacterium</i>	<i>Actinomycetota; Actinomycetes; Bifidobacteriales; Bifidobacteriaceae</i>	↑[28,29,31–33]	
<i>Akkermansia</i>	<i>Verrucomicrobiota; Verrucomicrobiae; Verrucomicrobiales; Akkermansiaceae</i>	↑[28,31,34]	
<i>Aquabacterium</i>	<i>Pseudomonadota; Betaproteobacteria; Burkholderiales; Burkholderiales genera incertae sedis</i>	↑[35]	
<i>Sphingomonas</i>	<i>Pseudomonadota; Alphaproteobacteria; Sphingomonadales; Sphingomonadaceae</i>	↑[35]	
<i>Escherichia/Shigella</i>	<i>Pseudomonadota; Gammaproteobacteria; Enterobacterales; Enterobacteriaceae</i>		↓[35]
<i>Pasteurellaceae</i>	<i>Pseudomonadota; Gammaproteobacteria; Pasteurellales</i>		↓[36,37]
<i>Lachnospiraceae</i>	<i>Bacillota; Clostridia; Eubacteriales</i>	↑[38]	↓[28,29,31–33]
<i>Ruminococcaceae</i>	<i>Bacillota; Clostridia; Eubacteriales</i>	↑[28]	
<i>Christensenellaceae</i>	<i>Bacillota; Clostridia; Eubacteriales</i>	↑[28,32]	
<i>Roseburia</i>	<i>Bacillota; Clostridia; Eubacteriales; Lachnospiraceae</i>		↓[31]
<i>Coprococcus</i>	<i>Bacillota; Clostridia; Eubacteriales; Lachnospiraceae</i>		↓[29,34]
<i>Blautia</i>	<i>Bacillota; Clostridia; Eubacteriales; Lachnospiraceae</i>		↓[29]
<i>Clostridium XVIII</i>	<i>Bacillota; Clostridia; Eubacteriales; Clostridiaceae</i>	↑[35]	
<i>Butyricicoccus</i>	<i>Bacillota; Clostridia; Eubacteriales; Clostridiaceae</i>	↑[35]	
<i>Anaerotruncus</i>	<i>Bacillota; Clostridia; Eubacteriales; Oscillospiraceae</i>	↑[35]	
<i>Lactobacillaceae</i>	<i>Bacillota; Bacilli; Lactobacillales</i>	↑[29,33,34]	↓[37,39]
<i>Holdemania</i>	<i>Bacillota; Erysipelotrichia; Erysipelotrichales; Erysipelotrichaceae</i>	↑[35]	

4. Homeostatic Changes in the Gut Microbiota of PD Patients

Gut microbes in the human body are always in a dynamic process of homeostasis. Compared to healthy individuals, gut microbial homeostasis is disrupted in PD patients. Common pathological changes have been detected in certain gut microbiota in many PD patients, suggesting that dysbiosis of gut microbiota is involved in the pathogenesis of PD. Table 1 (Ref. [28–39]) summarizes the relevant studies on the changes to gut microbial homeostasis reported recently in PD patients.

Akkermansia is a Gram-negative bacterium that increases gut permeability by degrading the gut mucus barrier, making the host more susceptible to attack by harmful substances and triggering gut inflammation and systemic inflammation [40]. The protein secreted by *Akkermansia* was found to increase the mitochondrial uptake of Ca^{2+} *in vitro*, leading to a large increase in reactive oxygen species (ROS) and significant aggregation of pathological α -synuclein. This protein can also trigger the accumulation of α -synuclein in enteroendocrine cells in mice, thereby stimulating the vagus nerve of the parasympathetic nervous system and exacerbating brain pathology [41].

The reduction in several bacteria (*Lachnospiraceae*, *Faecalibacterium* and *Coprococcus*) that produce short chain fatty acids (SCFAs) can lead to an inflammatory state in the gut and may be associated with recurrent gastrointestinal symptoms in PD patients [31,34]. The reduction in *Lachnospiraceae* and the increase in *Lactobacillus*, *Chris-*

tensenellaceae, *Butyricicoccus* and *Clostridium XLVB* have been associated with worse clinical characteristics, including cognitive impairment, gait abnormalities and postural instability [32,35].

Reduced *Prevotella* may be associated with lower levels of mucin and SCFAs, leading to increased risks of gut permeability and inflammation [42]. Reduced *Prevotella* is also associated with lower levels of neuroprotective factors such as thiamin, folate and hydrogen sulfide. Growth hormone-releasing peptides produced by *Prevotella* can also play a protective role in the progression of degenerative diseases by altering the intensity of mitochondrial respiration, maintaining ROS levels, inhibiting the accumulation of pathological α -synuclein, and maintaining dopamine function in the substantia nigra and striatum [42]. There is evidence that the faster the disease progress, the greater the difference in *Prevotella* count between PD patients and healthy individuals [30].

It is generally accepted that *Lactobacillus* and *Bifidobacterium* strains are beneficial for the regulation of gut microbiome homeostasis and for maintaining gut barrier stability [43]. Higher levels of *Lactobacillus* and *Bifidobacterium* strains are usually detected in PD patients. Contrary to popular perception, they do not appear to have the rightful role in PD for reasons that are not known. Some studies suggest that PD patients may have consumed more milk than the general population since milk increases the number of gut *Lactobacillus* and *Bifidobacterium* strains which could increase the risk of PD [44], although it does not

always show an increase [45]. Furthermore, the number of *Lachnospiraceae*, *Bifidobacterium* and *Lactobacillus* is positively correlated with levodopa dose. Long-term use of levodopa in PD patients can lead to an increased number of the aforementioned microbiome [46]. To avoid interference from treatments such as levodopa in the study of gut microbial homeostasis, researchers have studied untreated subjects with newly diagnosed PD. In such patients, the composition of the gut microbiome in their fecal samples was similarly altered. The abundance of *Lachnospiraceae*, in particular, was reduced in PD patients. However, no increase was found in the number of *Bifidobacteria* or *Lactobacillus* [47].

5. Therapeutic Means of Gut Microbial Intervention

Currently, symptomatic treatment is mainly used to improve the clinical manifestations and enhance the quality of life of PD patients. The most common approach is the use of levodopa, which supplements the deficiency in physiological brain dopamine and stimulates brain dopamine receptors. This approach has its drawbacks, however, since patients are inclined to develop tolerance to the drug in the late stages of treatment, and increased dosage tends to trigger a series of abnormalities in motor function. Moreover, the administration of levodopa does not stop disease progression. Levodopa is mainly used to improve the motor symptoms of PD patients, and many non-motor symptoms may not respond to dopaminergic therapy [48]. In addition, gut dysfunction in PD patients also weakens the absorption of levodopa. Therefore, there is an urgent need for new therapeutic methods to treat the clinicopathological manifestations of PD patients, including non-motor symptoms. The close correlation between gut microbiota and PD suggests it is important to trial the use of gut microbes to reduce mortality and morbidity after neurological injury in patients. Here, we focus on recent advances in the treatment of PD from the perspective of the microbiota-gut-brain axis.

5.1 Probiotics

One intervention is the use of probiotics or specific bacterial strains that may be beneficial to the host in PD patients. Using a synuclein disease model of *Caenorhabditis elegans*, Goya *et al.* [49] found the probiotic *Bacillus subtilis* strain had an inhibitory effect on α -synuclein aggregation through spores and vegetative cells. Sun *et al.* [50] reported that *Clostridium butyricum* could improve gut microbiome dysbiosis, movement defects, microglia activation and dopaminergic neuron loss in a mouse model. Liao *et al.* [51] found that oral administration of a novel psychobiotic strain of *Lactobacillus plantarum* PS128 in a mouse model of PD can increase the levels of norepinephrine and neurotrophic factor in the striatum, attenuate oxidative stress and neuroinflammation, improve locomotor behaviour, enrich the gut biological community, and in-

hibit the generation of the *Enterobacteriaceae* family and other harmful organisms that produce lipopolysaccharide (LPS) and peptidoglycan. Castelli *et al.* [52] synthesized a new preparation containing *Lactobacillus* and *Bifidobacterium* (SLAB51). This produced the neurotrophic factor brain-derived neurotrophic factor (BDNF) that slowed the death of dopaminergic neurons in mice, increased neuroprotective protein levels, and reduced brain damage and β -amyloid protein aggregation.

Tamtaji *et al.* [53] conducted a randomized, double-blind, placebo-controlled clinical trial of several probiotics (*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus royi* and *Lactobacillus fermentum*) in 60 PD patients for 12 weeks. Compared to placebo, probiotic supplementation was found to reduce the levels of high-sensitivity C-reactive protein and malondialdehyde and to have a positive effect on parameters such as motor function, insulin metabolism and oxidative stress in PD patients.

5.2 Faecal Microbiota Transplantation

The most direct way to alter the gut microbial homeostatic environment is through fecal microbiota transplantation (FMT), in which feces from healthy organisms are transplanted into subjects with a disturbed gut microbiota system. This technique has been used successfully for the treatment of recurrent or refractory *Clostridium difficile* infections. Moreover, it is currently being trialed for the treatment of several conditions, including ulcerative colitis, infant gut microbial repair, and neurological lesions [54].

FMT has been reported to reduce gut microbial dysbiosis, increase striatal dopamine and 5-hydroxytryptamine levels, decrease the expression of pathological α -synuclein at the substantia nigra pars compacta, attenuate physical damage in PD mice, and inhibit expression of the Toll-like receptors 4/myeloid differentiation factor 88/nuclear factor-kappa B (TLR4/MyD88/NF- κ B) signaling pathway in the gut and brain [55].

A prospective, single-study in PD patients found that FMT restored the overgrowth of gut microbiota, with an increased abundance of *Blautia* and *Prevotella* and a marked decrease in the abundance of *Bacteroidetes* [56]. Moreover, scores for the Parkinson's Disease Rating Scale (UPDRS) and the non-motor symptoms questionnaire (NMSs) declined significantly in PD patients. Guangzhou First People's Hospital in China will carry out a study on PD patients involving a 6-month treatment with FMT for analysis of gut microbiota diversity and evaluation of the efficacy and safety of FMT for constipation symptoms in patients receiving levodopa treatment (ClinicalTrials.gov Identifier: NCT04837313). A randomized, double-blind, placebo-controlled clinical trial on PD patients conducted by Ghent University in Belgium will examine the effects of FMT on serum marker levels, gut and central nervous system barrier function, and microbiota changes associated with motor and non-motor symptoms (ClinicalTrials.gov

Identifier: NCT03808389). A 6-month phase 2/3 clinical trial conducted by the Soroka University Medical Center in Israel will study the effect of using FMT to introduce or restore a stable, “healthy” gut microbial community on motor symptoms and constipation levels in PD patients (ClinicalTrials.gov Identifier: NCT03876327). A phase 1/2 clinical trial conducted by the Warsaw Medical University in Poland will evaluate the effect of FMT on tremor, slow movement and balance problems in PD patients within the first year of treatment, as well as on the frequency of constipation (ClinicalTrials.gov Identifier: NCT05204641).

5.3 Related Drug Therapy

In addition to the therapeutic strategy of using dopamine to stimulate dopamine receptors in the brain of PD patients, researchers have also explored the design of relevant drug regimens from a microbiota-gut-brain axis perspective.

Minocycline can attenuate the rotenone-induced progressive loss of tyrosine hydroxylase-immunoreactive neurons in rats [56]. Its antioxidant and anti-inflammatory properties may also provide protection against dopaminergic neurology in the *Drosophila* DJ-1A model of PD [57]. To evaluate the effect of minocycline on the progression of PD, a randomized, double-blind phase 2 trial involving 42 trial centres and 195 PD patients was carried out in the United States and Canada (ClinicalTrials.gov Identifier: NCT00063193). Unfortunately, minocycline showed no significant benefit for patients [58].

Doxycycline can block 6-hydroxydopamine (6-OHDA)-induced neurotoxicity in mice by inhibiting microglia and astrocyte expression [59]. In addition, it can inhibit LPS-induced dopaminergic neuronal degeneration by downregulating microglial histocompatibility complex II (MHC II) expression [60]. Doxycycline can also effectively eliminate cognitive and daily activity deficits in A53T mice by reducing the structural stability of pathologic α -synuclein and the activation of striatal glial cells [61]. An ongoing double-blind, placebo-controlled phase 2 clinical trial will randomize 60 PD patients into two groups (ClinicalTrials.gov Identifier: NCT05492019). The intervention group will be treated with levodopa plus doxycycline, while the control group will be treated with levodopa plus placebo. The effect of doxycycline on motor performance and cognitive function in PD patients will be assessed after 4 and 8 weeks.

Ceftriaxone can downregulate the levels of glial fibrillary acidic protein (GFAP) and ionized calcium binding adaptor molecule 1 (Iba1), which are markers of astrocytes and microglia, respectively. It can also decrease the abundance of gut *Aspergillus* and increase probiotic abundance while also increasing the production of tight junction proteins in the colon of a PD mouse model [62]. Ceftriaxone also increases the expression of the glutamate transporter protein glutamate transporter 1 (GLT1) in the brain,

delays the loss of neuronal and muscle strength, and increases survival in a mouse model of PD [63]. Of note, ceftriaxone may also enhance systemic inflammation in mice [64]. An exacerbated inflammatory response is associated with deterioration of the colonic structure and dysregulation of gut microbiota homeostasis. Researchers plan to conduct a randomized, double-blind, placebo-controlled, phase 2 clinical trial involving 106 participants to determine the potential efficacy and safety of ceftriaxone in patients with Parkinson’s dementia (ClinicalTrials.gov Identifier: NCT03413384).

Researchers have also investigated other drugs besides antibiotics for the treatment of PD from the perspective of the microbiota-gut-brain axis, but most are still in the animal testing phase. de la Cuesta-Zuluaga *et al.* [65] reported that diabetic participants taking metformin had a higher relative abundance of the probiotics *Butyrivibrio*, *Bifidobacterium bifidum*, *Megasphaera* and *Prevotella* than non-diabetic participants. Diabetic participants not taking metformin also had a higher relative abundance of the harmful microbe *Clostridiaceae02d06* and a lower abundance of the probiotic *Enterococcus casseliflavus* compared to non-diabetics. Hou *et al.* [66] found a dose-response correlation between metformin and the incidence of PD in type 2 diabetic patients. Diabetic patients treated with low doses of metformin were less likely to develop PD, while higher doses of metformin treatment were not neuroprotective. Another study evaluated squalamine the synthetic squalamine salt (ENT-01) for the treatment of PD symptoms. Experiments have shown that squalamine improved normal peristaltic behaviour in a mouse model of PD by competing with α -synuclein for membrane binding sites [64]. A clinical trial showed that squalamine could restore disordered colonic motility in humans, as well as safely and effectively correct long-term functional disorders such as constipation in >80% of PD patients [67]. Hou *et al.* [66] found that intraperitoneal administration of Osteocalcin (OCN) was effective in ameliorating motor deficits and dopaminergic neuron loss in a 6-hydroxydopamine-induced PD mouse model. Further antibiotic treatment and FMT experiments in PD mice confirmed that gut microbiota is the basis of OCN-induced protection. OCN increased the abundance of *Bacteroides* and *Firmicutes* in the gut microbiota of a mouse model of PD, thereby increasing the potential for microbial propionate production. Zhao *et al.* [68] found the gut microbiome could regulate the absorption of the imino amide derivative FLZ *in vivo*. Administration of FLZ can compensate for reduced FLZ absorption caused by the disruption of gut microbe homeostasis. This can improve gut microbiota homeostasis, reduce gut inflammation and barrier damage, inhibit TLR4/MyD88/NF- κ B signalling through the microbiota-gut-brain axis, repair rotenone-induced blood-brain barrier damage, and reduce neuroinflammation in mice.

As mentioned previously, gut microbes can use tyrosine decarboxylase to decarboxylate levodopa and thus reduce its efficacy. Researchers, therefore, designed a tyrosine mimic, (s)- α -fluoromethyltyrosine (AFMT), that can strongly inhibit ($IC_{50} = 4.7$ mM) tyrosine decarboxylase-induced levodopa peripheral decarboxylation *in vitro*, significantly increase the peak serum concentration of levodopa in mice, prevent decarboxylation of levodopa by the complex gut microbiota found in PD patients (e.g., fecal *Escherichia coli*), and reduce the dosage of levodopa [69].

5.4 Dietary Intervention

A Western diet (WD) high in fat and sugar can increase the abundance of microorganisms that produce harmful substances such as lipopolysaccharides, thereby inducing dysbiosis of the gut microbiota and increasing gut permeability. A WD can also induce damage to the blood-brain barrier and cause neuroinflammation associated with toxic amyloid aggregation, both of which are closely related to the development of PD [70]. In contrast, the Mediterranean diet (MeDiet), rich in foods such as tea, vegetables, nuts, olive oil and coffee, can exert neuroprotective effects and reduce the daily required dose of levodopa. MeDiet promotes beneficial microbiome metabolism, induces gut gluconeogenesis and the production of brain-derived neurotrophic factor (BDNF), and reduces the production of harmful substances such as trimethylamine N-oxide (TMAO) [12], thereby improving symptoms such as depression, constipation and daytime sleepiness in PD patients [71,72]. In addition, branched-chain amino acids (BCAAs) such as leucine, isoleucine and valine are commonly used as dietary supplements and essential amino acids to modulate brain function. A diet high in BCAAs can increase intestinal probiotics and attenuate inflammation levels. Experiments with a mouse model of PD have shown that BCAAs can even reverse motor and non-motor dysfunction, as well as reduce dopaminergic neuronal damage [73].

5.5 Other Methods

Using a mouse model of PD, Jang *et al.* [74] found that acupuncture can increase the number of dopaminergic fibers and neurons in the striatum and substantia nigra, block inflammatory responses and apoptosis, and improve the relative abundance of gut microbes. The effects of acupuncture on enhancing motor function and protecting dopaminergic neurons may be related to its regulation of gut microbial homeostasis. Zhang *et al.* [75] designed an optogenetically-engineered probiotic that released Exendin-4 in response to red light. This drug was fused to the antineoplastic Fc receptor and could be transported to the brain via the microbiota-gut-brain axis to modulate brain function.

6. Summary

A large body of research evidence links the microbiota-gut-brain axis to the development of human neurological disorders such as epilepsy, stroke, depression, Alzheimer's disease and PD. Gut microbiota and their metabolites can influence immune activation, neurotransmitter production and endocrine function in the body. Additional findings now support the Braak theory, which suggests that gut microbiota regulate brain nervous system function by regulating the production and transmission of pathological α -synuclein along the gut-brain axis. As a neurodegenerative disease of the elderly, PD has become a serious threat to the physical and mental health of people. The current treatment methods are mainly based on symptomatic treatment with oral levodopa. However, this approach can neither stop the progression of the disease nor work on most of the non-motor symptoms of the disease. Yet the emergence of the microbiota-gut-brain axis theory has provided a new therapeutic direction for the treatment of PD. This theory can help researchers to more accurately understand the gut microbial environment in Parkinson's patients, to continue to explore in depth the potential role these microbes play in the development of the disease, and how they can be used for possible early detection and effective intervention in the disease. In this review, a growing number of animal or human trials demonstrate this feasibility.

In the present work, we describe the microbiota-gut-brain axis and focus on the impact of gut microbiota on PD. We analyse the distinctive changes in the microbiota of PD patients, relate these changes to the disease, and evaluate various approaches to the treatment of PD from the perspective of the microbiota-gut-brain axis. Elucidation of the exact mechanism by which gut microbiota and their products affect PD progression is currently the most urgent issue with regard to therapeutic approaches involving the microbiota-gut-brain axis.

Additional gut microbes have now been identified following the development of microbial identification technologies such as metagenomics and *16S rRNA* gene amplifications. Although some common alterations have been detected in the gut microbiota of PD patients, many patients do not show highly consistent changes. This is probably because gut microbes are also influenced by diet, lifestyle habits, treatment status (drug/non-drug), personal constitution and geographical location. These variables increase the uncertainty around the impact of gut microbiota on the progress of PD. Accurate identification of microbes that exert a protective or pathogenic effect for PD is highly challenging due to the enormous diversity of the gut microbiome and the complex relationships between microbial members.

The primary means of treating the motor and non-motor symptoms of PD from the perspective of the microbiota-gut-brain axis include but are not limited to,

probiotics, FMT, dietary interventions, and related pharmacological treatments. Probiotic therapy appears to be more in line with the concept of microbiota-targeted therapy than FMT, which requires an understanding of the temporal and causal relationship between a specific probiotic and the development of PD. The applicability of the probiotic as a biomarker of PD needs to be assessed and the dose and course determined, as well as other medication details for the treatment of PD. FMT appears to be a “once only” solution for the repair of recipient gut microbial damage by transplanting donor feces directly into the recipient. In practice, however, there are many uncertainties associated with this technique. Firstly, the transplanted feces contain not only the target microbiota but also viruses, fungi, harmful metabolites, and so on that can increase the risk of infection when transplanted, especially in immune-restricted populations. More studies are needed that include purification of the microorganisms in donor feces. Secondly, FMT, that contains multiple microorganisms makes it very difficult to identify therapeutic mechanisms at the molecular level and to develop targeted microbiota therapeutic approaches. Finally, more clinical trials are needed to determine whether the transplanted fecal microorganisms will be rejected by the recipient and whether the transplanted fecal microorganisms will deliver long-term and stable effects. Furthermore, both the use of probiotics and FMT need to be considered in terms of their impact on the uptake and absorption of levodopa medication taken by PD patients. Provided that a balanced diet is maintained, a low-fat, low-sugar diet with characteristics of the MeDiet can alleviate gastrointestinal symptoms in PD patients and attenuate neuroinflammation. Antibiotics can inhibit or destroy certain microorganisms present at low concentrations, as well as promote the growth of other gut microbiota or the emergence of new microbial species. Thus, antibiotics may exert anti-inflammatory and neuroprotective effects, as well as anti-pathological effects on α -synuclein aggregation through the microbiota-gut-brain axis pathway. Although the effects of antibiotic treatment on gut microbial homeostasis are usually somewhat adjustable in healthy patients [76], it is worth exploring whether antibiotic treatment will aggravate imbalances in the fragile gut microbial system of PD patients.

At present, large clinical studies for the treatment of PD based on the microbiota-gut-brain axis theory are still lacking. Previous small but well-designed studies can be meta-analysed to provide new insights into the mechanisms involved in disease treatment. In addition, more animal or human trials on the treatment of PD are needed from the perspective of the microbiota-gut-brain axis. These studies should help to reveal the exact mechanisms of microbial-induced gut and systemic inflammation, especially at the molecular level. The biological signals produced by the gut microbiota are transmitted along the gut-brain axis to the central nervous system, where they act to regulate cells,

signaling pathways, and target tissues and organs. Further studies should aim to identify new biomarkers for early diagnosis and monitoring of disease progression and to develop more effective and personalized treatment strategies for disease management.

Author Contributions

WZ and XL mainly conceptualized the notion of this review manuscript. YLY and JYS revised the manuscript and contributed to literature review. TS, TTX, LHX, XFQ and QJZ contributed to the literature review. All authors contributed to the editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have contributed sufficiently to the work and agree to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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