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REVIEW ARTICLE

Microbial treatment: the potential application for Parkinson's disease

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Abstract

Alterations in the composition of the intestinal flora are associated with the pathophysiology of Parkinson's disease (PD). More importantly, the possible cause-effect links between gut flora and PD pathogenesis have been identified using PD animal models. Recent studies have found that probiotics improve the symptoms associated with constipation in PD patients. In addition, fecal microbiota transplantation (FMT) was recently shown to provide a protective effect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–induced neurotoxicity in mice. Effective microbial therapy for PD includes probiotics and FMT. Therefore, microbial therapy may be a useful and novel approach for treatment of PD. In this review, I discuss the use of microbial treatment in PD.

Keywords Probiotic treatment · Fecal microbiota transplantation · Parkinson's disease · Intestinal flora · MPTP

Introduction

Parkinson's disease (PD) is a second most common neurodegenerative disease, ranking only behind Alzheimer's disease (AD). PD affects more than six million people worldwide [1] and often presents with both motor and non-motor symptoms, including resting tremors, rigidity, bradykinesia, and gastrointestinal problems. The gastrointestinal alterations associated with PD have been extensively studied and verified with several clinical markers, such as the measurement of gastrointestinal transit time using a magnetic tracking system [2]. Before being diagnosed with PD, many patients reported constipation as one of the initial gastrointestinal symptoms associated with the disease [3, 4]. Furthermore, PD causes other gastrointestinal symptoms, including abdominal pain, bloating, and incomplete defecation. Many of these symptoms, including constipation, can be effectively treated using probiotics [5–7]. In addition to probiotics, microbial treatment may include fecal microbiota transplantation (FMT), which has been shown to be effective in the treatment of recurrent *Clostridium difficile* infection and possibly PD [8, 9]. In this review, I highlight the potential role of microbial treatment in PD, which may represent a novel therapeutic strategy for the clinical treatment of PD (Table 1).

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Probiotics linked to improved gastrointestinal symptoms in Parkinson's disease

Constipation is common in PD patients with a prevalence of 70–80% [11]. Previous studies have shown that constipation and infrequent bowel movements are direct risk factors of PD [12, 13]. As constipation severely affects the overall quality of life of PD patients [14], effective treatment options are needed in the clinic. The potential use of probiotics as an alternative treatment for PD patients has been well established.

The initial study demonstrated, for the first time, improvements in stool consistency and defecation habits in PD patients who used probiotics in the form of fermented milk containing *Lactobacillus casei* Shirota [6]. In addition, the results of a randomized placebo-controlled trial showed that intake of fermented milk, which contained fiber and multiple strains of probiotics, helped relieve constipation among PD patients [7]. In the two studies mentioned above, fermented milk drinks were used as the solvent. However, some studies have shown a positive association between dairy product consumption and an increased risk of PD [15, 16]. Hence, the potential adverse effects associated with the long-term use of fermented dairy products combined with probiotics are unknown. As an alternative, non-dairy probiotic products may be better treatment options. However, non-dairy probiotic products may also have an effect on constipation in PD patients. The administration of two

Table 1 Comparison of studies using microbial treatment in Parkinson's disease (PD) including a study with an animal model

Element	*N*	Type	Treatment duration	Concentrations	Disease model	Main results	References
Probiotics	40	*Lactobacillus casei* Shirota (in fermented milk)	1× daily for 5 weeks	6.5×10^9 CFU	PD patients	Improvements in stool consistency and defecation habits	[6]
Probiotic mixture with prebiotic fiber	80	*Streptococcus salivarius* subsp. *thermophilus*, *Enterococcus faecium*, *Lactobacillus rhamnosus GG*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Bifidobacterium* (fermented milk)	1× daily for 4 weeks	2.5×10^{11} CFU	PD patients	Helped relieve constipation	[7]
Probiotics	20	*Lactobacillus acidophilus* and *Bifidobacterium infantis* (tablets)	2× daily for 12 weeks	120 mg/day Bacterial counts*	PD patients	Alleviated the symptoms of abdominal pain and bloating	[5]
Probiotics	30	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum* (capsules)	1× daily for 12 weeks	8×10^9 CFU/day	PD patients	Decrease MDS-UPDRS scores	[10]
FMT	15	Fecal flora from normal C57BL/6 mice	1× daily for 7 days	2×10^7 CFU	MPTP murine PD model	Show neuroprotective effects on MPTP-treated PD mice by inhibiting glial cell activation and neuroinflammation	[9]

N, number of the intervention groups; *FMT*, fecal microbiota transplantation; *CFU*, colony-forming unit; *PD*, Parkinson's disease; *MPTP*, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; *MDS-UPDRS*, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale

*CFU value was unavailable

probiotics, *Lactobacillus acidophilus* and *Bifidobacterium infantis*, in tablets alleviated the symptoms of abdominal pain and bloating in PD patients [5].

Colonic transit time has been used to objectively evaluate the severity of constipation among PD patients [17]. Further studies are warranted to explore the effects of probiotics on gastrointestinal symptoms using the objective methods like colonic transit time, in addition to other self-report questionnaires like Rome III criteria. Probiotics can increase gut motility [18] as they directly stimulate intestinal smooth muscle cells [19]. The precise underlying mechanisms of probiotic in improving gastrointestinal symptoms in PD are not fully clarified. It is unknown whether probiotics alter the gut environment or inhibit harmful gut bacteria.

Irritable bowel syndrome (IBS)–like bowel symptoms have been reported in approximately 24.3% of PD patients [20]. Disruption of the gut microbiota in PD patients with IBS-like symptoms was linked to a lower abundance of *Prevotella* species in fecal samples from PD patients [20]. Lower *Bifidobacterium* species counts were also found in the stool specimens from patients with progressive PD [21]. Stool consistency and constipation are related to species richness and intestinal flora diversity [22]. Decreased *bifidobacteria* and *lactobacilli* were found in patients with functional constipation, and probiotics could ameliorate constipation and abnormal gut motility issues in the general population [23].

There are still many questions about the proper use of probiotic therapy for PD, including the most effective probiotics, along with the dosage and duration of therapy. The human microbiome is host to many strains of microbes, and a detailed analysis is crucial in determining which microbial communities may serve as potential disease biomarkers [24]. However, the identification of structural changes in the bacterial strains of PD, which regulate brain function and modulate the microbiota diversity, remains a challenge. Multi-omics approaches for studying intestinal flora include metagenomics, metaproteomics, and metabolomics. Currently, no studies have investigated the gut flora and their metabolites in PD patients using an integrative analysis of multi-omics after probiotic treatment.

It is unknown whether successful colonization in the gut and persistent exposure to probiotics will have on the enteric microbiota of PD patients. It is possible that the flora will revert to its original condition soon after stopping probiotic intervention. If probiotics are unable to colonize the intestines for extended periods, the continuous administration of probiotics may be required. In theory, the therapeutic effects of a single-strain probiotic and its effects on gastrointestinal symptoms are more straightforward to assess than multi-species probiotic supplements.

Probiotics improve gastrointestinal symptoms and more in Parkinson's disease

Delayed gastric emptying is common in PD patients [25–27], and it can negatively affect the absorption of some oral PD medications like levodopa [28]. Previously, the probiotic *Lactobacillus reuteri* DSM 17938 was shown to enhance gastric emptying in infants [29], suggesting that this therapy may be effective in PD patients. However, the effects of probiotics on gastric emptying and drug absorption in PD are still unknown.

Decreased L-dopa absorption and increased motor function fluctuations occur in PD patients with *Helicobacter pylori* (*HP*) infection [30], and the effects are reversed by *HP* eradication [31, 32]. Probiotic supplementation contributes to *HP* eradication, and it reduces the severity of antibiotic-induced adverse effects [33, 34]. The influence of probiotic treatment on the pharmacokinetics and pharmacodynamics of L-dopa in PD needs to be considered.

Laxatives may decrease the worsening of rigidity in PD patients [35]. It is possible that mechanical perturbations induced by laxatives may impact the intestinal microflora. More importantly, probiotic use can decrease MDS-UPDRS scores in PD patients [10]. However, its effect on the pathological changes in the brain is still unknown. As far as I know, it is unclear whether relief of constipation with probiotic therapy can slow down the progression of PD in patients.

Dementia and cognitive impairments are common symptoms and complications of PD, and cognitive functions are even impacted at early stages of the disease [36, 37]. *Bifidobacterium breve* strain A1 reversed cognitive dysfunction in a murine model of AD [38]. Probiotic supplementation using a mixed-species product that included *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* improved the mini-mental state examination (MMSE) scores in AD patients [39]. Furthermore, the SLAB51 probiotic formulation delayed the progression of AD in 3xTg-AD mice [40] and exerted a neuroprotective effect by reducing oxidative stresses in a transgenic murine model of AD [41]. While certain probiotic strains are useful for the treatment of AD, it is unknown whether these therapies may be an effective approach for PD-linked dementia.

Depression and anxiety are common in patients with PD-associated dementia [42]. It is well acknowledged that low serotonin levels have been observed in patients with depression. However, limited studies have explored the use of probiotics for mental health disease in PD patients. *Lactobacillus plantarum* PS128 can upregulate dopamine and serotonin levels in the striatum of the germ-free mice [43]. Interestingly, *Bifidobacterium longum* NCC3001 can decrease the depression scores in patients with IBS [44]. In addition, *Lactobacillus helveticus* and *Bifidobacterium longum*

can decrease the Beck Depression Inventory scores in patients with major depressive disorder [45]. Together, these studies have shown that probiotics may be useful for treating PD patients with depression or anxiety; however, it required for solid scientific evidence to prove.

Immunoregulatory effects of probiotics in Parkinson's disease

While different from traditional viewpoints, it is now believed that the brain is not an immune-privileged organ. Recent studies have shown that the infiltrating $CD4^+$ lymphocytes and peripheral monocytes into the central nervous system contributing to neurodegeneration in the animal models of PD may play an essential role in the pathophysiology of PD [46, 47]. The oral administration of *Pediococcus acidilactici* R037 attenuated experimental autoimmune encephalomyelitis (EAE) progression by inducing IL10-producing T regulatory type 1 (Tr1) cells [48]. In agreement with this study, *Lactobacillus plantarum* A7 and *Bifidobacterium animalis* were shown to favor regulatory T cell polarization and amelioratory EAE [49]. Moreover, probiotic administration suppresses the infiltration of $CD3^+$ T lymphocytes into the spinal cord of EAE mice [50]. In addition, probiotic treatment (*Lactobacillus*, *Bifidobacterium*, and *Streptococcus*) plays a part in modulating the anti-inflammatory effects on the peripheral immune system in patients with multiple sclerosis [51]. The pathophysiological role and the impact of probiotics on the anti-inflammatory and inflammatory roles of $CD4^+$ T cells in PD and the link between the immune response require further research. While probiotics may affect the immune cells and immune responses in PD patients, there are no reports that validate this hypothesis.

Cause or effect? Link between intestinal microflora changes and Parkinson's disease

Changes in the gut bacterial abundances of microbes, such as *Prevotellaceae*, have been reported in PD patients [52]. Moreover, alteration of fecal microbiota precedes the onset of brain pathology in rotenone-treated murine models of PD [53]. The intestinal flora changes as PD progresses, which directly correlates with the clinical features of the disease [54]. These studies suggested that alterations of intestinal flora may not just be a phenomenon of PD.

It is essential to determine whether alteration in the microbiota composition can cause the onset and progression of PD. The possible causal effects of changes in the gut microbiota on the pathophysiology of PD have been determined in animal experiments. For example, alpha-synuclein-overexpressing mice treated with gut microbes from PD patients showed aggravated motor deficits [55]. Short-chain fatty acids (SCFA) and intestinal flora metabolites are required for the activation of microglial cells. Intestinal microbes and SCFA regulate microglia in the central nervous system [56]. The effects of the microbiota in PD mice rely on the production of SCFA. The intestinal microbiota can be influenced by probiotics [57], and probiotic supplementation effects fecal SCFA levels [58, 59]. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–treated PD mice exhibited an increased presence of *Proteus mirabilis* in the feces. In addition, oral co-treatment with *Proteus mirabilis* aggravated the loss of dopaminergic neurons and motor impairment, along with activation of microglia in the substantia nigra and striatum in MPTP-treated mice [60]. It is difficult to confirm that specific gut-derived strains from PD patients cause PD or promote disease progression in clinical trials due to ethical reasons. In return, it is challenging to meet Koch's postulates completely.

Targeted neuroinflammation and glial cell activation in Parkinson's disease

Neuroinflammation is associated with the pathogenesis of PD [61]. Higher levels of endotoxin exposure have been found in PD patients [62]. Lipopolysaccharide (LPS) has been used to establish the PD animal model [63]. The gut is known to be a primary source of LPS. *B. longum* subsp. *infantis* may reduce gut-derived LPS in vitro [64]. Another study suggested that the administration of *Lactobacilli*-fermented cow's milk relieved LPS-induced neuroinflammation and memory deficits in mice [65]. In addition, mitochondrial dysfunction is another condition that exists in PD [66]. Prebiotics (xylooligosaccharide), probiotics (*Lactobacillus paracasei* HII01), and synbiotics can reduce hippocampal microglia activation and cognitive deficits, as well as attenuate the dysfunction of brain mitochondrion, in obese insulin-resistant rats [67]. The relationship between the pathophysiology of PD and gut-derived LPS exposure is not well known, and the effects of probiotics on gut-derived LPS, especially in the prodromal period of PD, need to be further studied.

Role of fecal microbiota transplantation in Parkinson's disease

FMT is a new treatment option that has achieved initial success in the treatment of *C. difficile* infection and IBS in patients [68]. Gut microbial dysbiosis and increased fecal SCFA concentrations have been observed in MPTP-treated PD mice. FMT from normal mice has shown neuroprotective effects on MPTP-treated PD mice by inhibiting glial cell activation and neuroinflammation [9].

It has been reported that SCFA can exacerbate motor symptoms in α-synuclein PD mice. However, fecal SCFA concentrations decreased following FMT [9].

Besides tracking changes in specific strains, the cause-effect link and mechanisms following FMT need to be identified. FMT is thought to provide full-spectrum microbiota or complex microbiota transplantation. Currently, the long-term effects and potential adverse effects for PD patients have not been reported. FMT may reconstruct the intestinal flora, alter the microbial diversity of the gut, and restore the abnormal intestinal microflora in a holistic and wide-range manner. Compared to host genetics, environmental factors like diet and FMT are believed to have a greater impact on the intestinal flora [69, 70]. FMT may be categorized as an intervention for postnatal factors. As the intestinal flora differs in mice from different feeding environments [71], additional studies having specific and consistent feeding conditions are needed.

FMT treatment can relieve constipation symptoms in patients with slow transit constipation [72, 73]. When used in combination with soluble dietary fiber, FMT is effective for both short- and long-term treatments of slow transit constipation in the general population [74, 75]. The gut microbiota and its metabolites from patients with slow transit constipation may play a role in the regulation of gastrointestinal motility [76, 77]. Currently, it is unknown whether FMT is equally effective in PD patients with constipation through manipulation of the microbiota-gut-brain axis.

FMT has been approved by the United States Federal Drug Administration (FDA) for the treatment of recurrent *C. difficile* infection [8]. However, one study has suggested that FMT may have complicated and unpredictable impacts on the immune system of patients [78]. The ethical issues surrounding the use of FMT, such as selection and screening of appropriate donors, risk and benefit assessment, a potential impact on emotional and behavioral regulation, long-term security, and other ethical issues, need to be considered [79, 80].

Conclusions

In conclusion, microbial therapies may be beneficial for PD patients suffering from gastrointestinal disorders. However, probiotics should not be considered a panacea for patients with PD when the data is limited, the quality of evidence is poor, or there are mixed data. The roles of probiotic therapy should not be exaggerated as the effects of exogenously administered probiotics on the residential bacterial populations and intestinal microenvironments in PD patients are still unknown. The findings between various studies of distinct probiotic strain types, strain combinations, treatment duration, and varying dosages need to be considered in both animal and clinical studies. The animal models have limitations, and whether the results of animal experiments can be extrapolated to humans is unknown. Strain-level differences in the gut microbiomes contribute to the pathological processes of PD, and reproducible microbial causation is the key to this problem. In the future, we need to consider the impact of environmental and dietetic factors on clinically relevant patient outcomes in the experimental design. The composition and diversity of the intestinal microflora and baseline symptoms vary between people, so the microbial treatment for PD may be individualized. Improvement of the current treatments requires more information about the microbial colonization of the gut, strategies to inhibit the growth of harmful bacteria, and methods for increasing some of the beneficial metabolites.

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Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

Ethical approval This article does not contain any studies with human or animals performed by any of the authors.

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