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## Relationship among Parkinson's disease, constipation, microbes, and microbiological therapy

Xin-Yang Yuan, Yu-Sen Chen, Zhou Liu

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### Abstract

This comprehensive review elucidates the complex interplay between gut microbiota and constipation in Parkinson's disease (PD), a prevalent non-motor symptom contributing significantly to patients' morbidity. A marked alteration in the gut microbiota, predominantly an increase in the abundance of *Proteobacteria* and *Bacteroidetes*, is observed in PD-related constipation. Conventional treatments, although safe, have failed to effectively alleviate symptoms, thereby necessitating the development of novel therapeutic strategies. Microbiological interventions such as prebiotics, probiotics, and fecal microbiota transplantation (FMT) hold therapeutic potential. While prebiotics improve bowel movements, probiotics are effective in enhancing stool consistency and alleviating abdominal discomfort. FMT shows potential for significantly alleviating constipation symptoms by restoring gut microbiota balance in patients with PD. Despite promising developments, the causal relationship between changes in gut microbiota and PD-related constipation remains elusive, highlighting the need for further research in this expanding field.

**Key Words:** Parkinson disease; Constipation; Gut microbiota; Prebiotics; Probiotics; Fecal microbiota transplantation

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**Core Tip:** This comprehensive review explores the intricate relationship between gut microbiota and constipation, a prevalent non-motor symptom observed in Parkinson's disease (PD). Notably, we discuss the significant alterations in gut microbiota, particularly the increase in the abundance of *Proteobacteria* and *Bacteroidetes*, associated with PD-related constipation. Although currently available treatments are safe, their effectiveness in providing symptom relief remains suboptimal, necessitating the development of innovative therapeutic approaches. This review delves into the potential of therapies based on microbiological interventions such as prebiotics, probiotics, and fecal microbiota transplantation, in alleviating these symptoms.

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## INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder with an increasing incidence worldwide[1]. The doubling of PD cases between 1990 and 2016 is expected to result in more than 12 million patients globally by the year 2050[2,3]. PD is characterized by both motor symptoms (*e.g.*, bradykinesia, resting tremor, and rigidity) and non-motor symptoms (*e.g.*, constipation, depression, impaired olfaction, and rapid eye movement sleep behavior disorder)[4]. Constipation is considered one of the most common precursor symptoms of PD and persists throughout the clinical stages of the disease, with its prevalence increasing as the disease progresses[5,6]. For patients with PD, constipation significantly reduces their ability to carry out daily activities and their overall quality of life[7]. Hence, effective therapeutic approaches to control PD-related constipation are urgently required. The pathological mechanisms of PD-related constipation remain unknown, but they may be associated with recto-anal dysfunction or smooth muscle dystonia in the gastrointestinal tract[8,9]. The role of intestinal microorganisms has attracted increasing research attention in recent years. Accumulating evidence reveals a relationship between gut microbiota and PD-related constipation[10-12]. Consequently, traditional treatment options are shifting toward microecological interventions[13-16]. This review summarizes currently available evidence supporting the roles of gut microbiota in the pathogenesis and treatment of PD-related constipation.

## MICROBIOTA-GUT-BRAIN AXIS

The role of intestinal microbes in the central nervous system (CNS) has garnered increasing interest recently. The gut microbiota is a complex ecological community comprising hundreds of millions of microbes that live in the gut and regulates both normal physiology and disease susceptibility through its collective metabolic activities and host interactions[17]. A growing body of research linking PD to the microbiota-gut-brain axis suggests that gut microbiota and microbial metabolites have an important role in PD pathogenesis by influencing neuroinflammation, barrier function, and neurotransmitter activity[18,19]. The microbiota-gut-brain axis includes the autonomic nervous system, the enteric nervous system (ENS), the hypothalamic-pituitary-adrenal axis, and the intestinal microbes[18]. The gut microbiota and the brain can communicate directly through various signaling molecules or indirectly through the gut-brain axis; similarly, the brain can influence the microbes directly or indirectly through alterations to the gut microbiota environment[20].

## BRAAK'S HYPOTHESIS

The pathological hallmarks of PD are loss of dopaminergic neurons together with abnormal accumulation of  $\alpha$ -synuclein ( $\alpha$ -syn) in the substantia nigra and the striatum[21]. Braak *et al*[22] and Hawkes *et al*[23] noticed  $\alpha$ -synuclein-containing inclusion bodies in the intestines of patients with sporadic PD and hypothesized that the pathology of Lewy body in PD might begin in the gastrointestinal tract and then spread to the brain through the vagal nerve. Human  $\alpha$ -syn fibrils were injected into the gut tissue of healthy rodents and transported through the vagus nerve to the dorsal motor nucleus of the vagal nucleus in the brainstem. These results provide the first direct experimental proof that  $\alpha$ -syn can propagate from the gut to the brain[24]. Vagotomy has protective effects on the subsequent development of PD, as it can attenuate the pathological spread of  $\alpha$ -syn, dopaminergic neuronal degeneration, and motor dysfunction. The vagus nerve is an important route for the transmission of pathological  $\alpha$ -syn into the CNS[25-28]. These findings demonstrate that  $\alpha$ -syn detection in the ENS could provide an opportunity to identify early PD neuropathology before the disease spreads to other regions and motor symptoms become evident. Shannon *et al*[29] reported  $\alpha$ -syn detection in the neurites of the colonic submucosa in colonic biopsies collected 2-5 years before motor symptom onset in patients with PD[29]. This evidence suggests that  $\alpha$ -syn detection in colonic mucosal biopsy samples could serve as a presymptomatic biomarker for PD. Additional evidence revealing  $\alpha$ -syn accumulation in colonic biopsies for up to 8 years before motor symptom

manifestation further supports the potential of enteric  $\alpha$ -syn as a diagnostic biomarker for PD[30]. Pouclet *et al*[31] performed a comparative analysis of  $\alpha$ -syn deposition using biopsy samples collected from the rectum, descending colon, and ascending colon of 26 patients with PD and 9 control subjects. The authors discovered that 23%, 42%, and 65% of patients with PD had  $\alpha$ -syn deposition in the rectum, descending colon, and ascending colon, respectively, while control subjects had no  $\alpha$ -syn deposition. These findings indicate that enteric  $\alpha$ -syn detection has the potential to be used as a sensitive, PD-specific, and clinically useful biomarker for early PD detection.

## CONSTIPATION IN PD

Constipation, a prevalent non-motor symptom of PD, has been observed in as many as 90% of patients and is a notable early manifestation and risk factor for PD[32-34]. It is nearly three times more prevalent in patients with PD than in healthy individuals[8,35]. Research indicates that the severity of PD-related constipation helps diagnose the PD stage, with 67% sensitivity and 90% specificity[36]. A Taiwanese study revealed that constipation severity correlates with the probability of PD development[37]. A meta-analysis supported this finding, indicating a 2.27-times higher risk of PD in individuals with constipation[33]. Constipation has a significant 76.56% effect on PD and is mediated by gut microbial changes, as a result of altered gut conditions caused by constipation[12,38]. These changes may result in intestinal inflammation and PD symptoms[38]. Causes of PD-related constipation include delayed colon transit and outlet obstruction[8,39]. The clinical course of PD worsens with constipation, resulting in evident severe motor and non-motor symptoms[7,40]. The severity and frequency of constipation also increase as PD advances[41,42]. A unique correlation between gut health and cognitive function has been documented in patients with PD[43]. Studies from Spain suggest a link between constipation and cognitive decline in PD[44]. The presence and severity of constipation are associated with rapidly progressive dementia and reduced subcutaneous fat [45,46].

Evidence suggests an association between gastrointestinal dysfunction and PD medication[47]. Compared to patients with PD who have a normal colonic transit, those with a slow colonic transit require a considerably higher levodopa equivalent daily dose[48]. This indicates that slow colonic transit may delay peak plasma concentration and cause a reduction in the clinical efficacy of levodopa. Long-term PD-related constipation can lead to an abnormal overgrowth of bacterial decarboxylases in the gut[49]. Du *et al*[11] reported a significant increase in the abundance of the order *Lactobacillales* in the intestines of patients with PD-related constipation. Levodopa plasma availability has a negative association with *Lactobacillus* abundance[50], particularly as several bacterial species of the genus *Lactobacillus* contain genes encoding tyrosine decarboxylase[51]. This enzyme can convert levodopa, a common drug used for PD treatment, into dopamine, affecting blood dopamine levels and potentially causing motor fluctuations. This may necessitate more frequent administration of levodopa and decarboxylase inhibitor treatments[51]. Complex interactions occur between anti-PD medications and gastrointestinal symptoms[52]. Healthy rats treated with PD medication for 14 days exhibited significantly reduced gut motility and altered microbiota composition, including increased abundance of *Bifidobacterium* and *Lactobacillus* and decreased abundance of the families *Prevotellaceae* and *Lachnospiraceae*[50]. Alterations in microbiota composition may lead to microbial metabolite changes, leading to constipation. A comprehensive meta-analysis demonstrated that pramipexole administration increased constipation risk relative to placebo[53]. Evidence suggests that constipation marginally increased after 1 year in patients with PD on dopaminergic medication, particularly levodopa[54]. Another randomized, double-blind trial showed that pramipexole extended release led to a higher constipation likelihood versus placebo in patients with early PD[55]. A high levodopa equivalent dose increases constipation risk, which nearly doubles with the combination of levodopa and a dopamine agonist[56].

### Slow colon transit

Approximately 80% of patients with PD exhibit a slow colon transit, often twice as long as that recorded in healthy control subjects[39,57,58]. This delayed motility is a sign of impaired peristalsis, which depends on the ENS, a network of two plexuses (myenteric and submucosal) within the gut walls[59]. A significant number of these plexus neurons express vasoactive intestinal peptide (VIP) and nitric oxide synthase – both being crucial for muscle relaxation and vasodilation [60]. PD-associated Lewy bodies are present in VIPergic neurons of the ENS, implying that a slower intestinal transit could primarily result from impaired reflex relaxation caused by the loss of inhibitory motor neurons[61]. Evidence indicates Lewy body-containing neurons in the sympathetic ganglia are immunoreactive to tyrosine hydroxylase, implying that the slow transit could be directly linked to the involvement of colonic myenteric plexus in the PD course [62]. Additionally, the loss of dopaminergic neurons in the ENS likely contributes to slow-transit constipation. Studies have found that dopamine inhibits the release of acetylcholine and slows intestinal motility through presynaptic D2 receptors[63]. Age-related loss of excitatory cholinergic neurons in the colon may also be a factor for the slow colonic transit in PD[64,65]. The type of constipation influences the risk of PD development, and people with slow-transit constipation have a very high likelihood of developing PD[66]. Therefore, individuals aged over 65 years with newly diagnosed slow-transit constipation should be considered for PD screening[66].

### Outlet obstruction

More than 60% of patients with PD experience pelvic floor dyssynergia, an uncoordinated action of defecation muscles leading to outlet obstruction[67]. Normal defecation requires the relaxation of pelvic floor and sphincter muscles and a swift return of muscle activity post-defecation. The increase in intra-abdominal pressure, aided by the contraction of glottic, diaphragmatic, and abdominal wall muscles, acts synergistically with the inhibition of pelvic floor and external anal sphincter muscles[68]. In patients with PD, constipation often correlates with a paradoxical contraction of the

puborectalis muscle. This abnormal muscle behavior results in defecation obstruction, a decrease in the anorectal angle, and paradoxical perineum ascent[39,69]. PD-related constipation is indicative of significantly weaker gastrointestinal tract function, with slow transit suggesting colonic ENS involvement and outlet obstruction (dystonia) suggesting direct muscle involvement in PD[39]. The severity and duration of PD are closely associated with the degree of constipation[70].

## GUT MICROBIOTA AND PD

In the context of gut microbiota and PD, functional gut changes in a PD mouse model appear well before the onset of motor symptoms, suggesting a potential gut origin for PD[71]. Alteration in gut function could influence PD progression by modifying gut microbiota composition[72]. Several studies have proposed that gut microbiota alteration could trigger PD development[73,74] and incite immunological activation[75]. Persistent immune responses in the gut can increase intestinal permeability, allowing microbial products and inflammatory mediators to escape from the gut, thereby stimulating systemic immune responses[76]. This proinflammatory immune activity and related conditions can elevate levels of  $\alpha$ -synuclein ( $\alpha$ -syn) in the gut[77]. Pathologic levels of  $\alpha$ -syn can propagate in a prion-like manner from the gut to the brain through the vagus nerve[27,78,79]. One study suggested that oral administration of *Proteus mirabilis* stimulates  $\alpha$ -synuclein aggregation in the brain and colon, resulting in PD symptoms[80]. Another research indicated that the abundance of specific bacterial families could identify patients with PD[36].

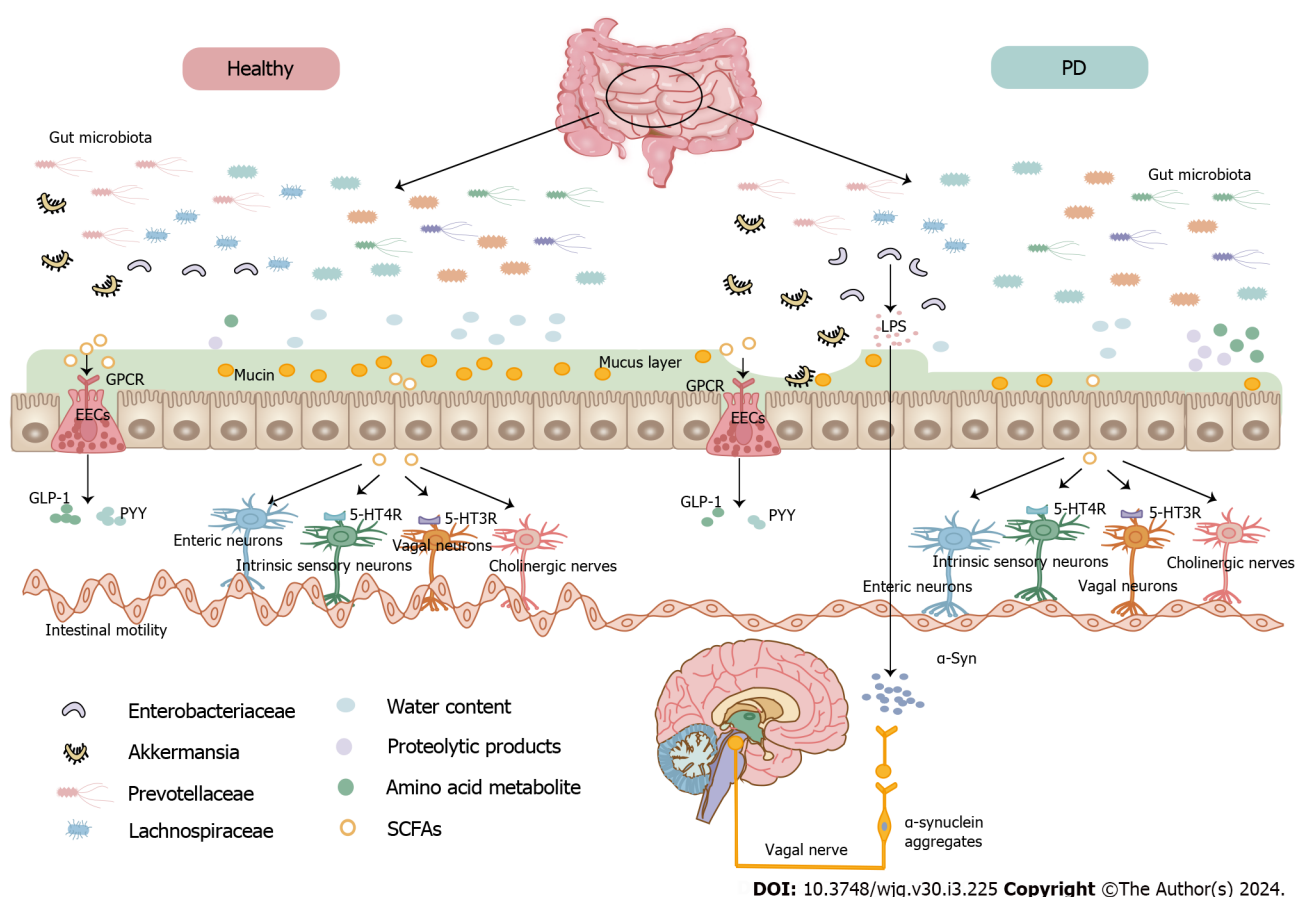
## GUT MICROBIOTA AND PD-RELATED CONSTIPATION

### **Mechanism of action between gut microbiota and PD-related constipation**

Current evidence suggests a delayed colon transit and outlet obstruction, both linked to alpha-synuclein-related neurodegeneration in the ENS, are primary factors for PD-related constipation[36,81]. However, emerging research points out to the imbalance in gut flora as a significant player in the development and progression of PD-related constipation[82]. Studies have found that excessive pre-synaptic  $\alpha$ -synuclein production in the colonic myenteric ganglia could cause early defecation impairment[83]. This finding is supported by the fact that transgenic mice overexpressing  $\alpha$ -synuclein show impaired colonic transit[84,85]. Moreover,  $\alpha$ -synuclein overexpression in the CNS can alter gut function[86,87]. Notably, transplantation of PD microbiota into humanized mice worsened motor symptoms and intestinal dysfunction, implying that  $\alpha$ -synuclein overexpression and microbiota imbalance both contribute to disease progression[72]. Research also suggests that gut microbiota may significantly influence gut motor function[88,89]. This finding was confirmed in a study in which aryl hydrocarbon receptor expression induced by the gut microbiota in enteric neurons affected gut motility[90]. In a mouse model of PD induced by rotenone, gut microbiota was seen to influence gastrointestinal dysfunction, indicating its possible role in PD[91]. Distinct differences in gut microbiome between patients with PD and individuals without PD have been identified[92]. A study of 197 patients with PD demonstrated that higher microbial diversity in the gut correlated positively with stool firmness, implying a link between higher microbial diversity and constipation[93]. Furthermore, most PD studies have reported a decrease in the abundance of the families *Prevotellaceae* and *Lachnospiraceae*, accompanied by an increase in the abundance of the family *Verrucomicrobiaceae* (including the genus *Akkermansia*)[94-97]. This suggests a complex interplay between gut microbiota and PD-related constipation.

Studies reveal that gut microbiota dysbiosis may reduce stool water content, and *Prevotella* enterotypes increases the stool water content[98,99]. Indeed, patients with *Prevotella*-enriched enterotypes showed less severe constipation[100]. Hydrogen sulfide secreted by *Prevotella*, known for protecting dopaminergic neurons, may decrease in concentration in patients with PD who have reduced *Prevotella* enterotypes, leading to constipation because of increased hydrogen sulfide absorption[101]. Hydrogen sulfide can inhibit colonic contractility by affecting cholinergic and tachykinergic excitatory pathways mediated by neurons[102]. *Prevotellaceae* and *Lachnospiraceae*, which produce short-chain fatty acids (SCFAs), can promote gastrointestinal peristalsis[103]. A correlation was found between the genus *Akkermansia*, particularly *Akkermansia muciniphila*, and colon transit time[104]. Uncontrolled growth of *Akkermansia muciniphila* may degrade the mucus layer, leading to drier or harder stools[105,106]. A study on 52 patients with PD found that Enterobacteriaceae, abundant in the colon of patients with PD, negatively correlated with stool frequency[107]. Enterobacteriaceae produce Curli, an amyloid protein that can promote the aggregation of  $\alpha$ -syn in the intestine and brain[80,108]. Gut-restricted amyloid inhibitor treatment in mice alleviated motor and constipation-like symptoms[108]. Both commensal and pathogenic bacterial metabolites can influence gut functions[93,109] (Figure 1). SCFAs, glucagon-like peptide 1 (GLP-1), and peptide tyrosine tyrosine (PYY) can modulate gut sympathetic activity and gastrointestinal motility, highlighting the link between gut microbiota and neuronal function[110]. Additionally, SCFAs activate G-protein-coupled receptors on enteroendocrine cells, mediating GLP-1 and PYY secretion[111]. *In vitro* studies showed that SCFAs stimulate colonic contractions through an enteric reflex involving local sensory and cholinergic nerves[112] and regulate colonic motility through enteric neurons[113]. Changes in the cholinergic phenotype caused by butyrate have a prokinetic effect on colonic motility[99,113]. Alterations in dopamine, 5-HT<sub>4</sub> receptors, and  $\beta$ <sub>3</sub>-adrenoceptors likely lead to colonic dysmotility and constipation in patients with PD[114]. The  $\beta$ <sub>3</sub>-adrenoceptor in colonic interstitial cells of Cajal inhibits colonic motility by inhibiting pacemaker potential[115]. Dopamine inhibits gastrointestinal motility by activating D<sub>1</sub> receptors[116,117], while 5-HT promotes gut motility primarily through the 5-HT<sub>4</sub> and 5-HT<sub>3</sub> receptors[118,119]. SCFAs can activate 5-HT<sub>4</sub> receptors of intrinsic sensory neurons, triggering a peristaltic colonic reflex[120]. Butyrate, which modulates gastrointestinal motility by stimulating 5-HT<sub>3</sub> receptors of the vagal sensory fibers[121,122], negatively





**Figure 1** Changes in microbiota composition and metabolites have been associated with the pathogenic mechanisms of Parkinson's disease-related constipation. Microbiota in patients with Parkinson's disease exhibited a shift in colonic microbiota metabolism away from carbohydrate fermentation and toward proteolysis, resulting in decreased short-chain fatty acids (SCFAs) production and increased proteolytic metabolite levels. Reduced SCFAs production causes a delay in colon transit time. Enhanced proteolytic fermentation has been linked to increased colon transit time. GLP-1: Glucagon-like peptide 1; PD: Parkinson's disease; PYY: Peptide tyrosine tyrosine;  $\alpha$ -syn:  $\alpha$ -synuclein; 5-HT4R: 5-HT4 receptors; 5-HT3R: 5-HT3 receptors; EECs: Enteroendocrine cells; GPCR: G protein-coupled receptors; LPS: Lipopolysaccharide; SCFAs: Short-chain fatty acids.

correlates with constipation severity[123] and increases mucin secretion[124]. Mucin acts as a lubricant, protecting the mucosa and aiding stool excretion[125]. Acetic acid is positively associated with defecation frequency in patients with PD [126].

A study identified higher levels of the harmful amino acid metabolite p-cresol sulfate in the cerebrospinal fluid of patients with PD[127]. The protein degradation byproducts p-cresol and phenylacetylglutamine are also found elevated in the serum of patients with PD, with strong associations with stool consistency and constipation[93]. Glycerolipids, sphingolipids, and sterol lipids are positively associated with constipation in patients with PD[123]. Additionally, constipation positively correlated with pantothenic acid, D-ribose, L-lactic acid, D-alanine, and xanthine in the Luxembourg Parkinson's Study[128]. In summary, the altered microbiota composition in PD-related constipation might lead to changes in microbial metabolites, especially SCFAs, suggesting the potential for manipulating SCFAs as a novel therapeutic strategy in PD-related constipation. Correlations between PD-related constipation, microorganisms, and their metabolites are summarized in Table 1.

### Gut microbiota in PD-related constipation

Research indicates that the primary microorganisms in patients with PD-related constipation are those belonging to Proteobacteria and Bacteroidetes[14]. According to a study, the most prevalent bacteria in the fecal microbiota of patients with PD-related constipation were from the phylum *Bacteroidetes*, genus *Bacteroides*, order *Bacteroidales*, class *Bacteroidia*, and family *Bacteroidaceae*. The study also noted a significantly higher abundance of *Bacteroides* and a considerably lower abundance of *Faecalibacterium* in patients with PD-related constipation than in healthy controls[129]. Additionally, Du *et al* [11] reported that *Bifidobacteriales*, *Lactobacillales*, *Bacillales*, *Peptostreptococcales*, *Tissierellales*, *Desulfovibrionales*, and *Coriobacteriales* were the most abundant microorganisms in the gut of patients with PD-related constipation. These patients also exhibited significantly higher levels of *Bacillus*, *Alistipes*, *Bifidobacterium*, *Romboutsia*, *Adlercreutzia*, *Desulfovibrio*, *Butyrivibrio*, *Bilophila*, *Intestinibacter*, *Holdemania*, *UCG\_002 Actinomyces*, *Lachnospiraceae\_UCG\_008*, *Gordonibacter*, *Raoultibacter*, *Odoribacter*, *Oscillibacter*, *Eubacterium\_nodatum\_group*, and *uncultured species* than healthy individuals[11]. Interestingly, the gut microbiota of patients with chronic constipation is predominantly characterized by reduced abundance of *bifidobacteria* and *lactobacilli* and increased abundance of *Bacteroidetes*[130-133].



Table 1 Correlation between Parkinson's disease-related constipation and microorganisms and their metabolites			
	Positive	Negative	Ref.
Microbial diversity	Alpha diversity		[93,100]
Gut microbiota	<i>Dorea</i> , <i>Oscillospira</i> , <i>Ruminococcus</i> , <i>Lactobacillus plantarum</i> subgroup, <i>Bifidobacterium</i> , <i>Verrucomicrobiaceae</i> , <i>Bradyrhizobiaceae</i>	<i>Faecalibacterium</i> , <i>Roseburia</i> , <i>Enterobacteriaceae</i> cluster, <i>Atopobium</i> cluster	[36,93,100,107,128]
Metabolites	p-cresol and its sulfated form, phenylacetylglutamine, xanthine, D-alanine, L-lactic acid, D-ribose, pantothenic acid, glycerolipids, sphingolipids, sterol lipids	Butyrate, acetic acid	[93,128,123,126]
Enterotype	<i>Firmicutes</i>	<i>Prevotella</i>	[100]

## MICROBIAL TREATMENT FOR PD-RELATED CONSTIPATION

The current treatments for PD-related constipation mainly include prokinetics and laxatives. While these traditional therapies can be safe and effective, they are often limited in fully relieving clinical symptoms, indicating a need for more effective treatments[134,135]. Recent insights into the association between gut microflora and PD-related constipation have led to research exploring how altering gut microflora through prebiotics, probiotics, and fecal microbiota transplantation (FMT) might provide a cure. These interventions could supplement traditional treatments for PD-related constipation.

### Prebiotics

Prebiotics are selectively utilized substrates that confer health benefits to host microorganisms[136]. Reports suggest that prebiotic fibers can alleviate constipation and improve bowel movements[137]. In particular, diets rich in insoluble fiber improved constipation in patients with PD[138], and a study reported that psyllium is useful in treating constipation in patients with PD, noting that it increased stool frequency and weight, with, on average, three bowel movements per week [139].

### Probiotics

Probiotics are live microorganisms that confer health benefits to the host when administered in sufficient amounts and are thought to be another potential treatment for PD-related constipation. They can strengthen the gut barrier and restore normal intestinal microbiota[140], suggesting its potential as a novel treatment strategy for PD-related constipation[141,142]. Initial studies have shown promising results; For instance, patients with PD who took *Lactobacillus casei* Shirota for 5 weeks showed improved stool consistency[16], and those who took probiotics containing *Lactobacillus acidophilus* and *Bifidobacterium infantis* for 3 months experienced reduced abdominal pain and bloating[10]. Further research showed an increase in the number of complete bowel movements in patients with PD-related constipation after drinking fermented milk containing multiple probiotic strains and prebiotic fiber for 4 weeks[143]. A subsequent study reported that taking a multi-strain probiotic combined with prebiotic fiber for 8 weeks improved whole-gut transit time and the frequency of bowel opening in patients with PD-related constipation[144]. Additionally, a randomized controlled trial of 72 patients with PD-related constipation showed that multi-strain probiotics significantly improved weekly spontaneous bowel movements frequency and quality of life scores associated with constipation[15]. Du *et al*[11] reported that multi-strain probiotics effectively improved constipation symptoms and stool consistency in patients with PD, even altering the composition of their gut microbiota.

### Fecal microbiota transplantation

FMT is a novel treatment approach that alleviates constipation by restoring the intestinal microenvironment. This method is based on the premise that alterations in the microbiome may affect gut motility through the production of different microbial-derived metabolites, and correcting these disruptions might improve the clinical symptoms[145]. FMT has shown promising results in treating PD-related constipation, as evidenced by increased abundance of *Firmicutes* and decreased abundance of *Proteobacteria* and *Bacteroidetes* in treated patients, leading to effective relief of constipation and tremors[14]. More recent studies support the beneficial role of FMT in improving PD-related constipation symptoms[13]. One study highlighted that FMT significantly reduced *Bacteroidetes* and increased *Prevotella* and *Blautia* in patients with PD-related constipation. Surprisingly, after FMT, the abundance of several other bacterial groups also increased at different times, accompanied by significant decreases in the patients' Wexner constipation scores and resolution of their constipation symptoms[129]. Such findings underline the therapeutic potential of FMT in rebuilding the gut microbiota of patients with PD-related constipation. Microbial alterations in PD-Related constipation after microbial treatments are summarized in Table 2.

## CONCLUSION

In prodromal PD, abnormalities related to  $\alpha$ -syn can be detected in the colon. Subsequently,  $\alpha$ -syn spreads from the gut to the brain through the vagus nerve, which may lead to the development of PD. Constipation is considered one of the

**Table 2** Microbial alterations in Parkinson's disease-related constipation after microbial treatments

Microbial treatments	Study design	Participant	Duration	Microbial alterations		Results	Ref.
				Increased	Decreased		
Probiotics	Randomized controlled clinical trial	46	12 wk	<i>g_Christensenella_sp._Marseille-P2437</i>	<i>g_Eubacterium_oxidoreducens_group</i> , <i>g_Eubacterium_hallii_group</i> , <i>s_Odoribacter_sp._N54.MGS-14</i> and <i>Prevotellaceae</i>	The probiotics group increased the average number of complete bowel movements per week as compared to the control group. The improvement rate of constipation in the probiotics group was significantly higher than that in the control group	[18]
FMT	Case report	1	3 d	<i>Firmicutes</i>	<i>Proteobacteria</i> , <i>Bacteroidetes</i>	After FMT, patients successfully defecated within 5 min and maintained daily unobstructed defecation until the end of follow-up	[14]
FMT	A prospective, single-center study	11	1 d	<i>Blautia</i> , <i>Prevotella</i>	<i>Bacteroidetes</i>	The PAC-QOL and Wexner constipation scores both decreased significantly	[129]

FMT: Fecal microbiota transplantation; PAC-QOL: Patient assessment of constipation quality of life.

precursor symptoms of PD, potentially stemming from  $\alpha$ -syn pathology in the ENS. The exact mechanisms driving PD-related constipation are still largely unknown, with potential causes ranging from outlet obstruction to delayed colon transit. Current evidence shows a correlation between PD-related constipation and changes in gut microbiota, suggesting a complex interplay between the gut microbiome and PD-related constipation. However, whether the onset of PD-related constipation precedes intestinal dysbiosis or vice versa is still unknown. Despite the unclear cause-effect relationship, studies indicate that gut microbiota dysbiosis can exacerbate constipation and that restoring the gut microbiota can mitigate these symptoms, suggesting gut microbiota as a potential therapeutic target for PD-related constipation. Microbiological intervention treatments for PD-related constipation, including prebiotics, probiotics, and FMT, can prove beneficial and possibly more effective than traditional treatments.

This review covered longitudinal studies on gut dysbiosis in PD-related constipation. However, it has a few weaknesses. The limited number of studies may not have accurately captured the full longitudinal changes in the microbiota associated with PD-related constipation. Furthermore, there is a scarcity of clinical studies examining intestinal flora specifically in PD-related constipation, making it difficult to infer the particular microbial taxa linked to this condition. In addition, as most studies have been conducted at the phylum and genus levels, further research at the species and strain levels could provide greater mechanistic insights. Therefore, future studies should focus on identifying specific bacterial species that promote PD-related constipation development. Finally, pinpointing the causative microbes could enable targeted microbial therapies for PD-related constipation in the future. However, more rigorous clinical studies are needed to elucidate the precise microbiota compositional and functional changes underlying PD-related constipation before such therapeutic approaches can be applied. However, this is a nascent field of research with various limitations and challenges and hence requires future extensive research.

## FOOTNOTES

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