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# Microbiome-Gut-Brain Axis: A New Perspective on Parkinson's Disease

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**Abstract:** ***Parkinson's disease (PD) is a common degenerative disorder of the central nervous system with an increasing incidence. Its pathological hallmarks include dopaminergic neuronal degeneration and loss, along with abnormal aggregation of α-synuclein. The underlying mechanisms remain incompletely understood. Recent studies indicate that gut microbiota play a significant role in the onset and progression of PD through the microbiota-gut-brain axis. They not only influence intestinal barrier permeability via immune, endocrine, and neural systems but may also be implicated in the origin of pathological α-synuclein, thereby affecting PD progression. Currently, modulating the gut microbiota has become a key direction for PD prevention and treatment. Approaches such as fecal microbiota transplantation, probiotic supplementation, dietary adjustments, and traditional Chinese medicine can all regulate the gut microbiota, suggesting future research directions. This review examines the relationship between the gut microbiota and Parkinson's disease, as well as therapeutic strategies targeting the gut microbiota, aiming to provide new perspectives for the diagnosis and treatment of Parkinson's disease.***

**Keywords:** Parkinson's disease, Microbiota-gut-brain axis, Gut microbiota, Therapeutic strategies.

## 1. Introduction

Parkinson's disease (PD) is a progressive, multifocal neurodegenerative disorder characterized by the degeneration and loss of dopaminergic neurons in the substantia nigra of the midbrain, alongside the pathological formation of Lewy bodies due to abnormal misfolding of α-synuclein (α-Syn). Its pathological process extends beyond the central nervous system and autonomic nervous system, affecting multiple brain-gut axis systems, including the intestinal barrier, enteric nervous system, and neuroendocrine-immune pathways. The precise mechanisms underlying its pathogenesis remain incompletely understood, though it is widely recognized as a multifactorial complex disorder. Potential contributing factors have been proposed from various perspectives [1], encompassing neuroendocrine mechanisms, inflammation, immunity, and endotoxins. PD is typically recognized as a movement disorder characterized by symptoms such as muscle rigidity and tremor. However, recent studies indicate that non-motor symptoms emerge early in the disease course, including sleep disturbances, hyposmia, cognitive decline, and gastrointestinal dysfunction [2]. Growing evidence indicates the involvement of the microbiome-gut-brain axis (MGBA) in PD onset and progression, particularly prominent in patients exhibiting early-stage gastrointestinal dysfunction. Approximately 80% of patients in the early stages of PD experience constipation symptoms [3]. The onset of gastrointestinal dysfunction symptoms may precede typical motor symptoms [4], suggesting the MGBA holds potential research value as a mechanism and therapeutic target for PD.

Understanding the brain-gut interaction in PD patients is crucial for unraveling the relationship between microbial activity and the underlying pathophysiology of PD. This research may not only identify novel therapeutic targets for PD but also enable personalized prevention and treatment strategies to halt disease progression. This review analyzes and synthesizes literature on gut microbiota, MGBA, and PD, outlining potential pathways through which gut microbiota mediate PD pathophysiology and elucidating mechanisms for PD treatment targeting gut microbiota. It offers new perspectives for the diagnosis and management of this disease.

## 2. Pathophysiology of Gastrointestinal Dysfunction in Parkinson's Disease

α-Synuclein plays a central role in the pathophysiology of PD. Characteristic neuropathological changes in PD include abnormal folding of α-Synuclein within neurons and degeneration and loss of dopaminergic neurons in the substantia nigra. Studies reveal widespread abnormal α-Syn aggregation in intestinal neurons within the mucosa, submucosa, and myenteric plexus of PD patients during the disease prodromal phase. These neurons are interconnected via the brainstem vagus nerve and the dorsal motor nucleus of the vagus nerve [5]. Therefore, Braak et al. [6] proposed that Lewy body pathology in PD may originate in the gastrointestinal tract. Abnormal α-Syn aggregates may diffuse through the central nervous system via postganglionic enteric ganglion fibers along the vagus nerve in a "prion-like" manner, potentially through a disrupted intestinal barrier.

## 3. Microbial-Gut-Brain Axis and Pathological Mechanisms in Parkinson's Disease

### 3.1 Microbial-Gut-Brain Axis

The gut-brain axis (GBA) represents a bidirectional pathway connecting the gut and central nervous system, with gut microbiota serving as a key factor participating in the bidirectional regulatory mechanism between the gut and brain through the GBA. Recent studies indicate that gut microbiota directly or indirectly modulate brain function through five pathways: neurotransmission, neuroendocrine signaling, neuroimmunology, gut-derived microbial metabolites, and the intestinal barrier and blood-brain barrier [7]. This connection originates during fetal development and persists throughout

the entire lifespan [8].

### 3.2 Gut Microbiota

Changes in the gut microbiota generate toxic byproducts that affect the enteric nervous system, leading to the production of α-Syn. The process by which α-Syn travels upward along the vagus nerve, through the medulla and brainstem to reach the cortex, involves not only exosomal transport but also vesicular exocytosis and microphagocytosis as primary modes of neuronal diffusion [6]. Furthermore, research indicates [9] that abnormal α-Syn aggregation may be influenced by specific gut microbiota. These microorganisms ferment dietary fiber to produce short-chain fatty acids (SCFAs), which serve as crucial metabolites and key mediators in brain-gut axis interactions [10]. Short-chain fatty acids primarily consist of acetate, propionate, and butyrate. Both propionate and butyrate can mediate PD pathogenesis. Butyrate, in particular, is crucial for maintaining intestinal barrier integrity. When short-chain fatty acids decrease, intestinal barrier function declines and permeability increases, facilitating easier transmission of α-Syn from the gastrointestinal tract to the brain [11]. Studies of PD patients' gut microbiota reveal [12] a significant reduction in butyrate-producing bacterial abundance in fecal samples. Conversely, healthy controls exhibit a higher abundance of mucosa-associated bacterial populations within the Faecalibacterium family, including Faecalibacterium prausittis and Faecalibacterium anti-inflammatorye. Additionally, Prevotellaceae—which participate in mucin formation and short-chain fatty acid production through fiber fermentation in the sigmoid colon—were reduced in PD patients' intestines. This decline in Prevotellaceae leads to decreased intestinal mucus and increased intestinal permeability, facilitating α-Syn's passage through the intestinal barrier into the enteric nervous system. Thus, altered gut microbiota disrupts the intestinal microenvironment, leading to sustained α-Syn expression in the gut. Microbial communities in the human gut transmit direct or indirect signals to the central nervous system via the gut-brain axis. Dysbiosis disrupts the intestinal barrier, allowing signals of increased inflammation and bacterial byproducts to be transmitted through the gut-brain axis to the central nervous system [13]. Gut microbiota-induced systemic chronic inflammation primarily refers to excessive inflammation caused by intestinal mucosal immune dysregulation. It is often influenced by dietary components and age, exacerbated by the formation or disruption of the intestinal barrier, and triggers various central nervous system diseases through neural, endocrine, immune, and metabolic signaling mechanisms along the gut-brain axis. Ultimately, it compromises the integrity of the blood-brain barrier (BBB), leading to neurodegenerative lesions [14]. Dysfunction of the MGBA may influence the pathogenesis and pathophysiology of gastrointestinal disorders such as IBS and constipation. Beyond this, it also plays a role in the onset and progression of numerous neurological diseases, including PD, Alzheimer's disease, and depression. In recent years, numerous studies in clinical trials and animal experiments have provided evidence supporting a close connection between the gut and PD. For instance, significant differences in fecal microbiota composition have been observed between PD patients and healthy subjects, as well as between PD patients and PD animal models, before and after ketogenic diet treatment [15].

### 3.3 Dysbiosis of the Gut Microbiota in PD Patients

In recent years, an increasing number of studies have confirmed that the gut microbiota of PD patients exhibits significant differences compared to healthy individuals. Mohammad Mehanna et al. [16] enrolled 30 PD patients and 35 age- and sex-matched healthy subjects as controls. Fecal samples were collected from each individual and analyzed using quantitative PCR to identify and quantify selected bacterial phyla, genera, and/or species. Results showed a significant increase in the Bacteroidetes phylum and a significant decrease in the Firmicutes phylum, the Firmicutes / Bacteroidetes ratio, and the Bifidobacteria phylum in PD patients. Comparing PD clinical phenotypes with controls revealed: - Mixed phenotype: significantly elevated Bacteroidetes, reduced Firmicutes, and Firmicutes / Bacteroidetes ratio - Tremor-dominant phenotype: reduced Bifidobacteria - Tremor, postural instability, and gait disorder (PIGD) phenotype: reduced Bifidobacteria. Fecal microbiome studies in Western PD patients revealed altered microbiota compared to healthy controls. American and Italian PD patients showed increased Proteobacteria and decreased Verruconaceae, while Northern European PD patients exhibited increased Lactobacillaceae and Akkermansia compared to controls. Finnish PD patients reported decreased Prevotella. These geographical differences in microbiota may be closely related to geography, diet, genetics, and lifestyle. In China, Liu Cong et al. [17] recruited 100 PD patients with pathological diagnosis and 100 healthy volunteers. This study analyzed the abundance of the genus Verrucomycetes, serum IFN-γ, and TNF-α levels. The results showed that the abundance of the genus Bacillus, serum IFN-γ, and TNF-α levels were significantly higher than those in healthy individuals. Furthermore, the abundance of the genus Bacillus in PD patients was positively correlated with their UPDRS III scores, Hoehn-Yahr staging, and NMSS scores ($P<0.05$). Therefore, substantial evidence supports a close relationship between the gut microbiota and PD.

## 4. The Microbial-Gut-Brain Axis-Based Therapeutic Approaches

Currently, there is no cure for Parkinson's disease (PD), and treatment primarily involves symptom relief through levodopa-based medications. However, levodopa therapy does not slow disease progression, and clinically, many patients with non-motor symptoms respond poorly to dopamine replacement therapy. In recent years, research into the relationship between the gut microbiota and PD has led investigators to explore preventing and treating PD by modulating the composition and distribution of gut bacteria. Imbalances in the gut microbiome—specifically between microbial composition, metabolic byproducts, and the host immune system—lead to increased intestinal barrier permeability. This allows harmful substances to enter the body, triggering pathological changes [18]. Restoring a healthy microbial community is fundamental to achieving microbiome-based therapies. Therefore, the core approach to microbiome therapy involves restoring dysfunctional gut microbiota to a state associated with health.

### 4.1 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is considered an effective therapeutic approach for restoring microbial balance. Its primary objective is to help rebuild a normal intestinal environment by transplanting fecal microbiota from healthy donors into the patient's digestive tract [19]. Currently, this therapy has been proposed as a potential treatment for neurodegenerative diseases such as PD, Alzheimer's disease, and epilepsy. FMT modulates the MGBA signaling pathway by reshaping the intestinal environment, thereby influencing key pathological processes, including intestinal barrier function, blood-brain barrier permeability, neuroinflammation, and neurotransmitter metabolism. This offers a novel perspective for microbial-based therapies targeting the aforementioned neurodegenerative conditions. The process involves donor screening, fecal sample homogenization, filtration, and enrichment for specific microbial communities, culminating in transplantation via colonic administration or oral intake of freeze-dried microbial preparations in enteric-coated capsules [20]. Gastrointestinal dysfunction, primarily constipation, is a common non-motor symptom in PD. Research indicates that α-Syn, a primary pathogenic factor in PD, appears in the gastrointestinal tract during the early stages of the disease and is transmitted to the central nervous system via MGBA [21]. Recent studies suggest that FMT can significantly improve constipation symptoms in PD patients [22]. Significant differences in gut microbiota richness and microbial structure were observed before and after FMT treatment in 11 PD patients. The abundance of the Bacteroidetes phylum decreased significantly, while the abundance of the genera Blautia and Prevotella increased significantly. Post-treatment, patients demonstrated significant reductions in Hoehn-Yahr (H-Y) staging, Unified Parkinson's Disease Rating Scale (UPDRS) scores, and non-motor symptom scores [23]. This suggests that FMT may restore the gut microbiota ecology in PD patients, thereby improving their motor and non-motor symptoms, demonstrating potential therapeutic value. Currently, FMT may be considered as one of the treatment options for PD, but its efficacy and safety remain to be verified. Donor FMT preparations may contain microorganisms from various unknown taxonomic groups, including bacteria, parasites, and viruses, and their specific composition remains unclear. Due to existing individual differences in microbiota, standardized production is not yet achievable. Future clinical applications require larger-scale and more rigorously designed clinical trials to further evaluate their efficacy and safety, and to identify methods for achieving standardized production.

### 4.2 Probiotic Supplementation

In 2013, the International Scientific Association for Probiotics and Prebiotics defined probiotics as live microorganisms that confer a health benefit on the host when administered in adequate amounts [24]. Currently, probiotics are primarily applied in clinical and health settings through pharmaceuticals, foods, dietary supplements, and formulated preparations. The most widely used strains include Lactobacillus, yeast, and Bifidobacterium, which play crucial roles in preventing endocrine disorders, central nervous system diseases, and various gastrointestinal conditions. Probiotics exert multifaceted effects by regulating intestinal microbial homeostasis and immune balance. Their core mechanisms involve enhancing the integrity of tight junctions in the intestinal epithelium, counteracting intestinal barrier damage, inhibiting pathogenic colonization, and modulating the intestinal immune response [25]. In one clinical trial [26], patients with PD and constipation were randomly assigned to receive either a multi-strain probiotic or a placebo daily. Supplementation with probiotics for 8 weeks significantly improved bowel movement frequency and intestinal transit time. Tamtaji et al. [27] investigated probiotics' effects on motor function and metabolic markers in PD patients. In this study, 60 patients were randomly assigned to two groups (1:1). The probiotic group received a multi-strain probiotic containing 8×10^9 CFU/day, while the placebo group received a placebo intervention for 12 weeks. Compared to the placebo group, probiotic intervention significantly improved symptoms such as resting tremor and bradykinesia in PD patients. These studies suggest that supplementing specific probiotics may offer potential therapeutic benefits for PD patients with severe constipation. However, further research is needed to validate the efficacy of probiotic therapy for PD, determine optimal strain combinations, dosage selection, treatment protocols, and the best duration of therapy.

### 4.3 Dietary Adjustments

Environmental factors such as dietary habits, antibiotic use, and exposure to toxins like pesticides can alter the composition and function of the gut microbiota, thereby becoming pathogenic factors for PD. The Western diet is characterized by high caloric intake, saturated fatty acids, high sugar consumption, and low fiber intake—all considered risk factors for PD [28]. Such dietary patterns exert adverse effects on beneficial gut bacteria.

Modifications in diet and lifestyle can significantly influence gut microbial abundance and the production of fermentation byproducts like short-chain fatty acids. The Mediterranean diet pattern is widely recognized as an exemplary lifestyle approach, capable of preventing the onset and progression of chronic and inflammatory diseases through dietary means, thereby promoting human health. Its defining characteristics include substantial consumption of fruits, vegetables, salads, whole-grain bread, potatoes, legumes, nuts, and seeds. Its core principle lies in using olive oil as the primary fat source while reducing consumption of red meat and processed meats. The Mediterranean diet exerts direct effects through monounsaturated fatty acids, tocopherols, and polyphenolic compounds, while its low saturated fat content and favorable linoleic acid/alpha-linolenic acid ratio exert bidirectional regulation on the immune system and inflammatory responses [29]. The Mediterranean diet correlates with improved health outcomes across multiple conditions, including cardiovascular disease, obesity, metabolic syndrome, and PD. Adherence to this diet is significantly associated with a lower incidence of prodromal PD. A case-control study in older adults found that higher Mediterranean diet adherence was linked to a markedly reduced probability of prodromal PD, while lower diet scores correlated with earlier PD onset [30]. A recent single-center randomized clinical trial [31] randomized 80 PD patients into a Mediterranean diet group

(n=40) and a control group (n=40). The intervention group received a personalized 10-week dietary plan based on the Mediterranean diet. Cognitive function was assessed using the Montreal Cognitive Assessment at baseline and study completion. Adherence to the Mediterranean diet significantly improved scores in PD patients across dimensions, including executive function, language, attention, concentration, and proactive memory, ultimately enhancing the total cognitive assessment score. Thus, dietary modification may represent a potential intervention strategy to slow the onset and progression of PD.

### 4.4 Traditional Chinese Medicine

In recent years, both basic research and clinical trials have demonstrated that traditional Chinese medicine plays a crucial role in the prevention and treatment of Parkinson's disease (PD). Its mechanism of action, particularly its connection to regulating gut microbiota composition, has emerged as a key research focus. Resveratrol exhibits significant therapeutic effects in PD mouse models. Its mechanism likely involves repairing the intestinal barrier, reducing intestinal and neuroinflammatory levels, thereby markedly alleviating motor dysfunction and neurological lesions in PD mice while decreasing dopaminergic neuron degeneration and loss [32]. Nardostachyos regulates gut microbiota composition and suppresses expression of proinflammatory factors in the gut and nervous system, thereby reducing abnormal folding and aggregation of α-Syn in the gut and brain, ultimately protecting dopaminergic neurons [33]. Traditional Chinese medicine can influence PD progression by regulating gut microbiota, offering not only novel therapeutic strategies for clinical management but also new insights into the modern mechanisms underlying TCM treatment for PD. This further expands the scope for personalized PD therapies.

## 5. Conclusion

The close association between MGBA and neurological disorders has emerged as a research hotspot in recent years. The gut microbiota directly or indirectly regulates central nervous system function through multiple regulatory pathways, including the vagus nerve, neuroimmunomodulation, neurotransmitter metabolism, and microbial metabolites. In the field of neurodegenerative diseases, the pathogenesis of Parkinson's disease (PD) is particularly closely related to MGBA. It has been suggested that an altered gut microbiota is a primary cause of gastrointestinal symptoms in early-stage PD patients. The mechanism may involve dysbiosis leading to chronic inflammation of the intestinal barrier and peripheral blood, increased abnormal aggregation of α-Syn, and subsequent retrograde diffusion of α-Syn via enteric nerves to the central nervous system. This pathological mechanism provides theoretical support for therapeutic approaches such as FMT, probiotics, dietary adjustments, and traditional Chinese medicine interventions. Current animal studies indicate that probiotics and FMT can regulate gut microbial homeostasis, suppress oxidative stress, reduce neuroinflammation, and promote neurotrophic factor expression, thereby alleviating symptoms of neurodegenerative diseases. However, FMT and probiotic therapies face numerous challenges in clinical translation for PD. These challenges primarily manifest in the following aspects: FMT involves donor selection and potential ethical issues related to metabolism or immunity; research struggles to identify PD-specific microbiota due to the high heterogeneity of individual microbiomes influenced by environmental and dietary factors; existing evidence indicates a limited number of probiotic strains with neuroprotective effects, and key parameters such as dosage standards and administration protocols remain unconsensus. These obstacles have resulted in insufficient clinical research data accumulation while simultaneously highlighting the immense potential of PD and MGBA research. Advancing the clinical translation of MGBA theory will provide scientific foundations for early intervention and disease treatment in PD.

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