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FROM GUT TO BRAIN: TARGETING THE MICROBIOTA AXIS FOR NOVEL THERAPEUTIC AVENUES IN PARKINSON'S DISEASE

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Abstract: Parkinson's disease (PD) is a prevalent neurodegenerative disorder, with increasing evidence highlighting a strong link between its pathogenesis and intestinal microbiome dysbiosis. This review systematically elucidates the mechanistic pathways of the microbiota–gut–brain axis in PD, emphasizing how gut dysbiosis promotes α-synuclein misfolding and propagation via the vagus nerve, thereby initiating neuroinflammation and dopaminergic neuronal loss. It further examines the critical role of the microbiota–immune–neural signaling network in driving disease progression. In addition, the therapeutic potential and current limitations of microbiota-targeted interventions, including fecal microbiota transplantation, prebiotics, probiotics, and dietary modulation, are evaluated. Collectively, current evidence highlights the gut–brain axis as a key framework in understanding PD etiology and underscores the intestine as a promising site for early intervention and the development of mechanism-based therapies.

Keywords: Parkinson's disease; Gut microbiota; α-synuclein; Neurodegenerative disease; Neuroinflammation; Microecological therapy

1 INTRODUCTION

Globally, Parkinson's disease (PD) represents one of the leading neurodegenerative conditions, second only to Alzheimer's disease in prevalence. Epidemiological data indicate that by 2021 the global PD population had risen to approximately 11.77 million, with incidence increasing sharply with age [1]. The key pathological signatures of PD include a gradual degeneration of dopaminergic neurons within the substantia nigra pars compacta, accompanied by striatal dopamine depletion and the abnormal misfolding and accumulation of α-synuclein (α-syn) into Lewy bodies. Current therapeutic options primarily rely on symptomatic control, such as levodopa administration. However, long-term treatment is often complicated by diminishing efficacy, motor fluctuations, and dyskinesias, and does not halt neurodegenerative progression. Thus, there is an urgent need to identify novel therapeutic targets and disease-modifying strategies [2].

Gene–environment interactions have increasingly been recognized as central contributors to PD pathogenesis, with perturbations of the gut microecological environment gaining particular attention as a critical environmental factor [3]. PD presents with both motor and non-motor manifestations; the latter—such as constipation—may precede motor symptoms by over a decade. Prospective evidence indicates that individuals exhibiting two or more prodromal non-motor features have a tenfold increased risk of developing PD compared with the general population, consistent with a model in which early pathogenic events may originate within the gastrointestinal tract.

The gut–brain axis (GBA) refers to an integrated signaling system through which the gut microbiota and intestinal milieu interact dynamically with neural pathways of the central nervous system. Information flows along this axis through neural pathways (including the vagus nerve), the hypothalamic–pituitary–adrenal (HPA) axis, immune signaling, and microbial metabolites, and has been implicated in a wide spectrum of neurological and psychiatric disorders [4]. Clinically, gastrointestinal dysfunction is highly prevalent among PD patients, and its underlying mechanisms closely correlate with gut microecological imbalance. In general, patients with PD exhibit diminished levels of short-chain fatty acid (SCFA)–producing taxa such as Bifidobacterium and Faecalibacterium, along with increased abundance of potentially pro-inflammatory bacteria including Akkermansia and members of Proteobacteria. Microbial dysbiosis can compromise intestinal barrier integrity, promote endotoxin translocation, and trigger local inflammatory responses while accelerating pathological α-syn misfolding. Abnormal α-syn species can then propagate retrogradely from the enteric nervous system to the brain via the vagus nerve, eliciting neuroinflammation and dopaminergic neuronal death.

Given that current pharmacological treatments inadequately address PD-related dysbiosis and that microecological therapies such as fecal microbiota transplantation (FMT), probiotics, and dietary modulation remain underexplored in clinical practice, this review summarizes the microbiota–immune–neural interactions of the GBA in PD. We highlight the interplay between gut microbiota alterations, α-syn pathology, and neurodegeneration, and critically assess the translational potential and challenges of existing microecological intervention strategies to inform future therapeutic development.

2 GUT MICROBIOTA CHARACTERISTICS AND DYSBISOS PATTERNS IN PARKINSON'S DISEASE

2.1 Common Alterations in Gut Microbiota Composition in Patients with Parkinson's Disease

A substantial body of research has demonstrated that PD is associated with notable shifts in gut microbial community structure. Several studies, including those by Hey and Duan, reported significant reductions in Shannon and Chao1 indices, suggesting decreased microbial diversity in PD. Conversely, a large-scale analysis by Walters et al. did not detect significant diversity differences, attributing discrepancies to confounding influences such as diet, medication, and geographic variation. As a result, conclusions regarding microbial diversity in PD remain inconsistent.

Despite variations observed across diversity indices, shifts in microbial taxonomic profiles exhibit a notably consistent directional pattern. A predominant finding across the literature is the decreased abundance of butyrate-producing genera—notably Faecalibacterium and Roseburia—coupled with an increased prevalence of pro-inflammatory taxa such as Akkermansia and several groups within the Proteobacteria phylum [5]. This dysbiotic state, marked by the depletion of beneficial short-chain fatty acid producers and the expansion of inflammatory microorganisms, is postulated to drive compromised intestinal epithelial integrity and sustain a state of chronic, low-grade inflammation.

2.2 Functional and Metabolic Consequences of Gut Microbiota Dysbiosis

Gut dysbiosis disrupts not only community structure but also the functional metabolic landscape. Nair et al. demonstrated that decreased SCFA production compromises blood–brain barrier integrity and promotes microglial activation, thereby exacerbating neuroinflammation. Erny et al. further reported that butyrate enhances tight junction protein expression in brain endothelial cells, strengthening barrier function and mitigating inflammatory responses. In contrast, studies by Zhao and Li have shown that detrimental metabolites such as lipopolysaccharide (LPS) and hydrogen sulfide (H_2S) induce oxidative stress, facilitate α-syn aggregation, and aggravate neuronal damage [6].

Clinical evidence supports these mechanistic insights. A randomized controlled trial by Scheperjans et al. found that FMT transiently ameliorated certain non-motor symptoms, though its overall efficacy did not differ significantly from placebo. Bruggeman et al. further suggested that baseline microbial composition may influence treatment response. Collectively, existing studies fall into two mechanistic paradigms: a "loss-of-protection" model, driven by reduced SCFA production and compromised barrier function, and a "harmful activation" model mediated by LPS, oxidative stress, and related toxic metabolites. Future research should prioritize functional rather than purely compositional analyses, with aims to restore butyrate-producing microbial networks and reduce harmful metabolite production.

3 CORE MECHANIS BY WHICH GUT MICROBIOTA DRIVE THE PATHOGENESIS OF PARKINSON'S DISEASE

3.1 Enteric Origin and Propagation of Pathological α-Synuclein

Accumulating experimental and clinical findings indicate that disruptions in the intestinal microbiota facilitate α-synuclein misfolding and may act as an initiating event in disease pathogenesis. Animal studies by Sampson and Kim showed that dysbiosis upregulates α-syn expression in the intestinal wall, after which pathological species travel retrogradely to the brainstem. Challis et al., however, detected α-syn aggregation even in germ-free mice, indicating that microbial factors are influential but not indispensable [7]. Additional studies report that amyloid-like bacterial components, such as those secreted by Escherichia coli, may accelerate α-syn aggregation through cross-seeding mechanisms, whereas SCFAs including butyrate appear to counteract this process [8]. These findings collectively imply that the gut microenvironment promotes α-syn pathology through inflammatory activation, barrier dysfunction, and direct protein–protein interactions. Further delineation of strain-specific contributions and metabolite-mediated effects is essential for clarifying α-syn dynamics from initiation to central deposition.

3.2 Microbiota–Immune–Neuroinflammatory Axis

Gut dysbiosis can initiate intestinal inflammation and amplify central neuroinflammation via immune signaling, forming a self-reinforcing "microbiota–immune–neuroinflammation" loop. Activation of the TLR4/NF-κB pathway by LPS is associated with increased release of inflammatory mediators, exemplified by IL-1β and TNF-α, M1 microglial polarization, and subsequent degeneration of dopaminergic neurons. Mouse studies by Zhou and Nair demonstrated that LPS-induced gut inflammation is accompanied by elevated brain inflammatory markers and dopaminergic cell loss [9]. In contrast, Barichella et al. observed that peripheral cytokine levels are not consistently elevated in PD patients despite evident dysbiosis, suggesting modulation by genetic or metabolic factors [10]. Moreover, the finding that peripheral T cells can recognize α-syn epitopes supports the possibility of autoimmune responses triggered by microbial mimicry. Thus, immune and inflammatory mechanisms represent critical modulators of PD progression.

3.3 Metabolic Pathways Mediating Neurodegeneration

Gut microbial metabolites can influence neuronal health by altering energy metabolism, promoting oxidative stress, and regulating neurotransmitter synthesis. Reduced butyrate levels in PD, reported by Duan and Qian, are associated with M1 microglial activation and worsened neuroinflammation [11]. Conversely, Aho et al. found normal or elevated SCFA levels in some early PD cases, suggesting stage-dependent or bidirectional effects [12].

Disturbances in bile acid metabolism also appear relevant. Elevated secondary bile acids, such as deoxycholic acid, have been linked to mitochondrial dysfunction, while ursodeoxycholic acid shows neuroprotective potential [13]. Additionally, a shift toward the kynurenine pathway of tryptophan metabolism leads to quinolinic acid accumulation, triggering excitotoxicity via NMDA receptor overactivation [14]. Collectively, metabolic disruptions act through multiple converging pathways, underscoring the need to develop functional biomarker panels that integrate SCFAs, bile acids, and other metabolites for precision therapeutic stratification.

4 GUT MICROBIOTA–TARGETED THERAPEUTIC STRATEGIES FOR PARKINSON'S DISEASE

4.1 Fecal Microbiota Transplantation (FMT)

FMT provides a direct means of reshaping the gut microecological environment. Preclinical studies show that transplanting fecal microbiota from PD patients into germ-free mice induces motor deficits and neuroinflammation, whereas transplantation from healthy donors mitigates these effects. Clinical trials led by Xue and Bruggeman similarly reported improvements in constipation and partial amelioration of motor symptoms following FMT [15-16]. However, challenges—including a lack of standardized donor screening, uncertain long-term safety, and unresolved ethical issues—currently hinder broad clinical adoption.

4.2 Probiotic-Based Interventions

Probiotics, prebiotics, and synbiotics have gained attention due to their safety and ease of administration. Strains such as Lactobacillus and Bifidobacterium improve intestinal barrier function and reduce systemic inflammation. Double-blind randomized trials conducted by Tan and Barichella showed that formulations containing Lactobacillus acidophilus and Lactobacillus rhamnosus alleviate constipation and are associated with decreased levels of systemic inflammatory indicators, including C-reactive protein and interleukin-6 [17-18]. Nonetheless, Hill-Burns et al. highlighted that baseline microbiota composition significantly influences probiotic colonization and therapeutic outcomes, with some patients experiencing transient gastrointestinal symptoms [19]. Thus, strain specificity, host–microbe interactions, and colonization durability remain key challenges.

4.3 Dietary Interventions

Dietary modification offers a practical approach to modulating gut ecology. High-fiber, polyphenol-rich dietary patterns such as the Mediterranean diet promote SCFA-producing taxa and mitigate oxidative and inflammatory stress. Studies by Perez-Pardo and Maraki reported improvements in motor function and disease progression with Mediterranean diet adherence in both animal models and clinical cohorts [20]. In contrast, Paoli found that long-term ketogenic diets may reduce microbial diversity and increase metabolic burden despite short-term metabolic benefits [21]. Future efforts should integrate dietary responsiveness with microbial metabolic profiling to develop precision nutrition-based strategies.

4.4 Antibiotic and Bacteriophage-Based Therapies

Microbiota-modulating therapies based on antibiotics or bacteriophages remain experimental. Although broad-spectrum antibiotics transiently decrease microbial load, they often induce dysbiosis and weaken immune barriers. Keshavarzian and Yarza reported that prolonged antibiotic use depletes beneficial taxa and elevates inflammatory markers [22]. Conversely, Tetz proposed that excessive bacteriophage activity may destabilize microbial ecosystems and promote neuroinflammation [23-24]. Overall, while these modalities provide novel mechanistic insights, their therapeutic applications require extensive validation through rigorous clinical trials.

5 CONCLUSION

This review synthesizes accumulating evidence supporting a central role of the gut microbiota–brain axis in the pathogenesis of PD and highlights its promise as a therapeutic target. Gut dysbiosis, characterized by reduced short-chain fatty acid–producing bacteria and enrichment of pro-inflammatory taxa, disrupts intestinal barrier integrity and induces local and systemic inflammation, thereby promoting the misfolding and prion-like propagation of α-syn. The subsequent transmission of pathological α-syn to the central nervous system via the vagus nerve triggers microglial activation, sustained neuroinflammation, and progressive degeneration of nigral dopaminergic neurons, providing strong support for a gut-originated pathogenic cascade in PD.

Based on this microbiota–immune–neural interaction framework, microbiota-targeted interventions have emerged as promising adjunctive therapeutic strategies. Approaches including fecal microbiota transplantation, probiotics, prebiotics, synbiotics, and dietary modulation may restore microbial homeostasis, reinforce intestinal barrier function, and modulate immune responses. However, their clinical translation is constrained by limited standardization, substantial interindividual variability in treatment response, and a paucity of long-term efficacy and safety data.

Future research should focus on establishing definitive temporal and causal relationships between gut dysbiosis and α-syn pathology through longitudinal, multi-omics–integrated studies. The development of precision microbiota-based therapies, guided by patient stratification and rigorous randomized controlled trials, will be essential to determine true disease-modifying potential. Collectively, advances in gut microbiota research may enable a paradigm shift from symptomatic management toward mechanism-based intervention in PD.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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