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The Role of Gut Microbiome Dysbiosis in Alpha-Synuclein Aggregation and Parkinson's Disease Progression: Can Microbial Markers Predict Clinical Outcomes?

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Abstract:

Background: Growing research indicates that an imbalanced gut microbiome may interfere with gut-brain axis, potentially worsening alpha-synuclein (α-syn) buildup in early Parkinson's disease (PD). This review aims to provide an overview and critically discuss the current knowledge about gut bacteria influencing α-syn pathology and assesses if specific microbial patterns can forecast disease progression, a possible method of diagnosis before traditional PD symptoms, and maybe as a treatment option to abate PD progression. ***Summary:*** Gut microbiome imbalances may speed up α-syn-related damage in early PD through immune, neural, metabolic, inflammatory pathways. The confirmed involvement of the GI tract could serve as progression markers, opening doors for potential alternative diagnosis. Consequently, therapeutic strategies that target the gut microbiome, such as dietary interventions, probiotics, and FMT are being explored as potential ways to mitigate disease progression. ***Methodology:*** We reviewed various studies, literature reviews, original papers, published on Pubmed between 2015–2022 to investigate relationships between PD and microbiota-gut-brain axis disruptions, α-syn spread in PD. Key evidence came from Histopathology, Immunocytochemistry, Neuroimaging (fMRI) of PD patients, investigations of bacteria metabolites, antibiotic-induced microbiota depletion, and probiotic/prebiotic interventions. ***Results:*** GI symptoms, such as constipation, IBD, etc often precede motor symptoms, which indicates early involvement of the gut-brain axis. The data we referenced indicates that gut microbiota alterations play a significant role in PD development. For example, lower levels of Prevotella and higher levels of *Enterobacteriaceae* have been linked to PD symptoms. Some microbes like *Lactobacillus*, *Bifidobacterium*, and *Akkermansia* are found in higher amounts in PD patients compared to anti-inflammatory bacteria in healthy control groups.Furthermore, Dysbiosis leads to increased intestinal

permeability and systemic inflammation, potentially triggering α-syn aggregation in the ENS. Studies have shown that fecal microbiota transplants from PD patients to mice exacerbate motor symptoms, highlighting a causal link. ***Key Messages:*** Gut microbiome imbalances may speed up α-syn-related damage in early PD through immune, neural, metabolic, inflammatory pathways. The confirmed involvement of the GI tract could serve as progression markers, opening doors for potential alternative diagnosis. Consequently, therapeutic strategies that target the gut microbiome, such as dietary interventions, probiotics, and FMT are being explored as potential ways to mitigate disease progression.

Keywords: **Parkinson's disease, Microbiota-Gut-brain axis, Microbiome dysbiosis, Alpha-synuclein.**

Introduction:

Parkinson's disease (PD) is described as a progressive, multisystem, multicentric neurodegenerative disease affecting aging population, since it concomitantly involves the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system (ANS), adaptive immune system (AIS), and gastrointestinal (GI) tract. Clinically, it is characterized by the accumulation and aggregation of alpha-synuclein (α-syn) in the substantia nigra in the CNS and in other neural structures. PD is symptomatically characterized by the occurrence of both motor and non-motor symptoms (NMS). The classical motor symptoms like bradykinesia, resting tremor, muscle rigidity, gait imbalance and late postural instability are secondary to the death of dopamine-generating cells in the substantia nigra. There is also a wide spectrum of non-motor manifestations involving for example mild-to-severe cognitive impairments, olfactory (loss of smell), GI (affecting up to 80% [4]) such as upper gastrointestinal dysmotility, constipation, IBD, cardiovascular, and urogenital systems, erectile dysfunction, some of which may pre-date the onset of the hallmark neurological features of PD by 10–20 years [8]. It has become evident that the different levels of the brain-gut axis including the ANS and the ENS may be affected in PD. Emerging evidence suggests that gut dysbiosis is linked to the onset and progression of PD. On one hand, dysregulation of the brain-gut-microbiota axis in PD may result in GI dysfunction. On the other hand, this dysregulation may also significantly contribute to the pathogenesis of PD itself, supporting the hypothesis that the pathological process is spread from the gut to the brain [1,2].

Alpha-synuclein (α-syn), a presynaptic protein that under physiological conditions helps regulate synaptic vesicle trafficking and neurotransmitter release [1]. In PD, however, α-syn misfolds into oligomeric and fibrillar aggregates that accumulate in Lewy bodies and neurites, impairing neuronal function and triggering neurodegeneration [1,7]. α-syn has been observed to bind to toll-like receptor 2 (TLR2; a pattern recognition receptor important for pathogen recognition) on microglia (the resident macrophage alongside astrocytes and oligodendrocytes).

Braak hypothesised that an unknown pathogen (bacterium, fungi, archaea, viruses, protozoa, and single-celled organisms) in the gut could be responsible for the initiation of sporadic PD, and they presented a staging system for PD based on a specific pattern of α-syn spreading [9]. Braak et al. also postulated a dual-hit hypothesis, PD α-synucleinopathy begins in the periphery, gains access to the CNS via retrograde transport along vulnerable neuronal projections within the ENS, and ascends caudo-rostrally from the lower brainstem in various distinct stages. The disease may start in the ENS and then spread retrogradely toward the CNS or vice versa. Retrograde transport (from gut to brain) of α-syn can be concomitant with anterograde (from brain to gut) diffusion.

Indeed, α-syn deposits have been detected in gastric, duodenal, and colonic biopsies of individuals years before motor symptoms emerge [8, 9] and gut dysbiosis—characterized by altered short-chain

fatty acid production—appears to promote both local inflammation and α-syn aggregation [4, 5, 7]. Modulation of the gut microbiota therefore holds promise not only for elucidating early biomarkers but also for therapeutic intervention in PD [2, 3, 6]. Consequently, α-syn in the GI tract is a highly specific finding that could be used to confirm a clinical diagnosis of PD.

The gut microbiota refers to the collection of all individual microbes (bacteria, fungi, archaea, viruses, protozoa, and single-celled organisms) [3], that colonizes the human GI tract. A bidirectional communication system between the gut microbiota and the brain has been recognized, known as the "microbiota-gut-brain axis". The dysbiosis of gut microbiota is implicated in the development and progression of PD and other synucleiopathies. For that reason, the gut microbiome is proposed as a druggable target in PD. The gut microbiome and brain communicate through various pathways such as the vagus nerve, ENS, the immune system, the blood brain barrier (BBB), in situ generation of microbial metabolites, and may involve an increase in putative pathobionts (*Bifidobacterium*, *Lactobacillus*, *Clostridia,* etc). These putative pathobionts may work together to potentially impair the intestinal barrier and/or BBB integrity, stimulating systemic and neural inflammation.
Because the compositions of the intestinal microbiota vary from country to country even in healthy individuals, gut dysbiosis observed in PD largely differs from report to report [5].
Among the metabolites, short-chain fatty acids (SCFAs) have received attention for their potential effects on PD pathophysiology. Exactly how gut microbes and SCFAs, ;i,e; the exact mechanisms and outcomes that affect PD progression is not well understood. SCFAs—the byproducts of bacterial fermentation of dietary fiber—get into the systemic circulation, cross the BBB, and exert their effects on microglia in the brain [7]. SCFAs-producing bacteria may reduce or increase outside of an "optimal range" [5]. SCFAs (e.g., acetate, propionate, and butyrate) in the colon at physiological conditions are weak acids. Humans produce an abundance of SCFAs—acetate (60%), propionate (25%), and butyrate (15%). Lachnospiraceae, Roseburia, and Faecalibacterium produce short-chain fatty acids (SCFAs), especially butyric acid [5]. Despite its lower abundance, butyrate is the most pharmacologically active SCFA. [7]. The PD microbiome is characterized by a decreased level and diversity of SCFA-generating bacteria, especially those that generate propionic acid and butyric acid [7].

Bacterial Metabolites:

SCFA:

The presence of healthy intestinal microbiota promotes the integrity of the BBB through regulation of tight junction protein expression (e.g., occludin and claudin-5) mediated by SCFAs [3]. SCFAs play an important role in maintaining intestinal barrier integrity, influence the ENS; SCFAs are also associated with local intestinal inflammation, systemic inflammation and neuroinflammation, stimulate systemic anti-inflammatory properties, promote normal microglial development, and potentially affect epigenesis in the CNS [5].
First, the decrease of SCFA-producing bacteria and the increase of mucin-degrading *Akkermansia* are likely to increase the intestinal permeability to expose the intestinal neural plexus to toxins like lipopolysaccharide and pesticides, which would lead to abnormal aggregation of α-syn. The increased intestinal permeability is underscored by decreased serum LPS-binding protein in PD. Second, the decrease of SCFA-producing bacteria also aggravates microglia-mediated inflammation in the CNS[4]. Klann E M et al. noted some inflammatory biomarkers and SCFAs in the stool are both inversely correlated with microbial alpha diversity in the gut, with some bacterial taxa being directly

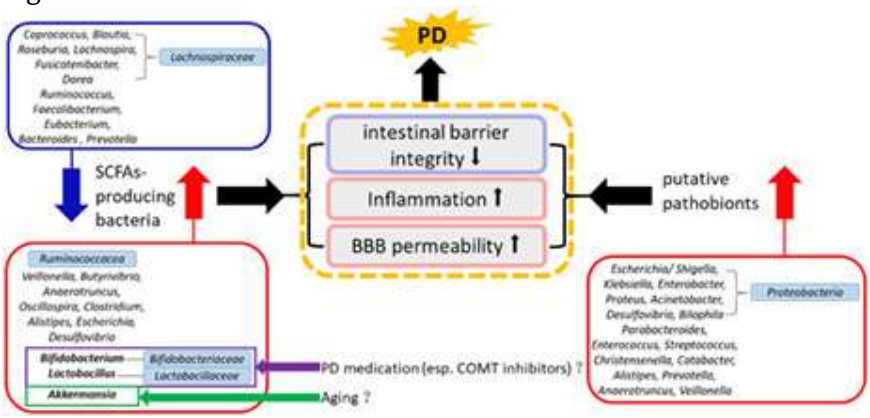
correlated with SCFA levels (↓SCFAs: *Akkermansia*, *Escherichia/Shigella*, *Flavonifractor*, *Intestinimonas*, *Phascolarctobacterium*, *Sporobacter*; ↑SCFAs: *Butyricicoccus*, *Roseburia*) [3].

LPS

Bacterial production of endotoxins (e.g., lipopolysaccharide) capable of altering immune response, initiating proinflammatory pathways, and directly damaging intestinal epithelial cells [3]. In the bloodstream, over produced [7] lipopolysaccharide (LPS) interacts with immune cells, upregulates systemic expression of proinflammatory cytokines (e.g., TNF and interleukins) and inflammation, and, in high concentrations, may directly disrupt the BBB to induce neuroinflammation. LPS also could activate microglia in the brain, leading to a further increase in ROS/RNS (reactive oxygen species and reactive nitrogen species) [7]. Exacerbated activation of microglia is associated with neuroinflammatory processes. Excessive activation of microglia to the M1 phenotype and the concomitant increase in pro-inflammatory cytokines and enzymes such as TNF-alpha, IL-1, IL-6, IL-23, IFN-gamma, and COX-2 are thought to contribute to neuroinflammatory and neurodegenerative processes; while the M2 phenotype is neuroprotective and anti-inflammatory [7]. Conversely, the M2 polarization stimulates anti-inflammatory cytokines such as IL-4 and IL-13, and upregulates arginase-1, tumor growth factor beta-1, and selected chemokines. LPS, an inflammagen that also induces pro-inflammatory factors, including TNF-alpha, IL-1beta, IL-6, and COX-2, in dopaminergic neurons, resulting in the depletion of striatal dopamine.

Based on these results, it is conceivable that inhibition of microglial overactivation or enhancement of the anti-inflammatory M2 phenotype through modulation of the differentiation of microglia may be a therapeutic strategy to inhibit PD progression [7]. This could enhance the phagocytic and clearance ability and decrease the pro-inflammatory and neurotoxic factors [7]. Thus, gut-derived SCFA metabolites could affect microglial behavior through G protein-coupled receptor signaling (e.g., GPR41, GPR43, and GPR109A) [5,7].

Figure 1:



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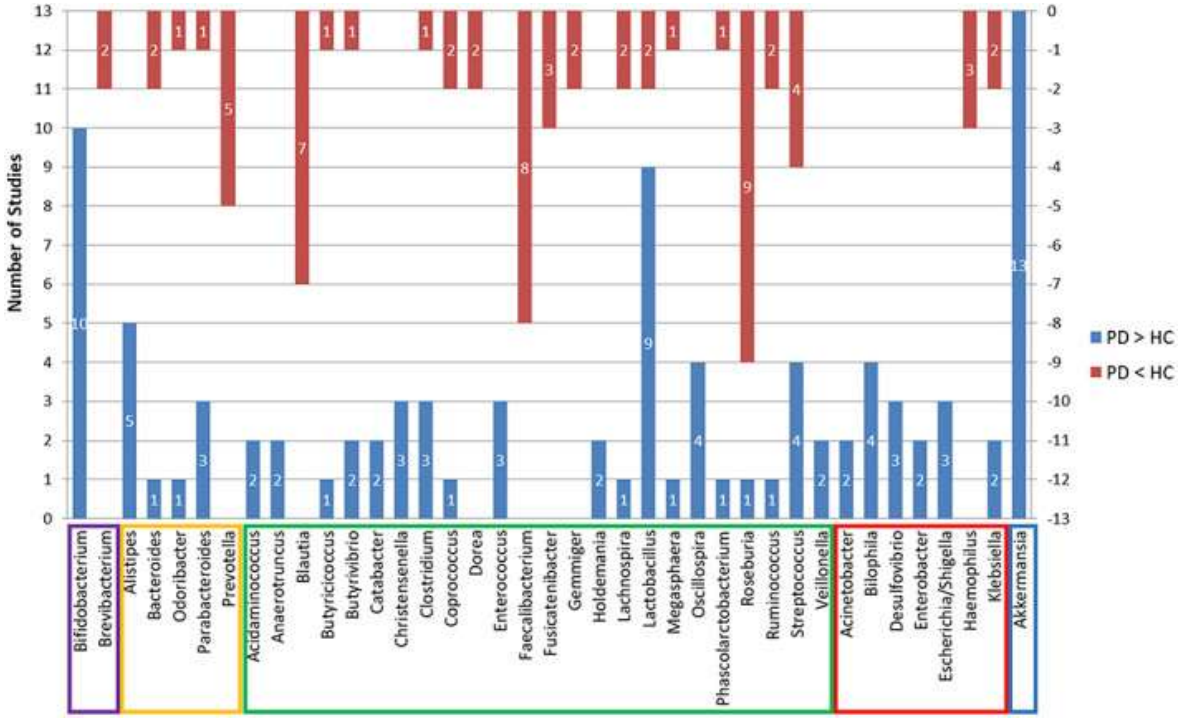
Microbiota-Gut-Brain Axis:

Hirayama et al. found that enterobacteria that were increased in PD at the genus level were *Akkermansia* and *Catabacter* and those that were decreased in PD at the genus level were *Roseburia*, *Faecalibacterium*, and *Lachnospiraceae*. At the family level, Lactobacillaceae and Akkermansiaceae were increased in PD. In addition, *Akkermansia* was increased with progression of PD, whereas *Faecalibacterium* and *Roseburia* were decreased with progression of PD in their dataset. 100 or more PD patients also show an increase of *Akkermansia* and decrease of *Lachnospiraceae*, *Roseburia*, and *Faecalibacterium* in PD. *Lachnospiraceae*, *Roseburia*, and *Faecalibacterium* produce SCFAs, especially

butyric acid. In addition, Lactobacillaceae is often reported to be increased in PD [4].
Their KEGG Orthology Set Enrichment Analysis (KOSEA) revealed that metabolisms of butyrate and propionate were changed in the intestinal microbiota in PD. Which was found to be in with decreased abundance of SCFA-producing bacteria in PD. Control microbiota was enriched in pathways related to carbohydrate degradation, whereas PD microbiota was enriched in pathways related to nucleic acid degradation and amino acid metabolism.[4]
Based on these results, 2 major microbiota networks are changed in PD. When the dietary fibers are defective, *Akkermansia muciniphila* degrades the gut mucus layer and increases the intestinal permeability. *Faecalibacterium* and *Roseburia* that are decreased in PD are butyrate-producing bacteria. Butyrate, as well as other molecules in SCFAs, induces the expression of anti-inflammatory cytokines. SCFAs also bind to G-protein-coupled receptors and exert an anti-inflammatory effect by increasing and/or activating regulatory T cells. The mucin-degrading *Akkermansia* and LPS-producing Gammaproteobacteria were increased in PD patients. Both dysbiosis should lead to increased intestinal permeability, motor impairment, nigral aggregation of α-synuclein fibrils, dopaminergic neuronal loss, and reduction in striatal dopamine [4]. *Escherichia coli* promotes the aggregation of α-syn in both the gut and the brain, resulting in behavioral deficits, intestinal dysfunction, and motor impairments.

Zhe et al. classified gut microbiota into alpha and beta diversity, with alpha diversity based on the number of individual species detected, and beta diversity assessing how different the gut microbiome composition is between subjects. The Chao1 index and Shannon index represent sample richness and diversity, respectively, at the level of alpha diversity. They found eight studies showing significant differences in sample richness between PD cases and HCs; six studies that displayed significantly higher diversity in the PD group than in the HC group [5].

Figure 2:



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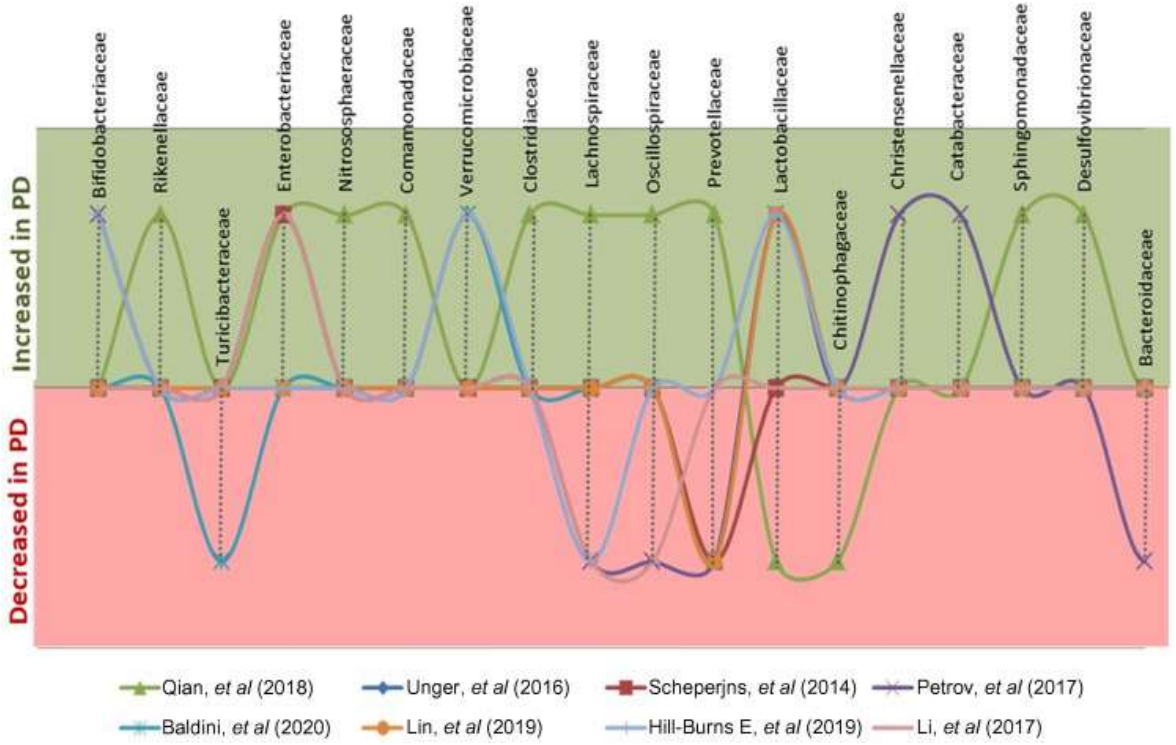
The genera identified by more than two studies as increased in PD were *Bifidobacterium*, *Alistipes*, *Christensenella*, *Enterococcus*, *Oscillospira*, *Bilophila*, *Desulfovibrio*, *Escherichia/Shigella*, and *Akkermansia*, while *Prevotella*, *Blautia*, *Faecalibacterium*, *Fusicatenibacter*, and *Haemophilus* had *three* or more reports of being lower in PD patients. More than one report demonstrated that Bacteroides, *Odoribacter*, *Parabacteroides*, *Butyricicoccus*, *Butyrivibrio*, *Clostridium*, *Coprococcus*, *Lachnospira*, *Lactobacillus*, *Megasphaera*, *Phascolarctobacterium*, *Roseburia*, *Ruminococcus*, *Streptococcus* and *Klebsiella* were altered in both directions [5]

Zhe et al. observed that some of the bacterias that have the capacity to produce SCFAs, such as *Lachnospiraceae* (*Coprococcus*, *Blautia*, *Roseburia*, *Lachnospira*, *Fusicatenibacter*, and *Dorea*), *Ruminococcus*, *Faecalibacterium*, *Eubacterium*, *Bacteroides* and *Prevotella* showed a decrease in the PD group microbiome compared to the control group. Simultaneously, they found that some of the SCFAs-producing bacteria, such as *Ruminococcaceae*, *Veillonella*, *Butyrivibrio*, *Anaerotruncus*, *Oscillospira*, *Clostridium*, *Lactobacillus*, *Alistipes*, *Bifidobacterium*, *Escherichia*, *Desulfovibrio* and *Akkermansia* were increased in PD patients [5].

Increased relative abundance of the orders Clostridiales, Lactobacillales, and Bacteroidales were observed in fecal samples from individuals who were designated ultra-high-risk [6].

Figure 3:



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Summary of PD microbiome profiles obtained in eight studies. Increased relative abundance of Enterobacteriaceae in four studies and decreased Prevotellaceae in five studies are the most consistent findings. Lactobacillaceae was reported as enriched in four studies, though one cohort found it reduced in PD. *Lachnospiraceae* levels were lower in PD patients across three investigations, with one study reporting the opposite trend. Other families—such as Verrucomicrobiaceae, Rikenellaceae

and Bifidobacteriaceae—showed moderate enrichment (two to three studies), whereas Bacteroidaceae and Clostridiaceae yielded mixed results, underscoring cohort- and methodology-dependent variability.

Antibiotics

Antibiotics are also a useful pharmacological tool for investigating the impact of microbiota perturbations on the brain and behavior. They offer much greater temporal flexibility and specificity compared with the GF model of microbiota ablation as they can be delivered acutely or chronically at any stage across an animal's lifespan [e.g., during periods of potential vulnerability such as the early postnatal period, adolescence, or in aging]. Additionally, the ability to titrate the dose of antibiotics allows for a greater level of control over the extent of microbiota depletion, from minor perturbations to the microbiota through subtherapeutic doses of a single antibiotic, to cocktails of antibiotics designed to substantially ablate the entire microbiota.

Supplementation with pre- and probiotics during adolescence could improve resiliency toward the development neurodegenerative disorders through modulation of various biomolecules known to reduce inflammation and promote neurogenesis (ferulic acid), suppress TNF production and decrease TLR signaling (histamines), reduction of reactive oxygen species accumulation (ROS), and improvement of synaptic plasticity (ghrelin) [3]

The versatility and applicability of antibiotics make them an extremely important resource for researching the microbiota-gut-brain axis, and they are expected to play a central role in upcoming studies within this area.

Autopsy:

α-syn accumulation is more widespread and is present in the majority of cases in the GI tract at autopsy. It is seen in the stomach and duodenum in the early stages of the disease. Immunoreactivity was seen in gastric biopsies taken 6 and 8 years prior to the onset of the first motor symptoms as noted by the patients. Therefore offering alternative sites to biopsy for diagnosis. Some of the positive GI biopsies showed inflammation, which was related to an associated inflammatory bowel disorder, and a previous

A study by Shannon K M [9] specifically included a control group with IBD which all were negative, suggesting that the α-syn accumulation is not secondary to inflammation. In patients from whom there were serial biopsies present once immunoreactivity is detectable, it remains so throughout the course of the disease [8].

Neuroimaging (fMRI):

An fMRI analysis showed that when compared placebo, *B. longum* strain reduced responses to negative emotional stimuli in multiple brain areas (including the amygdala and fronto-limbic regions). The probiotic marginally reduced depression but not anxiety while increasing quality of life (QOL) scores in patients with IBS, with improvements associated with changes in brain activation [6].

Prebiotic/Probiotic:

Probiotics, through their interactions with the host microbiota and intestinal epithelium, have been shown to exert a wide range of effects upon host health, ranging from improving metabolism, immunity, endocrine function, and slowing aging. These include inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), resistant starch, and other soluble dietary fibers, etc. Prebiotic supplementation has been demonstrated to reduce stress responsiveness, anxiety, and depressive-like behavior, as well as facilitate changes in hippocampal synaptic efficacy, including increased

hippocampal brain-derived neurotrophic factor (BDNF) expression, general hypothalamic neuronal activity, and enhanced cognition and learning [6]. Fiber rich diet enhances the growth of colonic bacteria that produce SCFA, which have systemic anti-inflammatory effects [3]. Fiber Rich diet enhances the growth of colonic bacteria that produce SCFA, which have systemic anti-inflammatory effects. Therefore, intervention studies with probiotics and prebiotics offer promising ways to bring benefits in elderly's health. [2]

Conclusion:

Emerging evidence strongly supports the gut-to-brain spread of alpha-synuclein (α-syn) pathology in Parkinson's disease (PD), with misfolded α-syn aggregates in the ENS and findings of early GI involvement and may extend along the peripheral autonomic nervous system to the dorsal motor nucleus of the vagus lend support to the hypothesis that PD may originate within the GI tract [8]. Facilitated by gut microbiome dysbiosis, which compromises intestinal barrier integrity, promotes systemic inflammation, and accelerates α-syn aggregation. Our current knowledge on the association between gut microbiota and PD indicates 2 pathomechanisms: First, the decrease of SCFA-producing bacteria and the increase of mucin-degrading *Akkermansia* are likely to increase the intestinal permeability to expose the intestinal neural plexus to toxins like lipopolysaccharide, which lead to abnormal aggregation of α-synuclein [4]. Decreased Prevotella (linked to mucin production) and increased Enterobacteriaceae and Akkermansia, which correlate with clinical severity and may serve as diagnostic biomarkers. Inhibition of microglial overactivation or enhancement of the anti-inflammatory M2 phenotype through modulation of the differentiation of microglia may be a therapeutic strategy to inhibit PD progression [7].Therapeutic strategies targeting the gut microbiome-such as fecal microbiota transplantation (FMT), probiotics, and dietary interventions-show promise in preclinical studies by restoring microbial balance, reducing inflammation, and mitigating α-syn. For instance, higher intake of fiber and healthy diets enhances butyrate-producing bacteria (Butyricicoccus, Coprococcus), which strengthen gut barrier function and suppress neuroinflammation. These findings underscore the gut microbiome's dual role as a diagnostic tool and therapeutic target, offering novel avenues for personalized, mechanism-based strategies to manage PD risk and progression.

Authors Contributions:

Conceptualization: Asadullah Hussain Mohammed Athaullah Hussain, Dineshbaba Murugavel, Hafsa Fathima Athaullahhussain.
Formal Analysis: Asadullah Hussain Mohammed Athaullah Hussain.
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Writing - Review Editing: Asadullah Hussain Mohammed Athaullah Hussain, Rahul Rabindar.

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Ethical approval:

Not applicable.

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Data Availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest:

The authors declare that there is no conflict of interest.

Citations:

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