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"Emerging Insights Into Gut Microbiota And Alpha-Synuclein Pathology In Parkinson's Disease"

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Abstract:
Parkinson's disease (PD) is primarily recognized for its hallmark motor impairments. However, a variety of non-motor symptoms often appear earlier in the disease course and significantly impact patients' quality of life. Despite extensive research, no current treatments effectively alter the progression of the disease. The most widely used therapeutic approach—levodopa—works by restoring dopamine levels to ease motor dysfunctions, but it has limited effects on non-motor symptoms. Among these, gastrointestinal issues are particularly common and are frequently linked to the build-up of alpha-synuclein and chronic, low-grade inflammation within the enteric nervous system (ENS). Emerging research indicates that the ENS may play a crucial role in the development and progression of PD, potentially acting as a gateway through which the disease advances toward the central nervous system (CNS). The gut-brain axis, a bidirectional communication network between the gut and the brain, is believed to be significantly involved in this process. Dietary factors can influence this axis either by modifying the gut microbiome or by impacting neuronal function in both the ENS and CNS. This review explores the growing body of evidence supporting the idea that Parkinson's may originate in the gut and discusses how nutritional interventions could potentially alter disease outcomes or help alleviate both motor and non-motor symptoms. Parkinson's disease is a progressive neurodegenerative disorder marked by the buildup of misfolded alpha-synuclein proteins, known as Lewy bodies, within dopaminergic neurons in the substantia nigra and related neural networks. This accumulation contributes to the emergence of both motor symptoms—such as bradykinesia, tremors, rigidity, and gait disturbances—and non-motor symptoms, including gastrointestinal dysfunction, urinary and genital complications, loss of smell, and cognitive decline. Although significant strides have been made in understanding this condition, the precise biological mechanisms that trigger and drive its progression are still not fully understood. Emerging research points to a possible connection between gut microbiota and brain function, a dynamic relationship commonly referred to as the microbiome–gut–brain axis. Growing evidence indicates that non-motor symptoms, especially gastrointestinal issues, often arise before motor symptoms and a formal diagnosis, suggesting that this axis may play a crucial role in the disease's pathology. This review aims to examine current findings on how gut microbiota may influence Parkinson's disease. It will explore the involvement of alpha-synuclein in non-motor symptom development, the hypothesized pathways linking gut microbes to brain function, and research on the impact of prebiotic and probiotic therapies. The review will also consider potential strategies for prevention and treatment that target the microbiome–gut–brain connection in Parkinson's disease.

Keywords: *Parkinson's disease (PD), Neurodegenerative disorder, Alpha-synuclein, Lewy bodies, Substantia nigra, Motor symptoms, Non-motor symptoms, Bradykinesia, Tremors, Rigidity, Gait disturbances, Gastrointestinal dysfunction ETC.*

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I. Introduction:

Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative disorder, affecting nearly 1% of individuals over the age of 65 (Nussbaum, 2003). Over the last thirty years, the global burden of PD has more than doubled, rising from 2.5 million cases in 1990 to over 6.1 million in 2016 (GBD 2016 Parkinson's Disease Collaborators, 2016; Rocca, 2018). This upward trend is anticipated to persist due to the aging global population. Additionally, period effects indicate a rising age-adjusted incidence rate of PD, particularly among males (Rocca, 2018). Projections suggest that by 2030, the number of individuals with PD in the United States alone may approach 1,238,000 (Marras et al., 2018).[1] PD is a progressive neurological disorder characterized by the abnormal folding of the alpha-synuclein (α-syn) protein, which negatively affects the central, peripheral, and enteric nervous systems (Kouli et al., 2018). The disease arises from a complex interplay of genetic and environmental factors. Approximately 23 genes are linked to Mendelian forms of parkinsonism, while around 187 genes across nearly 90 loci have been implicated in idiopathic PD. Environmental contributors include factors such as traumatic brain injury, smoking, caffeine intake, and exposure to pesticides, herbicides, or heavy metals

(Kouli et al., 2018).[3] The accumulation of misfolded α-syn, forming Lewy bodies, leads to the deterioration of dopaminergic neurons in the substantia nigra and associated brain pathways (Spillantini et al., 1997, 1998; Trojanowski and Lee, 1998). This neuronal loss underpins both the motor symptoms—such as tremors, bradykinesia, rigidity, and postural instability—and non-motor symptoms including cognitive decline and gastrointestinal disturbances (Váradi, 2020). Interestingly, α-syn aggregates are not restricted to the brain; they have also been identified in the enteric nervous system, supporting the concept of a "gut-brain axis"—a bidirectional communication system linking the central and enteric nervous systems with gastrointestinal functions (Chao et al., 2020). [7]

II. Gut Pathology:

Research has increasingly highlighted the gut as a potential origin site for Parkinson's disease (PD) pathology. One of the key pathological hallmarks observed in the gastrointestinal tract of PD patients is the abnormal accumulation of alpha-synuclein, a misfolded protein also found in the brain of affected individuals. These deposits often appear in the enteric nervous system (ENS) well before the onset of motor symptoms, suggesting that PD-related changes may begin in the gut and subsequently spread to the central nervous system via the vagus nerve. In addition to alpha-synuclein pathology, low-grade intestinal inflammation, altered gut permeability, and microbiota dysbiosis have been consistently reported in PD patients. Such changes in gut structure and function may contribute to the disruption of the gut-brain axis, a critical communication pathway involved in maintaining neurological and gastrointestinal health. Furthermore, gastrointestinal symptoms like constipation, which can precede motor symptoms by several years, serve as clinical indicators of underlying gut dysfunction. These findings support the growing hypothesis that gut pathology is not merely a byproduct of PD but may actively drive or exacerbate disease progression.

Alpha-Synuclein Accumulation In The Enteric Nervous System (ENS):

Alpha-synuclein is a protein predominantly found in the central nervous system (CNS), particularly concentrated at presynaptic terminals, where it plays a role in neurotransmitter release and maintaining synaptic balance. A hallmark feature of Parkinson's disease (PD) is the abnormal presence of alpha-synuclein aggregates within neurons, forming Lewy bodies in the cytoplasm and Lewy neurites within axons and dendrites. Some researchers have proposed that alpha-synuclein may behave similarly to prion proteins, where its misfolded form can induce the misfolding of nearby alpha-synuclein molecules, potentially driving disease progression in a self-propagating manner.[5] Numerous clinical studies have demonstrated the presence of alpha-synuclein aggregates in the ENS of PD patients. These accumulations are found throughout the gastrointestinal (GI) tract, from the esophagus to the rectum, and affect both myenteric and submucosal nerve plexuses. Such pathological changes are associated with damage to enteric neurons and are believed to contribute significantly to gastrointestinal symptoms, such as constipation, commonly observed in PD.[9] The hypothesis introduced by Braak and colleagues suggests that PD pathology may begin in the olfactory bulb (OB) and/or the ENS, potentially triggered by unknown environmental toxins or pathogens. From there, the misfolded alpha-synuclein could spread to the substantia nigra (SN) and other regions of the CNS. The vagus nerve is considered a possible conduit for this spread, allowing the pathological protein to move from the gut to the brainstem, midbrain, and eventually to cortical areas. Additionally, the olfactory route may serve as a more direct pathway into the CNS via the olfactory tract. More recent findings suggest that such pathology might not always need an external trigger; instead, intestinal microbiota imbalances themselves may be sufficient to initiate these gut-originating pathological processes in PD.[21] Alpha-synuclein is a neuronal protein predominantly located at synaptic terminals and is highly concentrated in the brain (Figure 1A). It plays a critical role in the pathology of Parkinson's Disease (PD) and other neurodegenerative conditions such as Lewy Body Disease and Multiple System Atrophy. In these disorders, alpha-synuclein tends to misfold and aggregate abnormally, leading to the formation of toxic inclusions that interfere with normal synaptic transmission, cellular balance, and neuronal survival (Spillantini et al., 1997, 1998; Trojanowski and Lee, 1998; Stefanis, 2012).[24] Interestingly, alpha-synuclein is released through an unconventional secretion pathway (Lee et al., 2005, 2016; Emmanouilidou et al., 2010; Gustafsson et al., 2018). Although the precise biological mechanisms behind the release and uptake of its fibrillar forms remain unclear, extracellular alpha-synuclein has been detected in the brain and interstitial fluid of both rodents and humans, indicating a possible mechanism for spreading between cells (Emmanouilidou et al., 2011). Evidence from research involving primary neuronal cultures and in vivo brain studies suggests that nearly 70% of extracellular alpha-synuclein is secreted in response to neuronal activity, particularly involving glutamatergic synapses (Yamada and Iwatsubo, 2018). Additionally, the presence of misfolded alpha-synuclein is closely associated with activation of microglia and subsequent neuroinflammation (Alvarez-Erviti et al., 2011; Xia et al., 2019). However, it remains uncertain whether inflammation triggers alpha-synuclein misfolding or if, conversely, the accumulation of misfolded protein initiates an inflammatory response. The specific trigger responsible for initiating Parkinson's Disease (PD) through alpha-synuclein (α-syn) pathology remains unclear, and current evidence does not support

a single exclusive pathway. Various factors have been linked to the misfolding and aggregation of α-syn, such as changes in intracellular or extracellular pH levels (Buell et al., 2014), fluctuations in ionic concentrations (de Oliveira and Silva, 2019), and the presence of metal ions (Villar-Piqué et al., 2016). However, the exact biological mechanisms that drive these pathological changes are still not fully understood. One well-established risk factor is the persistent overexpression of the α-syn gene, as an increased gene dosage has been shown to correlate with an earlier onset of PD symptoms.

Alpha-Synuclein Propagation From The Enteric Nervous System To The Brain:

Environmental exposures, including toxins like pesticides and microorganisms such as gut and nasal microbiota, are believed to contribute to the early stages of Parkinson's disease (PD) pathology. These agents may trigger initial damage in the olfactory bulb (OB) and enteric nervous system (ENS) by causing inflammation of the mucosal lining and generating oxidative stress, which in turn promotes the accumulation of misfolded alpha-synuclein. Experimental studies have supported this theory, demonstrating that alpha-synuclein can travel in a retrograde manner from the gut wall to the brain, as observed in rodent models.[40] Further in vitro and in vivo research has shown that alpha-synuclein may spread between neurons through endocytic pathways, facilitating the transmission of pathology from cell to cell. In transgenic mouse models of PD, misfolded alpha-synuclein has been observed to migrate into transplanted neuronal precursor cells, forming protein inclusions. Similarly, postmortem analyses of PD patients who received fetal mesencephalic grafts revealed the presence of alpha-synuclein aggregates in the transplanted neurons, confirming its transmissible nature.[37] Supporting the theory of gut-to-brain transmission, a large epidemiological study found that individuals who underwent full truncal vagotomy—surgical removal of the vagus nerve—had a significantly reduced risk of developing PD. This finding emphasizes the potential role of the vagus nerve as a conduit for pathological alpha-synuclein to reach the brain. Additional animal studies have shown that oral administration of the pesticide rotenone can induce PD-like features without any detectable levels of the pesticide in the bloodstream or brain, suggesting that its effects on the ENS alone are sufficient to mimic disease progression.[25] In follow-up experiments, researchers demonstrated that surgical removal of both sympathetic and parasympathetic nerves could prevent the spread of alpha-synuclein to the brain following rotenone exposure. These findings underscore the critical role of the autonomic nervous system in the dissemination of pathology. Given the continuous environmental exposure of the OB and ENS through inhalation and ingestion, it is highly plausible that dietary factors, microbial imbalances, environmental toxins, and pathogens may initiate or facilitate PD progression—especially in individuals with a genetic predisposition.[17]

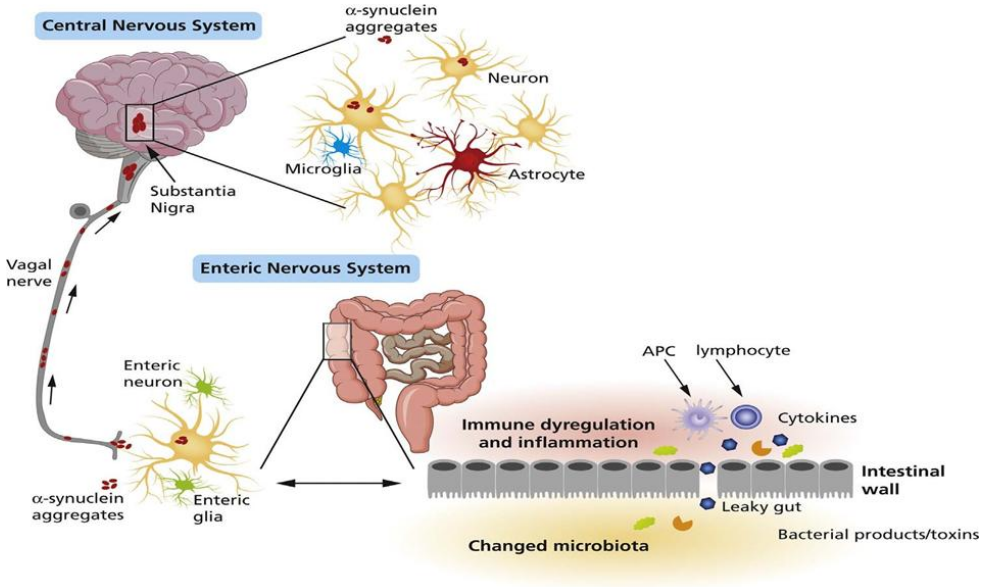

Figure: 1: Proposed Mechanism Of Alpha-Synuclein Accumulation And Propagation From The Gut To The Brain.

Alterations In Gut Microbiota Composition

Individuals with Parkinson's disease (PD) often exhibit increased intestinal permeability, commonly referred to as a "leaky gut", which is linked to the presence of alpha-synuclein aggregates in the gastrointestinal (GI) tract. This compromised barrier may allow bacteria and their inflammatory components, such as lipopolysaccharides (LPS), to cross into the body, promoting inflammation and oxidative stress within the gut.

These events are believed to contribute to the accumulation of pathological alpha-synuclein in the enteric nervous system (ENS) and may also disrupt the blood-brain barrier (BBB), thereby facilitating neuroinflammation and dopaminergic damage in the substantia nigra.[28] Supporting this mechanism, colonic tissue biopsies from PD patients have revealed elevated levels of pro-inflammatory cytokines—including TNF-alpha, IL-1 beta, IL-6, and IFN-gamma—alongside increased activation of enteric glial cells, indicating an inflammatory microenvironment in the gut. Emerging evidence points to a distinct gut dysbiosis in PD. A landmark 2015 study found a substantial reduction in Prevotellaceae in the fecal microbiota of PD patients, along with an overrepresentation of Enterobacteriaceae, which was associated with more severe motor symptoms like gait disturbances and postural instability. The reduction in Prevotella species could impair the production of short-chain fatty acids (SCFAs)—key compounds for gut health—and decrease the synthesis of essential vitamins like thiamine and folate, both of which are typically deficient in PD patients.[22] The drop in mucin production, attributed to low Prevotella levels, may also compromise the gut lining and enhance bacterial translocation. Additionally, altered microbiota compositions, such as increased Lactobacillaceae and decreased Prevotella, have been correlated with reduced ghrelin levels—a hormone important for maintaining nigrostriatal dopamine function—which is often diminished in PD. Further studies have shown reduced levels of beneficial butyrate-producing bacteria (e.g., *Blautia*, *Coprococcus*, and *Roseburia*) in PD patients, leading to a deficit in anti-inflammatory SCFAs. PD stool samples also exhibit increased expression of genes involved in LPS biosynthesis and type III secretion systems, both associated with inflammation and pathogenicity.

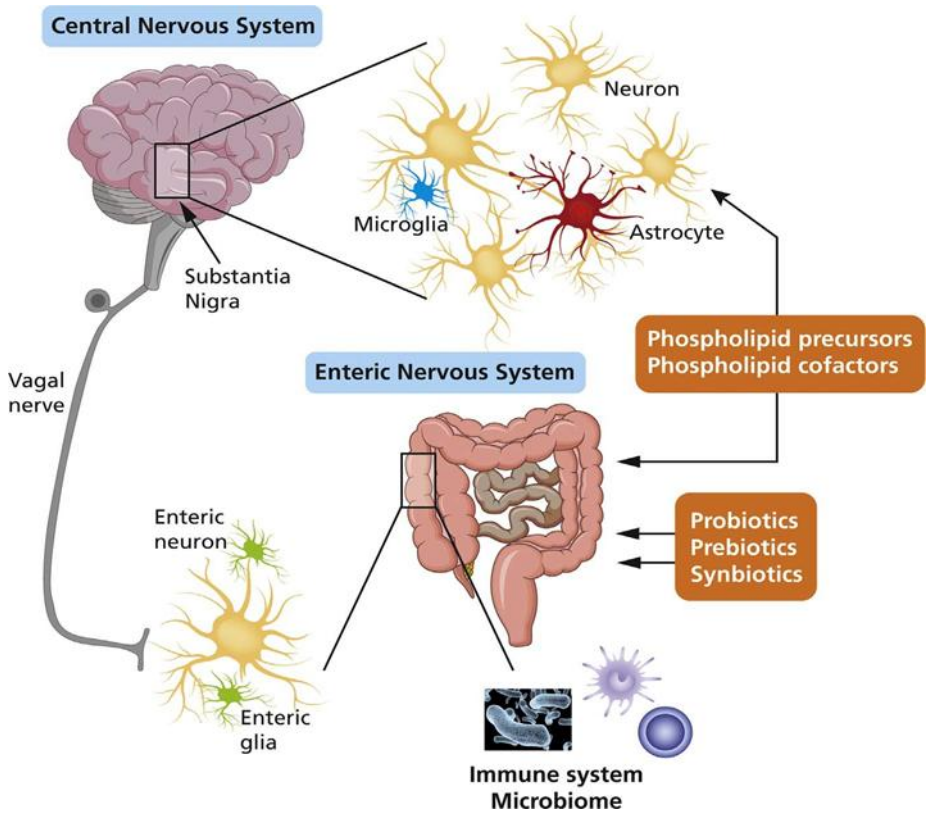

Figure: 2: Nutritional Interventions Involving Phospholipid Precursors And Essential Cofactors May Promote Neuronal Membrane Integrity, Improve Neurofunction, And Reduce Inflammation Across The Enteric And Central Nervous Systems, Thereby Alleviating Both Motor And Non-Motor Symptoms In Parkinson's Disease. Additionally, Probiotics, Prebiotics, And Synbiotics May Modulate Gut Microbiota Composition, Enhance Gut Barrier Function, And Attenuate Inflammation, Potentially Mitigating The Progression Of Neurodegeneration.

Recent investigations have confirmed that SCFA concentrations—especially acetate, propionate, and butyrate—are significantly lower in PD patients. These SCFAs support gut integrity and exert anti-inflammatory effects through receptor-mediated signaling and epigenetic regulation. Their deficiency could therefore contribute to GI dysmotility, a hallmark non-motor symptom of PD.[14] Another gut-related condition, Small Intestinal Bacterial Overgrowth (SIBO), has been found to be highly prevalent in PD. This disorder, characterized by an abnormal increase in bacteria in the small intestine, may result from impaired GI motility. Although SIBO does not necessarily worsen GI symptoms, it has been independently linked to greater motor symptom severity in PD

patients. It may also promote systemic inflammation via increased bacterial translocation.[18] Although it remains unclear whether gut microbiota changes are a cause or a consequence of PD, the cumulative evidence suggests that dysbiosis can promote inflammatory pathways and oxidative stress, potentially contributing to the progression of neurodegeneration in PD through mechanisms such as LPS-mediated inflammation.

III. Targeting The Gut-Brain Axis In Parkinson's Disease Through Nutritional Therapies:

Currently, there are no therapeutic strategies that effectively alter the course of Parkinson's disease (PD). Moreover, existing treatments do not specifically address the gut-brain axis, which could be key in halting the spread of pathological changes or managing motor and non-motor symptoms. Nutritional strategies, particularly those involving phospholipid precursors and microbiota-targeted interventions like prebiotics and probiotics, may offer complementary benefits to standard treatments—especially in mitigating gastrointestinal (GI) dysfunction, a common and troubling feature of PD.[9] Diet-based interventions could modulate the gut-brain axis either by influencing microbial composition and thereby PD progression, or by supporting neuronal activity in both the enteric and central nervous systems.

Nutritional Membrane Precursors And Co-Factors:

Combinations of specific nutrients, including phospholipid precursors and essential cofactors, have shown promise in addressing synaptic loss and membrane dysfunction in PD. These nutrients, which include uridine (as UMP), DHA (an omega-3 fatty acid), and choline, are vital for the creation and maintenance of neuronal membranes. By increasing their availability through diet, one may enhance the enzymes that drive phospholipid synthesis, offering functional support to neurons.[21] Adding cofactors such as B-complex vitamins, vitamin C, vitamin E, and selenium may further improve the uptake and metabolism of these precursors. Research in animal models indicates that these nutrient combinations can boost phospholipid levels, enhance synaptic density, and improve dopaminergic signaling. Such formulations have also shown to ease both motor and non-motor PD symptoms and mitigate inflammation and alpha-synuclein buildup in the colon.[13] Furthermore, dietary polyunsaturated fatty acids (PUFAs) like DHA may reduce neurotoxic effects and oxidative stress. Supplementation has demonstrated protective effects even when administered after symptom onset. Prebiotic fibers such as galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) may strengthen these benefits by modulating gut immunity and motility and potentially improving motor symptoms via gut microbiome interactions.[22]

Probiotics:

Probiotics, or beneficial microorganisms administered in sufficient quantities, can help restore microbial balance and support immune health. Common strains include Lactobacilli, Bifidobacteria, and Enterococci. These microbes may reinforce the intestinal barrier, regulate mucosal immunity, and deter harmful bacteria.[18] Evidence supports probiotics' role in enhancing intestinal function and relieving constipation—issues commonly experienced by PD patients. Some strains have also shown potential in improving mood and reducing anxiety or depression. In a PD-specific study, probiotic fermented milk improved constipation and abdominal discomfort.[1] By improving gut barrier function and limiting inflammation, probiotics may also enhance levodopa absorption and support cognitive health—adding potential value in PD management.

Prebiotics:

Prebiotics are indigestible dietary fibers, like GOS and FOS, that selectively encourage the growth of beneficial gut bacteria. These compounds produce metabolites such as short-chain fatty acids (SCFAs), which help regulate gut pH, enhance epithelial barrier integrity, and maintain immune balance.[2] Prebiotics are known to improve gut motility and reduce inflammation, which are relevant for PD's GI and systemic symptoms. In animal studies, they have also elevated brain-derived neurotrophic factor (BDNF) levels—an essential molecule for neuronal survival and synaptic plasticity. Despite these promising effects, the potential of prebiotics in PD patients remains largely unexplored. They could be particularly valuable given that PD is often associated with reduced levels of SCFA-producing bacteria.

Symbiotic:

Synbiotics combine both probiotics and prebiotics, with the prebiotic component specifically chosen to enhance the survival and activity of the probiotic strain. These formulations have demonstrated positive effects on immune response, microbiota balance, and GI function, making them particularly relevant for those with PD.

Table: A: Key Insight & Implications For Pd:

Aspect	Key Insight	Implications For Pd
Alpha-Synuclein Aggregation	Misfolded Alpha-Synuclein May Originate In The Enteric Nervous System (Ens).	Suggests Pd May Begin In The Gut And Propagate To The Brain Via The Vagus Nerve.
Microbial Dysbiosis	Pd Patients Exhibit Altered Gut Microbiota Composition (E.G., Decreased Scfa-Producing Bacteria).	May Contribute To Inflammation, Impaired Gut Barrier, And Neurodegeneration.
Gut Inflammation	Bacterial Translocation Can Trigger Immune Activation And Chronic Gut Inflammation.	Increases Alpha-Synuclein Aggregation And Systemic Inflammation.
Gut-Brain Axis	Communication Between Gut Microbiota And The Central Nervous System Occurs Via Neural, Hormonal, And Immune Pathways.	Highlights The Potential To Target Gut Microbiota To Modulate Brain Function.
Probiotics And Prebiotics	Supplementation Can Enhance Intestinal Integrity, Reduce Inflammation, And Possibly Influence Brain Health.	May Slow Pd Progression And Alleviate Gi And Neuropsychiatric Symptoms.
Dietary Interventions	Nutrients Like Dha, Uridine, Choline, And Fibers (Gos/Fos) Support Membrane Health And Beneficial Microbiota.	Could Reduce Alpha-Synuclein Accumulation And Motor/Non-Motor Symptoms.
Vagus Nerve Pathway	Alpha-Synuclein May Travel From Ens To Cns Through The Vagus Nerve.	Vagotomy Studies Support The Gut-Origin Hypothesis In Pd Pathology.
Microbiota-Driven Immune Response	Dysbiosis Can Activate Microglia And Promote Neuroinflammation In The Cns.	Indicates Microbial Modulation Could Help Regulate Neuroimmune Responses.

Potential Contributions Of Microbiota To Alpha-Synuclein Pathologies: Braak's Hypothesis:

Healthy gut microbiota play a crucial role in maintaining the integrity of the blood–brain barrier (BBB) by regulating the expression of tight junction proteins such as occludin and claudin-5. This regulation is largely influenced by short-chain fatty acids (SCFAs), which are metabolites produced by beneficial gut bacteria (Hoyles et al., 2018; Tran and Mohajeri, 2021). SCFAs also help preserve the intestinal barrier, preventing the translocation of harmful microbes into the bloodstream—an event known to trigger localized gut inflammation, systemic immune activation, and potentially, neuroinflammatory responses (Houser and Tansey, 2017; Wang et al., 2020).[24] However, when the gut microbiome becomes imbalanced—a state known as dysbiosis—there is often an overgrowth of harmful bacteria. These bacteria can secrete endotoxins like lipopolysaccharide (LPS), which disrupt gut barrier function by harming epithelial cells and activating immune responses that promote inflammation (Ghosh et al., 2020). Once LPS enters the bloodstream, it can interact with immune cells to stimulate the production of proinflammatory cytokines such as TNF and interleukins. In elevated levels, LPS can also compromise the BBB, contributing to inflammation in the central nervous system (Banks et al., 2015).[31] Remarkably, LPS has been shown to initiate the formation of distinct, self-propagating alpha-synuclein (α-syn) fibrils in animal models. These fibrils mirror the structural and functional abnormalities observed in Parkinson's Disease (PD), indicating that microbial endotoxins might influence disease progression at a molecular level (Kim et al., 2016). Research suggests that LPS may alter the normal aggregation pathway of α-syn by promoting the formation of nucleating intermediates, which eventually develop into abnormal fibrillar structures. These modified fibrils affect cellular uptake and toxicity patterns (Bhattacharyya et al., 2019).[17] There is growing evidence linking gastrointestinal symptoms and α-syn pathology in PD. Although α-syn is primarily located in the brain, it is also expressed by enteric neurons where it supports neurotransmission (Grathwohl et al., 2013). In patients with Parkinson's, pathological forms of α-syn have been detected in gastrointestinal tissue samples (Sánchez-Ferro et al., 2015), supporting the theory that PD may originate in the enteric nervous system (ENS). Moreover, misfolded α-syn has been identified in other peripheral tissues including the salivary glands, esophagus, and stomach (Fayyad et al., 2019), which may help explain some of the early, non-motor symptoms observed in PD.[21]

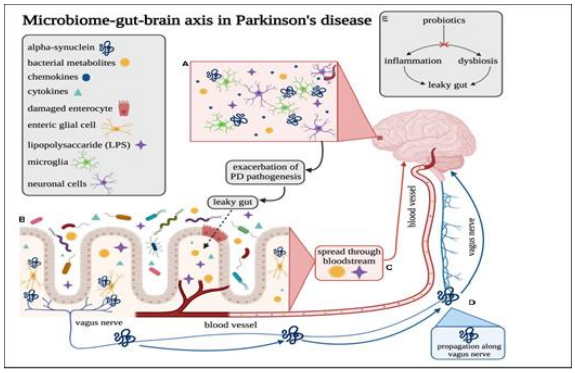

Figure: 3: Microbiome-Gut-Brain Axis In Pd

Gastrointestinal Symptoms And Peripheral Alpha-Synuclein Aggregation In Parkinson's Disease:

Non-motor symptoms such as excessive salivation, difficulty swallowing (dysphagia), delayed stomach emptying, and gastroparesis are commonly observed in individuals with Parkinson's Disease (PD). These symptoms often appear early and are linked to impaired gastrointestinal (GI) motility. In a study utilizing a transgenic mouse model of PD, the compound Posiphen—an inhibitor of amyloid precursor protein—was administered to suppress alpha-synuclein (α-syn) misfolding (Kuo et al., 2019). Treatment with Posiphen led to a restoration of normal motility in the distal colon, a key aspect of gut function. Since proper colonic movement helps sustain a healthy gut microbiome, this finding points to the potential of early interventions that target GI-related symptoms like constipation, which is frequently seen in the early stages of PD.[21] However, evidence for the diagnostic utility of α-syn detection in gut tissue remains inconsistent. For instance, one study found that the sensitivity of detecting α-syn in colon biopsies from PD patients was only about 14% (8 out of 57 samples) (Chahine et al., 2020). A broader meta-analysis encompassing 21 studies reported a pooled sensitivity of 57% and specificity of 82% for α-syn in colonic tissue, with an estimated odds ratio of 10 when compared to individuals without PD (Bu et al., 2019). These findings suggest that although the presence of α-syn in the gut may be involved in the disease process, it is neither essential nor definitive for diagnosing or predicting PD.[7] Notably, Braak and colleagues (2003), along with Hawkes et al. (2007), introduced a theory suggesting the gastrointestinal system may play a foundational role in the initiation and spread of PD. According to their hypothesis, a still unidentified pathogen might enter the body via the nasal cavity or gastric lining. This agent could potentially induce structural alterations in normal α-syn proteins, leading to their aggregation. From the gastric mucosa, the pathogen—or misfolded α-syn—may travel to the central nervous system (CNS) through retrograde transport pathways. Braak's model supports the idea that the pathological process of α-synucleinopathy may originate in the peripheral nervous system before reaching the brain.[2] According to Braak's hypothesis, misfolded alpha-synuclein (α-syn) may travel from the enteric nervous system (ENS) to the central nervous system (CNS) through retrograde transport along susceptible neural pathways. This transmission is proposed to begin in the lower brainstem and gradually progress in a caudo-rostral direction through defined pathological stages (Braak et al., 2003; Hawkes et al., 2007; Visanji et al., 2013). A key distinguishing feature of this theory is its suggestion that Parkinson's Disease (PD) might originate from an external trigger, such as a pathogen, rather than from intrinsic, central processes.[1] While the hypothesis has provided a framework for understanding the potential peripheral initiation of PD, it has been criticized for its limited applicability across the broader PD population—particularly among individuals who do not have the sporadic form of the disease. Nonetheless, several studies support certain elements of this model. For example, α-syn aggregates have been identified in the vagus nerve, and experimental evidence shows that this misfolded protein can propagate from the ENS to the CNS (Musgrove et al., 2019). In animal models, severing the vagus nerve (vagotomy) has been shown to prevent the spread of α-syn pathology, further supporting the involvement of this neural route (Kim et al., 2019).[9] Moreover, recent advances in experimental PD models involve the direct introduction of α-syn into the gastrointestinal tract. These models have successfully induced neurodegenerative changes characteristic of PD within the CNS (Uemura et al., 2018; Kim et al., 2019; Challis et al., 2020). Despite these promising findings, challenges remain. A comprehensive autopsy study involving 187 individuals, including those with PD, incidental Lewy body disease, and healthy controls, did not reveal a single case in which Lewy pathology was found exclusively in the gut without concurrent brain involvement (Beach et al., 2021).[1][7] These findings underscore the need for continued investigation to determine whether Lewy body pathology can independently originate in the gut, and whether such peripheral pathology corresponds to unique clinical features or health outcomes. Establishing this could inform new preventive or therapeutic strategies targeting early gastrointestinal involvement in Parkinson's Disease.

IV. Microbiota Composition And Metabolites Associated With Parkinson's Disease And Symptom Severity:

The human microbiome refers to the collection of microorganisms—including bacteria, fungi, viruses, and protozoa—and their collective genetic material inhabiting specific sites in the body (Ursell et al., 2012). Throughout an individual's life, the microbiota undergo dynamic changes, influenced by age (Badal et al., 2020), dietary habits (Frame et al., 2020), physical activity levels (Bycura et al., 2021), and the use of medications (Vich Vila et al., 2020). Within the gastrointestinal (GI) tract, a highly diverse and symbiotic microbial community interacts closely with intestinal epithelial cells and immune components. These microbes play crucial roles in maintaining gut health and facilitate bidirectional communication with the brain through the gut–brain axis, which is involved in brain development, neural regulation, and behavioral modulation (Yang et al., 2019).[1] Disruptions to this microbial balance, known as dysbiosis, have been implicated in various gastrointestinal and metabolic disorders such as inflammatory bowel disease (Greenblum et al., 2012), obesity (Turnbaugh et al., 2006), and diabetes (Qin et al., 2012). In addition, dysbiosis has also been linked to neuropsychiatric and neurodegenerative conditions including autism (Golubeva et al., 2017), major depressive disorder (Foster & Neufeld, 2013), Alzheimer's disease (Vogt et al., 2017), and Parkinson's Disease (PD) (Scheperjans et al., 2015a). For instance,

increased levels of *Akkermansia* have been consistently reported in individuals with PD across diverse geographical populations, suggesting a possible disease-related microbiota signature (Nishiwaki et al., 2020b). However, defining a universal "healthy" gut microbiota remains difficult due to individual variability and fluctuations over time.[13] A study involving 190 colonic tissue samples from participants with and without gastrointestinal disorders identified around 35,000 bacterial and archaeal species in the human gut, with the majority belonging to the *Bacteroidetes* and *Firmicutes* phyla (Frank et al., 2007; Rinninella et al., 2019). These beneficial microbes contribute to health by producing essential nutrients and fermenting indigestible fibers into short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate (Wells et al., 2017). SCFAs play multiple roles: they act as energy sources for intestinal cells, strengthen gut barrier function by regulating tight junction proteins, and modulate immune responses (Mathewson et al., 2016). Butyrate, in particular, supports immune balance by enhancing regulatory T cell populations (Tregs), which help control inflammation (Arpaia et al., 2013; Furusawa et al., 2013). Beneficial microbes such as *Faecalibacterium prausnitzii* contribute to anti-inflammatory effects by producing SCFAs and encouraging the release of anti-inflammatory cytokines while suppressing pro-inflammatory ones (Rossi et al., 2015; Lenoir et al., 2020).[21] A recent large-scale microbiome-wide association study involving two datasets (N = 333 and N = 507) found an increase in potentially harmful microbes and a decline in carbohydrate-metabolizing bacteria that produce SCFAs in people with PD (Wallen et al., 2020). These findings suggest that microbial imbalances may be linked to symptom severity in PD.[3] Furthermore, animal studies provide supporting evidence for this relationship. Germ-free mice, or those treated with broad-spectrum antibiotics to reduce gut microbes, exhibit physiological changes relevant to neurological diseases, such as increased blood-brain barrier permeability. In a small human study involving 14 patients with PD, antibiotic treatment led to significant improvement in motor symptoms, including reduced dyskinesia, shorter "off" periods, improved functionality, and less fluctuation in motor performance (Baizabal-Carvallo et al., 2021). These findings highlight the potential for microbiota-targeted therapies in the management of PD symptoms.

V. Gastrointestinal Symptoms, Gut Microbiota, And Their Link To Parkinson's Disease:

Non-motor symptoms such as gastrointestinal (GI) disturbances—including constipation—often appear well before the onset of classical motor symptoms associated with Parkinson's Disease (PD) (Klingelhoefer & Reichmann, 2015). In fact, more than 80% of individuals diagnosed with PD experience some degree of GI dysfunction during the progression of their condition (Pfeiffer, 2011). Supporting this, data from the Honolulu Heart Program indicated that males aged 51–75 who had less than one daily bowel movement had a 2.7-fold higher risk of developing PD compared to those with more frequent bowel movements (Abbott et al., 2001).[11] While research exploring the gut–brain connection in neurodegenerative diseases is still evolving, current evidence points toward the gut microbiome playing a role in initiating and advancing PD in certain individuals (Gorecki et al., 2019; Yang et al., 2019; Liu et al., 2020). There is increasing interest in the link between disrupted gut microbial diversity and conditions that are known risk factors or prodromal symptoms for PD, such as insomnia, REM sleep behavior disorder (RBD), and constipation. Notably, about 40–65% of individuals with RBD develop a neurodegenerative disease within a decade (Postuma et al., 2009; Heinzel et al., 2021), and in one study involving 172 RBD patients, 94% of those with additional neurodegenerative diagnoses had a synucleinopathy (Boeve et al., 2013). The gut microbiome may influence the connection between RBD and PD. For instance, individuals with RBD have shown increased levels of *Akkermansia*—a mucin-degrading bacterial genus commonly elevated in PD (Romano et al., 2021)—as reported in various studies (Heintz-Buschart et al., 2018; Nishiwaki et al., 2020a; Earley et al., 2019).[19] Colonic motility is regulated by circadian rhythms, akin to the suprachiasmatic nucleus in the brain. However, this rhythm can be disrupted by external stimuli such as light, diet, and exercise (Duboc et al., 2020). Disrupted sleep patterns have been associated with pathological processes like inflammation, stress responses, and impaired neural waste clearance, which may raise PD risk (Bohnen & Hu, 2019). Moreover, the spread of misfolded α-synuclein protein through brain networks—a key hypothesis in PD—may be influenced by sleep-related disturbances that alter neural circuits (Yau et al., 2018). These sleep issues, and their possible bidirectional relationship with microbial dysbiosis, may form a feedback loop contributing to PD progression. Numerous studies have identified distinct microbial patterns in PD patients compared to healthy individuals and even across PD subtypes (Heintz-Buschart et al., 2018; Heinzel et al., 2021). In one study using A53T transgenic monkey models of early-stage PD, researchers observed microbial changes resembling those seen in human PD—such as elevated *Akkermansia*, *Eggerthella*, and *Synergistetes*, and reduced *Prevotella* (Yan et al., 2021a). Human studies similarly report increased levels of *Akkermansia*, *Lactobacillus*, and *Bifidobacterium*, and decreased levels of *Prevotella*, *Faecalibacterium*, *Bacteroidetes*, and *Blautia* in individuals with PD (Keshavarzian et al., 2015; Scheperjans et al., 2015a; Li et al., 2017; Barichella et al., 2019).[17] These microbial imbalances—collectively termed **dysbiosis**—are thought to influence disease severity. For instance, the genera *Lactobacillus*, *Enterococcus*, *Escherichia*, and *Proteus* have been positively correlated with higher scores on the Unified Parkinson's Disease Rating Scale (UPDRS), indicating worse symptoms. In contrast, genera like *Blautia*, *Faecalibacterium*, and *Ruminococcus* show negative correlations with

UPDRS scores, implying a protective role (Li et al., 2017; Barichella et al., 2019). Additionally, the family *Lachnospiraceae* has been linked to reduced postural instability and gait disturbance, while *Enterobacteriaceae* has been associated with overall symptom severity (Scheperjans et al., 2015a). Markers of inflammation and levels of short-chain fatty acids (SCFAs) in stool samples tend to inversely correlate with microbial alpha diversity. Certain bacteria such as *Akkermansia*, *Escherichia/Shigella*, *Flavonifractor*, and *Sporobacter* are associated with reduced SCFA levels, while bacteria like *Butyricicoccus*, *Clostridium sensu stricto*, and *Roseburia* are associated with higher SCFA production. However, these findings are correlational, and various external factors—such as medication, diet, physical activity, and disease-related changes in gut transit—may also influence the microbiota.[18] It remains unclear whether the observed microbiota shifts are consequences of disease progression or act as causal contributors to PD onset. Considering the complexity of PD's clinical manifestations and the reciprocal relationship between host and microbial communities (Markello et al., 2021), it's plausible that microbiota alterations may serve both as consequences of PD and as drivers of its pathology. The influence of gut microbes on host physiology is determined not just by the types of microbes present but also by their abundance—both of which are shaped by intrinsic and extrinsic factors including genetics, age, diet, and medication use (Hasan & Yang, 2019). Healthy gut microbiota are believed to support neuroimmune balance within the central nervous system, while dysbiosis may trigger neuroinflammation and elevate the risk of neurodegeneration (Sampson & Mazmanian, 2015). This microbial imbalance can impair gut barrier function, leading to translocation of microbial products such as lipopolysaccharide (LPS) into systemic circulation and subsequent inflammatory signaling (Mulak & Bonaz, 2015).[1] Furthermore, certain bacteria may interact directly with the enteric nervous system via secreted amyloids and neurotransmitters, potentially influencing bowel motility through vagal nerve signaling (Bonaz et al., 2018). Some signs of dysbiosis, such as elevated urinary indoxyl sulfate and reduced *Prevotellaceae* abundance in stool, have been observed in PD (Cassani et al., 2015; Scheperjans et al., 2015a). Notably, lower *Prevotellaceae* levels are inversely associated with motor symptom severity as measured by UPDRS Part III (Gerhardt & Mohajeri, 2018), although the functional roles of different *Prevotellaceae* species in PD are still not fully understood.

VI. Microbiota, Intestinal Barrier Integrity, And Parkinson's Disease Pathophysiology:

Emerging evidence suggests a critical link between gut microbiota composition and increased intestinal permeability, which has been observed in patients with Parkinson's Disease (PD). This compromised gut barrier may contribute to the pathological misfolding and aggregation of α-synuclein, a hallmark feature of PD (Forsyth et al., 2011; Clairembault et al., 2015). Biomarkers indicating gut inflammation and impaired barrier function, such as elevated fecal levels of calprotectin, zonulin, and alpha-1-antitrypsin, have been reported in individuals with PD compared to healthy controls (Schwiertz et al., 2018).[10] Histological studies examining sigmoid colon tissue from PD patients have further demonstrated reduced expression of tight junction proteins such as ZO-1 and occludin, alongside abnormal localization of these proteins, signifying structural disruption of the gut epithelial barrier (Clairembault et al., 2015). To date, only a handful of studies—specifically four—have directly assessed intestinal permeability in PD, with three employing non-invasive sugar probe tests rather than tissue biopsies. Notably, one study identified a significant association between increased intestinal permeability and intestinal α-synuclein expression, the presence of *Escherichia coli*, and elevated serum levels of lipopolysaccharide-binding proteins (Forsyth et al., 2011).[11] Beyond their local effects, gut microbes may also influence neurodegenerative pathways by altering blood-brain barrier (BBB) permeability, thus potentially affecting α-synuclein accumulation in the central nervous system (Braniste et al., 2014). Although considerable data point to a connection between gut dysbiosis, inflammation, and PD development, the precise molecular pathways linking these factors remain largely undefined.[17] One potential contributor is the PINK1 gene, which is commonly mutated in familial forms of PD. PINK1 plays a key role in mitochondrial quality control and immune modulation (Gonçalves & Morais, 2021). Research by Matheoud et al. (2016) demonstrated that PINK1 can suppress antigen presentation originating from damaged mitochondria following lipopolysaccharide (LPS) exposure. More recently, they proposed that loss of PINK1 may result in the abnormal presentation of mitochondrial antigens after intestinal infection or stress, leading to impaired dopaminergic neuron function (Matheoud et al., 2019; Herrick & Tansey, 2019).[17] These findings are consistent with clinical observations where PD symptoms, particularly motor dysfunction, tend to worsen during peripheral infections (Umemura et al., 2014). Collectively, these insights suggest that PINK1 acts as an immune regulatory factor and that intestinal infections may serve as environmental triggers for PD onset or progression. This evidence supports the increasingly recognized role of the gut-brain axis in PD pathogenesis (Houser & Tansey, 2017).

VII.Potential Mechanisms Underlying Gut–Brain Axis Communication In Parkinson's Disease:

The concept of a two-way communication system between the gastrointestinal (GI) tract and the brain—commonly referred to as the gut–brain axis—has been explored for decades through numerous experimental approaches, including germ-free (GF) animal models, infection-based studies, and interventions using antibiotics,

prebiotics, and probiotics (Bravo et al., 2012). Increasingly, research indicates that commensal gut bacteria may influence the progression of Parkinson's Disease (PD) by modulating both immune and neural pathways, including the enteric and central nervous systems.[19] Neurologically, the GI tract is regulated by a sophisticated network involving the myenteric and submucosal plexuses, as well as enteric glial cells. Catecholaminergic neurons, which play a key role in dopamine signaling, are located in close proximity to the gut lumen (Chesné et al., 2019). The vagus nerve, a major component of the parasympathetic nervous system, connects the enteric nervous system (ENS) to central brain regions. Vagal afferents terminate in the mucosa of the gut and can respond to stimuli such as lipopolysaccharide (LPS), a proinflammatory endotoxin released by Gram-negative bacteria (de La Serre et al., 2015). Notably, elevated levels of LPS can stimulate these neurons, potentially leading to appetite suppression and weight loss—symptoms commonly seen in PD patients (Gakis et al., 2009).[19] In PD, microbial imbalance or dysbiosis has been linked to increased production of LPS and inflammatory cytokines, contributing to epithelial damage and weakening of the intestinal barrier (van IJzendoorn & Derkinderen, 2019). This increased permeability can facilitate the movement of bacteria-derived toxins and host-derived inflammatory molecules such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1 (IL-1) into systemic circulation (Obrenovich, 2018). Once in the bloodstream, these substances may compromise the blood–brain barrier (BBB), potentially promoting neuroinflammation and contributing to the pathogenesis and progression of PD (Brodacki et al., 2008; Rentzos et al., 2009; Eidson et al., 2017; Houser & Tansey, 2017; Kim et al., 2018; Rathnayake et al., 2019).[18] Germ-free animal models have offered crucial insights into the role of the microbiota in nervous system development. Animals raised in germ-free conditions show abnormal development in both the ENS and CNS. This includes slowed gastric emptying, prolonged intestinal transit, and disruptions in motility patterns like the migrating myoelectric complex. Additionally, these animals exhibit changes in gene expression tied to neurotransmission, muscle contractility, and brain-derived neurotrophic factor (BDNF) levels, which are vital for neuronal survival and function (Carabotti et al., 2015).[13] Moreover, these animals also display increased BBB permeability, likely due to the absence of beneficial microbial metabolites such as short-chain fatty acids (SCFAs), which normally support barrier function. Colonization of germ-free animals with healthy microbiota can reverse many of these abnormalities, reinforcing the critical role of microbiota in the maintenance of barrier integrity and neurodevelopment (Ma et al., 2019).[4] Altogether, these findings strongly support the existence of a dynamic and essential communication system between the gut and the brain. This interaction, largely mediated by gut microbiota, appears to be crucial not only for maintaining gut and neural function but also for understanding the pathophysiology of neurodegenerative conditions like PD.

VIII. The VAGUS Nerve As A Link Between The Gut And Brain:

The vagus nerve serves as a major conduit in the communication between the gut and the brain. This interaction can occur either directly via microbial signaling or indirectly through microbiota-stimulated enteroendocrine cells. These cells release various signaling molecules—such as cholecystokinin, 5-hydroxytryptamine (serotonin), and peptide YY—that activate vagal afferent neurons, ultimately relaying signals to the central nervous system (Bellono et al., 2017).[12] The possible involvement of the vagus nerve in Parkinson's disease (PD) has been investigated through several retrospective studies examining whether vagotomy—a surgical procedure that involves severing sections of the vagus nerve—has any influence on PD risk. A large cohort study involving more than 14,000 patients who had undergone vagotomy suggested a reduced risk of developing PD in individuals who received a **truncal vagotomy** (which severs both anterior and posterior vagal trunks), although the findings did not reach statistical significance (Svensson et al., 2015; Liu et al., 2017). In contrast, another study with over 9,400 vagotomized individuals followed across 7.3 million person-years reported no clear association between vagotomy and PD risk, indicating a lack of consensus on this potential protective effect (Liu et al., 2017).[10] Interestingly, some recent experimental findings challenge the idea that the vagus nerve is the sole or primary route of disease propagation. For instance, a non-human primate study revealed evidence of both upward (caudo-rostral) and downward (rostro-caudal) propagation of pathological alpha-synuclein (α-syn) without any associated damage in the vagus nerve, suggesting alternative routes of transmission (Arotcarena et al., 2020). Similarly, a rat model study found that overexpression of α-syn in the substantia nigra resulted in downstream pathological changes in the gut, including neuronal loss in the ileal submucosal plexus, increased glial cell activity in the myenteric plexus, disruptions in the gut microbiome, and altered bile acid metabolism. These changes indicate that brain-to-gut signaling pathways may operate independently of the vagus nerve (O'Donovan et al., 2020).[17] Together, these findings suggest that while the vagus nerve plays a significant role in gut–brain communication, it may not be the exclusive pathway for the progression of PD-related pathology. Further investigations are warranted to clarify the various mechanisms by which α-syn pathology propagates, which may have important implications for early detection and the development of targeted therapies.

IX. Gut Microbiota And Efficacy Of Immunotherapies And Medications For Parkinson's Disease:

Immunotherapy, widely recognized for its role in cancer treatment, is gaining attention as a potential therapeutic strategy for Parkinson's disease (PD) and other neurodegenerative disorders characterized by immune dysregulation. In PD, immune dysfunction often manifests as a reduction in both the number and activity of regulatory T cells (Tregs), which play a crucial role in suppressing excessive immune responses (Williams-Gray et al., 2018; Yan et al., 2021b). Research by Sulzer et al. (2017) revealed that T cells in individuals with PD can recognize specific α-synuclein-derived epitopes presented by certain MHC alleles, thereby initiating both helper and cytotoxic T-cell responses. Furthermore, α-syn-specific T cells have been linked with early or even preclinical stages of PD (Lindestam Arlehamn et al., 2020).[12] Emerging data suggest that gut microbiota-derived metabolites, especially short-chain fatty acids (SCFAs) such as butyrate, may enhance immunotherapy efficacy by promoting CD8+ T cell activation within the local tissue microenvironment (He et al., 2021). In support of this, Lione et al. (2021) observed that microbial diversity—particularly when disrupted using antibiotic cocktails—negatively affected the immune response following administration of a neoantigen-based cancer vaccine. Although the exact mechanisms connecting gut microbial activity to immune modulation in PD are still being uncovered, these findings support the concept that microbiota play a pivotal role in regulating host immunity and treatment responsiveness.[15] Building on this connection, Klann et al. (2020) investigated the gut microbiota's involvement in a novel adoptive T cell therapy targeting α-syn in PD. Following treatment, a clear divergence in gut microbial composition was observed between treated and control animals. Notably, bacterial taxa such as *Odoribacter*, known butyrate producers, were enriched in the treatment group. This points toward a dynamic interaction between the immune system and the gut microbiota in PD. However, whether these changes influence the therapeutic response or are a consequence of the intervention and disease progression remains unclear. Beyond immunotherapy, gut microbiota are also implicated in the absorption and effectiveness of orally administered PD medications. Certain bacterial strains, including *Enterococcus faecalis* and *Eggerthella lenta A2*, have been shown to metabolize L-dopa before it can reach the brain, thereby diminishing its efficacy (Rekdal et al., 2019). Additionally, anti-Parkinsonian drugs such as levodopa and LD-carbidopa intestinal gel are themselves capable of altering gut microbial composition and function (Melis et al., 2021). In a study of 107 PD patients, significant differences in gut microbiota profiles were observed between medication-naïve individuals and those receiving levodopa or LD-carbidopa intestinal gel. For instance, the LD-carbidopa group exhibited increased levels of *Enterobacteriaceae*, *Escherichia*, and *Serratia*, while both medication groups showed reduced abundance of *Firmicutes*, *Lachnospiraceae*, and *Blautia* compared to the naïve group. These shifts were also associated with metabolic signatures indicative of intestinal inflammation.[17] Such findings underscore a bidirectional relationship wherein gut microbiota influence drug metabolism and treatment efficacy, while the medications themselves reshape the microbial landscape. Targeting bacterial strains that inactivate PD drugs could offer a novel approach to enhance therapeutic outcomes. Similarly, consistent alterations in gut microbiota due to medication may justify probiotic supplementation to mitigate inflammation or dysbiosis-induced symptoms. A study by Hill-Burns et al. (2017), involving 197 PD patients and 130 controls, identified specific microbial signatures associated with commonly prescribed PD medications, including catechol-O-methyltransferase inhibitors, anticholinergics, and carbidopa/levodopa.[13] This interplay suggests that medication-induced changes in gut microbiota should be considered a confounding factor in microbiome research. To reduce variability, studies should ideally control for medication type, dosage, and duration. Additionally, identifying bacterial species associated with both PD pathology and treatment could improve patient stratification in future studies.

X. Microbiota-Targeted Interventions For Parkinson's Disease:

Emerging evidence suggests that targeted modulation of the gut microbiota through prebiotics and probiotics could offer a promising therapeutic approach in neurodegenerative conditions such as PD. During adolescence, such interventions may build resilience to future neurological decline by influencing biochemical pathways involved in neurogenesis and inflammation regulation. For example, microbial metabolites like ferulic acid can promote neuronal growth, while others such as histamines reduce pro-inflammatory cytokines like TNF-α and downregulate Toll-like receptor (TLR) signaling. Additionally, molecules like ghrelin contribute to improved synaptic plasticity and reduction of oxidative stress (Yahfoufi et al., 2020).[18] In PD, probiotic therapy is hypothesized to exert beneficial effects by correcting dysbiosis, reducing intestinal permeability ("leaky gut"), and suppressing gut inflammation (Castelli et al., 2020; Ghyselinck et al., 2021). A study using the *Caenorhabditis elegans* model demonstrated that supplementation with the *Bacillus subtilis* strain PXN21 could reduce pre-existing α-synuclein aggregates and prevent the formation of new ones. The authors attributed part of this effect to DAF-16, a transcription factor specific to the worm model, which is involved in stress response and longevity pathways (Goya et al., 2020).[17] Human trials exploring probiotics in PD remain limited but are expanding, particularly in addressing gastrointestinal symptoms like constipation—a common non-motor symptom in PD. A

randomized, double-blind, placebo-controlled clinical trial involving 120 PD patients with clinically confirmed constipation showed promising results. Participants receiving a daily fermented milk beverage containing both prebiotic fructooligosaccharides (FOS) and a multi-strain probiotic blend (including *Streptococcus*, *Enterococcus*, *Lactobacillus*, and *Bifidobacterium* species) experienced improvements in bowel movement frequency, stool consistency, and a reduced need for laxatives (Barichella et al., 2016). These findings support the role of microbiota-targeted interventions in alleviating PD-associated gastrointestinal issues and potentially modulating broader disease processes.[24] A randomized, double-blind, placebo-controlled trial conducted by Tamtaji et al. (2019) evaluated the effects of probiotic supplementation on motor function and metabolic outcomes in individuals with Parkinson's disease (PD). Participants were assigned to receive either a probiotic formulation (including *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum*, each at a concentration of 2×10^9 CFU) or a placebo, administered daily over a 12-week period. Results revealed that individuals receiving probiotics experienced an approximate five-point reduction in their Unified Parkinson's Disease Rating Scale (UPDRS) scores, in contrast to a four-point increase observed in the placebo group. However, as the study did not break down results by specific subcomponents of the Movement Disorder Society-UPDRS (MDS-UPDRS), it remains unclear whether the improvements were more closely tied to motor or non-motor symptoms. Despite the promising trend, a five-point reduction, given the full scale range of 0–195, may not represent a clinically meaningful improvement.[37] In addition to motor function, individuals in the probiotic group showed notable reductions in oxidative stress markers and reactive oxygen species—both implicated in α-synuclein aggregation (Scudamore and Ciossek, 2018)—as well as lower levels of C-reactive protein, insulin, and insulin resistance compared to the placebo group. Another mechanism potentially modulating gut microbiota involves the hypothalamic–pituitary–adrenal (HPA) axis, a key regulator of immune and inflammatory responses. A study using germ-free (GF) mice demonstrated that colonization with *Bifidobacterium infantis* was able to reverse stress-induced activation of the HPA axis, possibly through neural or cytokine-based signaling pathways (Miraglia and Colla, 2019). This suggests that probiotics may not only address PD-related symptoms but could also reduce systemic inflammation via modulation of hormonal and immune responses.[1] Mood-related comorbidities such as depression, anxiety, and apathy are also frequently reported in PD patients (Aminian and Strafella, 2013). Although no PD-specific studies have directly targeted the gut–brain axis for these symptoms, research in other neurological conditions offers valuable insights. For instance, administration of *Bifidobacterium breve* strain A1 in individuals with schizophrenia led to a 25% reduction in anxiety and depression symptoms (Okubo et al., 2019). Likewise, prebiotic interventions in children with autism spectrum disorder yielded similar beneficial outcomes (Grimaldi et al., 2018). These findings suggest the possibility of using microbial-based therapies to alleviate psychological manifestations in PD.[14] Mechanistically, microbial metabolites may influence host behavior by stimulating enteroendocrine cells, which in turn release hormones such as cholecystokinin and glucagon-like peptide 1 (GLP-1) (Noonan et al., 2020). GLP-1 has shown neuroprotective effects in Alzheimer's disease mouse models by inhibiting TNF production and preserving synaptic function (Kim et al., 2020). Meanwhile, cholecystokinin has been implicated in regulating gut motility and neural signaling via vagal afferents (Breit et al., 2018; Zhao et al., 2018). Probiotics, additional microbiome-modulating interventions include antibiotics, fecal microbiota transplantation (FMT), and dietary changes. While antibiotics carry the risk of promoting resistance and disrupting microbial diversity, certain agents like doxycycline have exhibited anti-inflammatory and antioxidant properties relevant to neurodegenerative diseases (Sultan et al., 2013; Santa-Cecília et al., 2019). Minocycline, for example, crosses the blood–brain barrier and has been shown to protect dopaminergic neurons in MPTP-induced PD models (Du et al., 2001), possibly by modulating Toll-like receptor 4 (TLR4), a receptor activated by lipopolysaccharides from Gram-negative bacteria (Velloso et al., 2015).[12] Studies have also observed a higher prevalence of bacteria such as *Escherichia coli* and *Ralstonia* species in PD patients, correlating with enteric nervous system inflammation and increased proinflammatory markers like TNF, IFN-γ, and various interleukins (Forsyth et al., 2011; Keshavarzian et al., 2015; Yang et al., 2019). Such inflammatory activity may potentially be mitigated by bacteriophages or targeted antibiotic treatments.[11] FMT, a process where gut flora from a healthy donor is transferred into a patient's gastrointestinal tract, has demonstrated efficacy in treating recurrent *Clostridium difficile* infections and is being explored for neurological conditions such as multiple sclerosis (Makkawi et al., 2018), autism (Kang et al., 2019), ALS (Mandrioli et al., 2019), and Alzheimer's disease (Sun et al., 2019). Similarly, dietary and lifestyle factors are gaining attention as potential adjunct therapies for PD. High intake of processed foods and a Western dietary pattern have been linked to gut dysbiosis, which could influence PD risk and progression (Scheperjans et al., 2015b; Jackson et al., 2019). Caffeine consumption has also been associated with altered gut microbiota and potentially protective effects against PD. One novel concept is molecular mimicry, which proposes that microbial proteins may resemble host proteins, thus triggering immune responses. For instance, α-synuclein may act as a microbial mimic, activating TLR2 on microglial cells (Kim et al., 2013). Supporting this, Sampson et al. (2020) demonstrated that curli proteins from *E. coli* promoted α-syn aggregation in Thy1-αSyn mice, leading to both gastrointestinal and motor symptoms. Similarly, administration of short-chain fatty acids (SCFAs) in α-syn

transgenic mice induced neuroinflammation and motor dysfunction, which was attenuated by minocycline treatment targeting TNF signaling (Miraglia and Colla, 2019).[8] Anti-TNF therapies, widely used for inflammatory conditions such as IBD, are now being investigated for neurodegenerative applications. A large-scale cohort study found that individuals with IBD who received anti-TNF treatment had a 78% lower incidence of PD compared to those without such treatment (Peter et al., 2018). Although promising, anti-TNF drugs are immunosuppressive and should be used cautiously, particularly in older adults. Emerging data from both human and animal studies point toward the potential of prebiotic and probiotic interventions to positively affect various PD-related outcomes—including improvements in gastrointestinal symptoms, reductions in inflammatory markers, better motor control, and lowered MDS-UPDRS scores (Tables 1, 2). However, more research is necessary to determine the long-term effectiveness and feasibility of such strategies.[6]

Table B (1) | Summary Of Recent Pre- And Probiotic Studies Related To Parkinson's Disease In Humans.

Study design	Sample size	Pre/probiotic	Frequency of use	Main findings
Randomized controlled trial	40 PD patients in probiotic arm	65 mL fermented milk drink containing 6.5 × 109 CFU of Lactobacillus casei Shirota daily	Once per day for 5 weeks	↑ Number of days with normal stool consistency; ↓ number of days feeling bloated, abdominal pain, and incomplete colon emptying
Double-blind, randomized, placebo-controlled trial	34 PD patients in probiotic arm; 38 PD patients in placebo arm	10 billion CFU of Lactobacillus acidophilus, L. gasseri, L. reuteri, L. rhamnosus, Bifidobacterium bifidum, B. longum, Enterococcus faecalis, E. faecium	Once per day for 4 weeks	↑ Number of spontaneous bowel movements, improvement of stool consistency and quality of life related to constipation
Double-blind, randomized, placebo-controlled trial	80 PD patients in pre/probiotic mixture arm; 40 PD patients in placebo arm	250 × 10^9 CFU of Streptococcus salivarius subsp. thermophilus, Enterococcus faecium, Lactobacillus rhamnosus GG, L. acidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus, Bifidobacterium (breve and animalis subsp. lactis)	Once per day for 4 weeks	↑ Number of complete bowel movements per week
Double-blind, randomized, placebo-controlled trial	30 PD patients in probiotic arm; 30 PD patients in placebo arm	2 × 10^9 CFU/g each of Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri, and Lactobacillus fermentum	Once per day for 12 weeks	↓ MDS-UPDRS, C-reactive protein, insulin, and malondialdehyde levels; ↑ glutathione levels, insulin sensitivity
Randomized placebo-controlled trial	40 total PD patients, all increased water (2 L/day) and fiber intake (20–25 g/day); 20 patients in trimebutine arm; 20 patients in probiotic arm	60 mg of Lactobacillus acidophilus and Bifidobacterium infantis	Trimebutine: 200 mg, 3 times per day for 3 months Probiotic mixture: 2 times per day for 3 months	Trimebutine: ↓ abdominal pain, bloating, constipation, incomplete defecation Probiotic mixture: ↓ abdominal pain and bloating
Double-blind, randomized, placebo-controlled trial	25 PD patients in probiotic arm; 25 PD patients in placebo arm	2 × 10^9 CFU each of Lactobacillus acidophilus, Bifidobacterium bifidum, L. reuteri, and Lactobacillus fermentum	Once per day for 12 weeks	↓ Expression of IL-1, IL-8, TNF (inflammatory cytokines); ↑ expression of TGF-β and PPAR-γ (immunoregulation factors)
Randomized placebo-controlled trial	22 PD patients in probiotic arm; 26 PD patients in placebo arm	Hexbio® - 30 × 10^9 CFU (107 mg each) of Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Bifidobacterium infantis, and Bifidobacterium longum; 2% fructo-oligosaccharide prebiotic	2 times per day for 8 weeks	↑ Average bowel opening frequency; ↓ gut transit time

A proactive approach to maintaining a neuroprotective gut microbiome throughout life may offer resilience against neurodegenerative conditions. Early diagnosis of PD subtypes could facilitate personalized interventions aimed at correcting gut dysbiosis. For instance, a study in Taiwan found that non-tremor dominant PD patients had a higher abundance of *Bacteroides* species—correlated with elevated TNF-α levels and motor symptom severity—while both tremor and non-tremor PD groups showed reduced levels of *Prevotella* compared to healthy individuals (Lin et al., 2019). These findings suggest that gut microbiota profiling may assist in the early identification of PD phenotypes, potentially leading to more targeted and effective therapies.

Table C (2) | Summary Of Recent Pre- And Probiotic Studies In Animal Models Of Parkinson's Disease.

Study design	Sample size	Pre/probiotic	Frequency of use	Main findings
Randomized	15 male C57BL/6 mice with	270 µl of SLAB51 (*Streptococcus*	Once per day for	Counteraction of 6-OHDA-induced
controlled trial	6-OHDA lesions; 15 male	*thermophilus*, *Bifidobacterium longum*,	2 weeks	effects; ↓ neuroinflammation
	C57BL/6 mice with no lesions	*B. breve*, *B. infantis*, *Lactobacillus*		
		acidophilus, *L. plantarum*, *L. paracasei*,		
		L. delbrueckii subsp. *bulgaricus*,		
		L. brevis)		
Randomized	10 MitoPark PD mice in	10^{10} CFU of *Bifidobacterium bifidum*,	Once per day for	↑ Motor coordination, preservation
placebo-controlled	treatment group; 10 MitoPark	*Bifidobacterium longum*, *Lactobacillus*	16 weeks	of TH+ cells in SNpc; ↓ gait
trial	PD mice in placebo group	*rhamnosus*, *Lactobacillus rhamnosus*		instability
		GG, *Lactobacillus plantarum LP28*,		
		Lactococcus lactis subsp. *lactis*		
Randomized	10 male Wistar rats in probiotic	2×10^9 CFUs each of *Lactobacillus*	Once per day for	↑ Rotational behavior and cognitive
placebo-controlled	and 6-OHDA arm; 10 male	*acidophilus*, *Bifidobacterium bifidum*,	2 weeks	function; ↓ lipid peroxidation and
trial	Wistar rats in 6-OHDA arm; 10	*Lactobacillus reuteri*, *Lactobacillus*		neuronal damage
	male Wistar rats in	*fermentum*		
	placebo/control arm;			
Randomized	8 groups (7 male C57BL/6	$8 \pm 2 \times 10^8$ CFU/mL each of	Once per day for	↑ Motor skills, TH+ cell counts,
placebo-controlled	mice each): treatment and	*Lactobacillus plantarum CRL 2130*,	3 weeks	IL-10 counts in serum/brain tissue;
trial	placebo groups for each	*Streptococcus thermophilus CRL 807*,		↓ IL-6 and TNF counts in serum
	individual probiotic strain,	*Streptococcus thermophilus CRL 808*		
	treatment and placebo groups			
	for 3-strain mixture			
Randomized	26 C57Bl6/J male mice in	VSL#3®: 5.4×10^9 CFU of	Once per day for	↓ LPS- and paraquat-induced
placebo-controlled	probiotic group; 26 C57Bl6/J	*Streptococcus thermophilus*,	4 weeks	weight loss
trial	male mice in dextran sodium	*Bifidobacterium breve*, *B. lactis*,		
	sulfate group; 26 C57Bl6/J	*Lactobacillus acidophilus*, *L. plantarum*,		
	male mice in placebo group	*L. paracasei*, *L. helveticus*		
Randomized	6 groups (12 male C57BL/6	10^7 or 10^9 CFUs of engineered	Once per day for 1	↓ MPTP-induced locomotor
placebo-controlled	mice each): MPTP only,	probiotic (MG1363-pMG36e-GLP-1)	week (pre- treatment	impairments, microglia and
trial	probiotic (10^7 CFU) prior to	that continually expresses GLP-1 (Chen	groups); Once per day	astrocyte activation, expression of
	MPTP, probiotic (10^7 CFU) and	et al., 2018)	for 14 days (treatment	inflammatory cytokines, enteric
	MPTP simultaneously, probiotic		for entire study period)	*Enterobacteriaceae*; ↑ TH+
	(10^9 CFU) prior to MPTP,			neurons, enteric *Lactobacillus* and
	probiotic (10^9 CFU) and MPTP			*Akkermansia*
	simultaneously, placebo group			

XI. Discussion And Future Perspectives:

With the global incidence of Parkinson's disease (PD) expected to rise substantially in the coming decades (Marras et al., 2018), it has become increasingly important to uncover the distinct pathological mechanisms contributing to its onset and progression. Among these, the gut–brain axis has garnered significant attention as a potential factor influencing disease development and trajectory.[7] Research into this field is rapidly evolving but remains complex, largely due to the numerous variables that can affect the gut microbiota's interaction with PD. These include dietary patterns, lifestyle choices, systemic inflammation, the presence of other health conditions, and the use of medications or supplements. Although growing evidence supports the relevance of the gut–brain axis in PD, further studies are necessary to clarify the extent of this bidirectional relationship and to uncover the underlying biological mechanisms.[15] Findings presented in this review suggest that α-synuclein aggregation along the gut–brain axis may not rely solely on the vagus nerve pathway. Other possible contributors include immune signaling, gut-derived hormones, and microbial metabolites. The initiation and spread of α-synuclein aggregates originating in the gastrointestinal tract might represent an early, preclinical stage of PD, potentially giving rise to the motor and non-motor symptoms that characterize the disease.[13] However, it remains unclear whether enterically derived pathological α-synuclein is a consequence of subtle changes in the brain that precede PD diagnosis, or whether disruptions in gut microbiota composition occur prior to and actively contribute to disease onset—or possibly both. Thus, pinpointing the direction and causality of this relationship is essential. Moreover, while results from animal models have provided valuable insights, their translational relevance to humans requires validation through well-designed clinical studies that consistently reproduce these findings in PD patients. A deeper understanding of the gut microbiota's role in PD pathogenesis may ultimately lead to the development of innovative diagnostic tools and targeted therapeutic strategies, improving disease management and patient quality of life.[3] Looking ahead, future research should also explore the practical aspects of microbiota-targeted therapies for PD—such as their effectiveness, patient adherence, and overall feasibility. Understanding how such interventions can be integrated into standard clinical care will be crucial in moving from theoretical promise to real-world application.

XII. Conclusion:

Despite advancements in symptomatic treatments, no current therapy can cure Parkinson's disease (PD). Levodopa remains the most commonly prescribed medication for managing motor symptoms; however, it does not halt neurodegeneration and has limited impact on non-motor manifestations. Additionally, gastrointestinal (GI) dysfunction in PD patients is known to contribute to variability in levodopa absorption and effectiveness.

Emerging evidence suggests that PD pathology may originate in the enteric nervous system (ENS), potentially triggered by environmental toxins or pathogens, and spread to the central nervous system (CNS) via transsynaptic, cell-to-cell transmission. The translocation of gut bacteria may further promote a pro-inflammatory state, capable of affecting the brain through systemic signaling and compromised blood-brain barrier function. Understanding the complex interplay between the gut and brain may offer valuable insights into PD progression and pave the way for novel therapeutic strategies. Future interventions—whether pharmacological or nutritional—should aim to address both motor and non-motor symptoms. Nutritional supplementation with membrane-forming precursors and cofactors may enhance neuronal membrane synthesis, support neural function, and reduce inflammation, thereby impacting both the ENS and CNS and improving PD-related abnormalities. Furthermore, probiotics, prebiotics, and synbiotics may help modulate gut microbiota composition, improve intestinal barrier integrity, and lower inflammatory responses, potentially slowing or preventing the advancement of neurodegeneration. These dietary approaches could positively influence PD pathogenesis. Notably, they have demonstrated benefits in alleviating GI dysfunction and may enhance levodopa bioavailability when co-administered—allowing for dose reductions and minimizing associated side effects. Given the promising preclinical data, there is a strong scientific basis for conducting rigorous, randomized, placebo-controlled clinical trials to evaluate the efficacy of dietary interventions—such as phospholipid precursors and microbiota-targeted therapies, alone or in combination—in individuals with PD.[OUT PUT]

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Abbreviation List:

S.NO	Abbreviation	Full Form
1	**PD**	Parkinson's Disease
2	**ENS**	Enteric Nervous System
3	**CNS**	Central Nervous System
4	**GBA**	Gut-Brain Axis
5	**α-syn**	Alpha-synuclein

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