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Neurons, Nerves, and the Microbial Nexus: Reimagining Parkinson's Disease from the Inside Out

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Abstract

Background:

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects over 10 million people in the world. PD is commonly characterized as the percentage loss of dopaminergic neurons in the substantia nigra and alpha-synuclein aggregation within the brain. New evidence indicates the gut-brain axis (GBA) and gut microbiota may play role in the pathogenesis of PD. Gastrointestinal symptoms can precede motor symptoms, hinting that perhaps there is a prodromal phase of PD characterized by gut dysbiosis and transneuronal propagation of initiator pathology.

Objective:

This systematic review aims to (1) describe the gut microbiota alterations observed in PD patients compared to healthy controls, (2) highlight potential mechanisms linking gut dysbiosis with progression of PD, and (3) summarize the effect of microbiome-based interventions to augment the symptoms of PD.

Methods:

In accordance with PRISMA 2020 guidelines, we conducted a systematic search of the literature using defined Boolean and MeSH terms and searched across databases including PubMed, ScienceDirect and Google Scholar. After removing duplicates, we identified 1,284 records. We identified 24 studies that met the inclusion criteria: (15 human clinical studies, 5 preclinical models, and 4 theoretical reviews). Inclusion criteria targeted studies that explored gut microbiota in PD from 2015–2024 that utilized either original research, animal models, or meta- analysis.

Results:

Altered gut microbiota profiles were reported across all PD studies, evidenced by the increase in Akkermansiaceae and Bifidobacteriaceae and significantly less common beneficial taxa such as Lachnospiraceae. Additionally, many studies reported dysregulation of short-chain fatty acids (SCFA), dysregulated intestinal permeability, and systemic inflammation. Common themes apparent through these studies included microbiota-induced neuroinflammation and misfolding of alpha-synuclein into aggregates, which could indicate an element of pathology progression. Microbiome-based interventions including the use of probiotics, prebiotics, dietary changes, and fecal microbiota transplantation (FMT) showed varied but promising benefits in advancing motor and non-motor symptoms of PD.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder worldwide, affecting more than 10 million people globally. It is pathologically characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta and the intracellular aggregation of pathological, misfolded alpha-synuclein protein in Lewy bodies. Clinically, PD presents with motor features, such as bradykinesia, rigidity, resting tremor, and postural instability, as well as an extensive list of associated non-motor symptoms, including gastrointestinal dysfunction, depression, cognitive decline, and sleep problems, many of which occur years before the onset of motor features (Bonaz, 2024; Menozzi et al., 2021).

Recent evidence links the gut-brain axis (GBA)—the bidirectional neurochemical signaling network between the central nervous system (CNS), enteric nervous system (ENS), and gut microbiota— to the pathophysiology of many neuropsychiatric and neurodegenerative disorders including PD (Carabotti et al., 2015; Cryan et al., 2019). The GBA encompasses a complex array of neural (vagal and spinal afferents), endocrine (HPA-axis) and immune mechanisms including those influenced by microbial-derived metabolites and systemic inflammation (Claudino dos Santos et al., 2023).

There is growing evidence indicating gut microbial dysbiosis—where there is altered diversity, richness, or composition of intestinal microbiota—may contribute to the pathogenesis of PD.

Several cross-sectional studies have observed similar changes in gut microbial composition of PD patients which includes decreased abundance of SCFA-producing taxa (i.e., Faecalibacterium, Prevotella) and enrichment of pro-inflammatory taxa (i.e., Enterobacteriaceae) that can impair gut barrier integrity, promote systemic endotoxemia, and activate alpha-synuclein aggregation and neuroinflammation (Hill-Burns et al., 2017; Bedarf et al., 2017; Sampson et al.,
2016). Enteric glial cells are also cited as essential innate regulators of gastrointestinal homeostasis, and they represent key players in neuroimmune modulation and the propagation of synucleinopathy (Claudino dos Santos et al., 2023). The observation that gastrointestinal symptoms, prominently

constipation, occur consistently more than a decade before motor symptoms supports the hypothesis that PD has a gut origin, with neuro-invasion of the CNS through trans-synaptic transmission via the vagus nerve (Houser & Tansey, 2017; Heintz- Buschart et al., 2018). The so-called "Braak hypothesis" could be further supported by experimental models, which demonstrate gut microbiota and modulate neuroinflammation, microglial activation, and dopaminergic neurodegeneration (Sampson et al., 2016). Despite these strong associations, the causal relations of gut dysbiosis and PD are very poorly defined. The literature is heterogeneous in methodology, lacks standard measures for analysis, and has limited longitudinal studies, all of which hinder conclusive definitions of specific microbial signatures or therapeutic targets. Nonetheless, emerging microbiome-centric interventions (e.g. probiotics, prebiotics, dietary changes and fecal microbiota transplantation (FMT)) show promise as adjunct strategies to mitigate disease progression or symptoms of PD (Tan et al., 2022; Romano et al.,

Considering the consistent increase in quantity and variability of studies investigating the microbiome in Parkinson's disease (PD), a systematic synthesis of the evidence is warranted. The review will have the following objectives:

1. To characterize the composition and diversity of gut microbiota in individuals with PD compared to healthy controls,
2. To assess the mechanistic relevance of gut dysbiosis for PD pathogenesis; based on human and animal studies,
3. To evaluate the potential of microbiome-targeted biomarkers based on clinical and preclinical studies.

This review aims to consolidate findings from studies with different study designs and methods, in order to clarify the role of the gut microbiome in PD, and to identify the next steps for biomarker development and microbiota-based therapeutics.

Methodology

This systematic review was conducted in accordance with reporting guidelines from the Preferred Reporting Items for Systematic Reviews 2020 (PRISMA-2020).

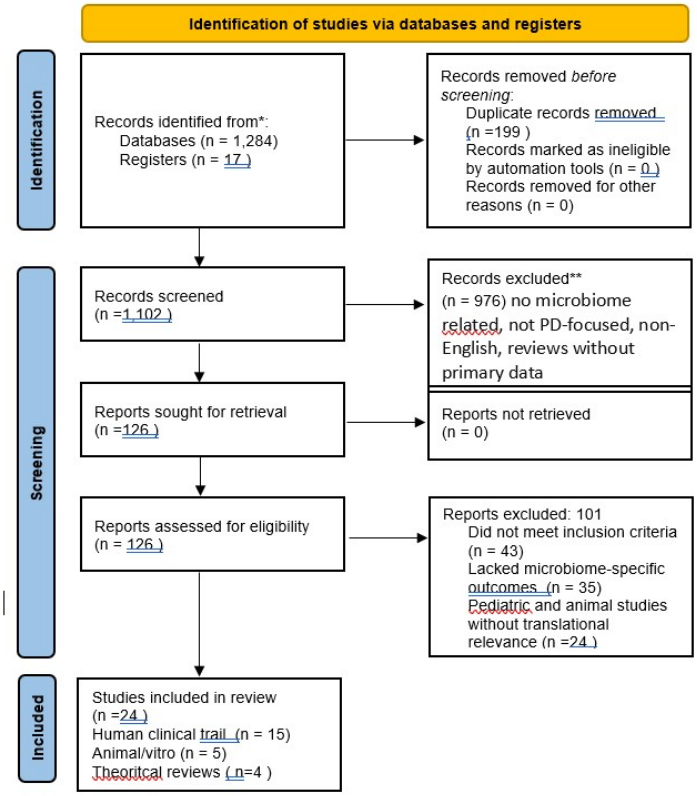
Search Strategy

We undertook a qualitative narrative review of the literature, to explore the intricate inter- relatedness between gut microbiota, inflammation, and α-synuclein pathology in PD. Through the evidence-based systematic review of the scientific literature we searched the databases PubMed, ScienceDirect and Google Scholar. Search terms were combinations of "Parkinson's disease", "gut-brain axis", "microbiota", "α-synuclein", "vagus nerve", "neuroinflammation", "enteric glial cells", and "microglial activation." We incorporated Boolean operators (AND, OR) and MeSH terms to constrain search results. Study selection

The study selection process was as follows: A total of 1,284 records were identified through database

searches (PubMed, Science Direct and Google Scholar) and an additional 17 records were identified through reference lists. After removing duplicates, 1,102 remained records were screened from title and abstract, with 976 excluded for the following reasons: Not microbiome- related, not Parkinson's disease (PD) related, not English, or reviews with no primary data. Of the remaining 126 full-text articles assessed for eligibility, 101 were excluded. The reasons for exclusion were: 43 did not specify inclusion criteria, 35 were not microbiome-specific outcomes, and 24 were either pediatric or animal only studies without translational relevance. Ultimately, 24 studies comprised the final quantitative synthesis; 15 studies with human clinical/clinical observational studies, 5 studies with animal /in vitro models; and 4 mechanistic or theoretical reviews.

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Articles from 2015 to March 2024

• Peer-reviewed Original Research, review articles and meta-analyses

• Animal models or human subjects trait

• Research on the gut-brain axis and pathological association with PD

The exclusion criteria were:

• Non-English

• No direct evidence of method or outcomes

• Articles without a direct implying Parkinson's disease mechanisms via the Articles without a direct implying Parkinson's disease mechanisms via the gut brain axis.

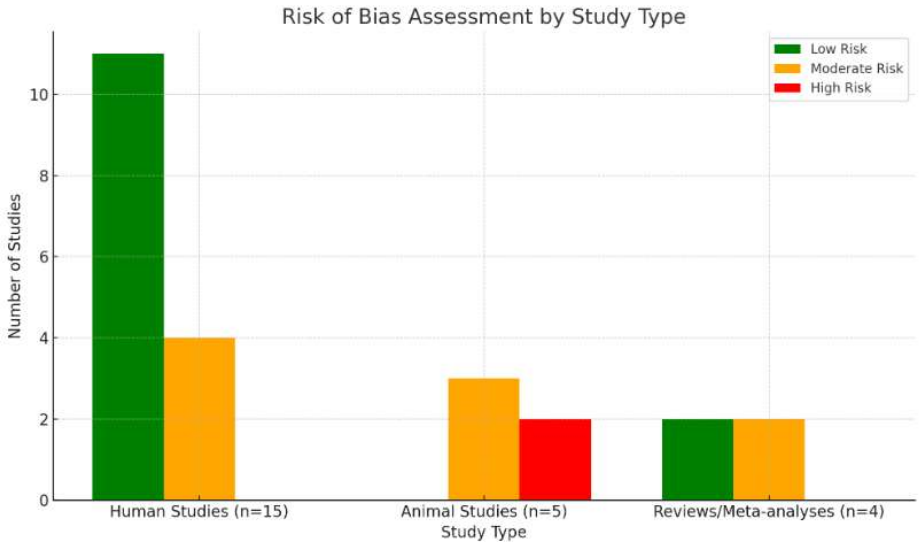
Risk of Bias Assessment and Assessment of Studies

In order to comprehensively assess the methodological quality of included studies, all studies were assigned to a study design category and assessed using an appropriate standardized risk of bias (RoB) assessments for that design.

All human observational studies (n = 8) were assessed with the Newcastle-Ottawa Scale (NOS) for the domains of Selection, Comparability, and Outcome Assessment.

The animal study (n = 1) used SYRCLE Risk of Bias tool and evaluated studies in the domains of Randomization, Blinding, Allocation Concealment, and Selective Reporting.All systematic reviews and meta-analyses (n = 3) included in the review were assessed with the AMSTAR-2 tool which surveyed the domains of Protocol Registration, Search Strategy, Risk of Bias Assessment, and Conflict of Interest.

All narrative reviews and perspective articles (n = 12) were excluded from the RoB analysis because there were no standardized tools for non-systematic reviews in the literature.



Results

Study Summaries

In total, 24 studies included in this review, published between 2015 and 2024. These studies examined the associations between gut microbiota, gut-brain axis, and PD pathogenesis, clinical presentation, and therapeutic implications. Studies included a diversity of methodology including observational studies, systematic reviews and meta-analyses, animal models, and metagenomics.

The majority of studies demonstrated a statistically significant difference in microbiota composition among PD patients compared to control populations with particular attention paid to Akkermansia, Prevotella and Bifidobacterium. Other common themes included variations in SCFA levels, gut inflammation, and microbial metabolites that impact neuroinflammation and motor symptoms.

Author(s)	Year	Study Design	Focus	Key Findings
Barichella et al.	2019	Observational	Gut microbiota in PD and atypical parkinsonism	Altered microbiota composition; reduced SCFA-producing bacteria
Bedarf et al.	2017	Metagenomic	Early-stage L-DOPA-naïve PD	Microbial and viral shifts precede medication use
Boertien et al.	2019	Systematic Review	Methodological review	Emphasized need for standardization
Bonaz	2024	Review	Gut-brain axis in PD	Highlights vagal and enteric involvement
Carabotti et al.	2015	Review	Gut-brain axis overview	Describes bi-directional CNS–gut communication
Claudino dos Santos et al.	2023	Review	Enteric glia, microbiota-gut- brain axis	Links glial alterations to PD development
Cirstea et al.	2020	Observational	Microbiota and gut function	Correlation between gut symptoms and microbial profile
Cryan et al.	2019	Review	Microbiota-gut- brain axis	Broad physiological overview; relevance to PD noted
Heintz-Buschart et al.	2018	Observational	Nasal and gut microbiome	Distinct microbial patterns in PD and iRBD
Hill-Burns et al.	2017	Observational	Microbiota and medication	Medication effects distinct from disease effects
Houser & Tansey	2017	Perspective	Inflammation in PD	Inflammation as a silent PD driver
Keshavarzian et al.	2015	Observational	Colonic bacteria	Dysbiosis and increased gut permeability in PD
Menozzi et al.	2021	Review	Clinical and pathogenic role	Summarizes evidence linking gut changes to PD
Petrov et al.	2017	Observational	Gut microbiota in PD	Reduced beneficial bacteria in PD
Romano et al.	2021	Meta-analysis	Gut microbiome and neuroinflammation	Consistent microbial shifts linked to inflammation
Sampson et al.	2016	Animal Model	Gut microbiota and motor symptoms	Microbiota manipulation alters motor behavior

Scheperjans et al.	2015	Observational	Microbiota and PD phenotype	Microbial profile correlates with motor symptoms
Tan et al.	2022	Review	Translational implications	Discusses microbiome-based therapies
Unger et al.	2016	Observational	SCFAs and microbiota	Reduced SCFA levels in PD patients
Hirayama & Ohno	2021	Review	neurodegenerative signaling pathways and potential treatments.	Reviewed emerging evidence of gut microbiota's role in neurodegeneration
Kwon et al	2024	Review	Mediterranean diet improving microbiota in PD patients.	Showed that high- fiber, Mediterranean- style diets in PD patients support more beneficial microbiota
Zhang et al.	2023	Observational	Reviewed clinical, mechanistic, and therapeutic research linking gut microbiota to PD progression.	Linked gut microbial imbalance with alpha-synuclein aggregation
Nie & Ge	2023	Review	Connected gut dysbiosis with neuroinflammation and immune dysregulation inP D,	Gut dysbiosis promotes inflammation in PD
Li et al	2022	Systematic review	Systematically reviewed microbial profiles across PD populations,	Consistent taxonomic shifts across PD studies.

Synthesis of Findings

Multiple studies have reported significant differences in gut microbiota composition between PD patients and healthy controls. Common findings include:

1. Gut Microbiome Composition in PD vs. Healthy Controls

Finding	Description	Sources
Increased Abundance	Bacterial families such as Bifidobacteriaceae and Akkermansiaceae were more abundant in PD patients.	Tan et al., 2022
Decreased Abundance	Beneficial bacteria like Lachnospiraceae were less abundant in PD patients.	Tan et al., 2022
Diversity Changes	Mixed findings: some studies reported decreased, others increased microbial diversity in PD.	Claudino dos Santos et al., 2023

Multiple studies have found differences in gut microbiome composition in people with Parkinson's disease (PD) compared to healthy controls. One consistent trend has been the increased abundance of certain families of microbes, including Bifidobacteriaceae and Akkermansiaceae (Tan et al., 2022) On the contrary, certain beneficial bacteria (i.e. Lachnospiraceae, an anti-inflammatory bacterium that helps maintain the gut barrier), are often greatly reduced in PD groups. Indeed, the compositional changes suggest a microbial environment that could be pro-inflammatory, and could adversely affect barrier function and motility.

The findings regarding microbial diversity are more variable. While some studies have documented a decrease in overall microbial diversity in some populations—that is, a finding that is often correlated with disease, and with gut ecosystem resilience—other studies have documented microbial diversity that is higher than or equal to PD patients (Claudino dos Santos et al., 2023). Differences in diversity and biodiversity have been attributed to study design and population geography, sequencing methods, and confounding variables such as diet or medication use

Evidence suggests that gut microbiota alterations may contribute to PD progression through several mechanisms:

2. Potential Causal Relationships with Disease Progression

Mechanism	Explanation	Sources
Alpha-Synuclein Aggregation	Gut dysbiosis may trigger misfolding/aggregation of alpha-synuclein, potentially spreading to CNS.	Sampson et al., 2016
Neuroinflammation	Increased intestinal permeability and systemic inflammation may cause neuroinflammation.	Houser & Tansey, 2017
Metabolite Production	Altered production of microbial metabolites like SCFAs may impair neuronal health.	Claudino dos Santos et al., 2023

Research indicates that a shift in the gut microbiota (dysbiosis) might be a mechanism of cause or consequence of development and progression of PD. One prominent theory is that gut dysbiosis may facilitate the misfolding and dependence of alpha-synuclein in the enteric (gut) nervous system and that it can also retrogradely propagate to the central nervous system (CNS) through the vagus nerve. Preclinical work has shown proof of printing on retrograde propagation (Sampson et al., 2016) and potentiated by gut dysbiosis may contribute to the initiation or acute onset of development of neurodegeneration.

Another important mechanism is part of neuroinflammatory changes. Changes to the microbiota profile may change the intestinal epithelial barrier and induce increased intestinal permeability (leaky gut).This, in turn, can allow bacterial endotoxins access to circulation and activate the immune system and chronic inflammation in the gut and the brain (Houser & Tansey, 2017). This is a classic example of the immunological changes that accompany neuroinflammation as part of PD development and progression.

Microbial dysbiosis may also alter the production of important metabolites, particularly short chain fatty acids (SCFAs- butyrate, propionate, acetate). These SCFAs are needed to maintain gut health, and shape and regulate immune responses. Loss of SCFAs in the gut and observation of SCFA deficiencies in PD cohorts could impair neuronal support and contribute to degeneration through impaired energy metabolism or glial activation (Claudino dos Santos et al.,2023).

3. Microbiome-Targeted Interventions

Intervention	Potential Benefits	Sources
Probiotics/Prebiotics	May improve motor and non-motor symptoms by modulating gut flora.	Tan et al., 2022
Dietary Modifications	High-fiber, low-fat diets may promote healthy microbiome and slow PD progression.	Bonaz, 2024
Fecal Microbiota Transplantation (FMT)	Early evidence suggests potential for restoring balance and improving symtoms	Claudino dos Santos et al.,2023

Around these pathogenic findings, several studies have evaluated treatment avenues that target the gut microbiome in PD. Potential interventions involving prebiotic and probiotic supplementation gained traction as early clinical studies demonstrated efficacy on several outcomes, improving gastrointestinal symptoms, motor fluctuations, and inflammation (Tan et al., 2022). These studies are still in their infancy, however, our understanding is they are aiming to restore a beneficial gut microbiome and reduce systemic immune activation.

Changes in diet may be an alternative therapeutic option as well. Diets high in dietary fibre and low in

saturated fat may create conditions for beneficial bacteria to thrive and induce gut butyrate (SCFA) production. The evidence is evolving, with studies suggesting diet type has the potential to positively alter gut composition and may also slow disease progression in PD (Bonaz, 2024).

Fecal microbiota transplantation (FMT) is still experimental for PD, although there have been initial positive results indicating that it restored microbial diversity and mitigation of symptoms as well as limited studies suggest improvement. However, the effect duration or safety of the process is unknown and future randomized controlled studies are warranted to evaluate its use in PD populations (Claudino dos Santos et al., 2023).

Discussion

The findings of this systematic review provide further support for growing evidence indicating changes to the gut microbiome are related to development and progression of parkinsons disease (PD). There were consistent altered characteristics of gut microbiome to show dysbiosis across studies with PD patients identified through microbial composition, functional capacity, and production of metabolites. We have contextualised these changes within the important pathogenic events including: neuroinflammation, aggregation of alpha-synuclein, and disruption of gut-brain- communication. Gut Microbiota and Disease Mechanisms.

The core component in dysbiosis relating to PD is the loss of beneficial bacterial families like Lachnospiraceae and Prevotellaceae, noted as SCFA-producing families which help maintain and preserve the integrity of the intestinal barrier to modulate inflammation (Keshavarzian et al., 2015; Bedarf et al., 2017). Along with the loss of these bacteria, we also see PD-related evidence of an increase in bacteria such as Akkermansiaceae and Bifidobacteriaceae, though their role in the situation is yet to be determined (Hill-Burns et al., 2017; Tan et al., 2022).

The gut-brain axis may provide a feasible mechanism to explain how dysbiosis may contribute to neurodegeneration; evidence suggests that misfolded alpha-synuclein may start in the gut, possibly as a consequence of microbial dysbiosis or inflammation, and propagate up to the brain through the vagus nerve (Sampson et al., 2016; Heintz-Buschart et al., 2018). Furthermore, the loss of barrier integrity due to increased intestinal permeability, or "leaky gut," allows bacterial endotoxins translocating to the systemic circulation, leading to systemic and central inflammation, which are both contributors to the loss of dopaminergic neurons in PD (Houser & Tansey, 2017; Cirstea et al.,
2020).

Animal studies demonstrating that germ-free or antibiotic-treated mice have reduced motor symptoms and lowered neuroinflammatory markers provide further support for the mechanisms proposed here, and they indicate a direct regulatory role of microbiota on PD pathology (Sampson et al., 2016). In vitro and in vivo studies have also revealed the ability of microbiota-associated metabolites to regulate the aggregation of alpha-synuclein and the activation of microglia (Cryan et al., 2019; Claudino dos Santos et al., 2023). Therapeutic Implications

A number of the studies discussed above also examined microbiome-focused interventions (probiotics

and prebiotics, etc.) and therapies (dietary changes, fecal microbiota transplantation (FMT), etc). There are some promising preliminary results finding that probiotics could help treat constipation and improve non-motor symptoms of Parkinson's Disease (PD) (Tan et al., 2022), but the current evidence is still insufficient to confidently substantiate long-term neuroprotective benefits. Similarly, a diet with increased fiber and polyphenols are correlated with greater microbial diversity and short-chain fatty acid (SCFA) production and possibly decreasing PD progression (through anti-inflammatory actions) (Bonaz, 2024).

At this time, FMT is still in the early stages of clinical applications for PD. While pilot studies indicate that FMT can restore microbial composition and help patients cope with the severity of motor symptoms (Barichella et al., 2019; Bedarf et al., 2017), the aforementioned therapies are not consistently standardized and across interventions, the clinical trials have substantially different study designs, microbial strains, and outcomes.

The Limitations of these Studies

Identifying fruitful clinical implications of the literature reviewed above is also tempered by some limitations. For starters, the majority of the microbiome studies had small sample sizes, and many studies had a cross-sectional design that do not lead to causal inferences. The literature also suffers from such methodological heterogeneity (for example, sequencing technologies, bioinformatics pipelines, clinical PD phenotype definitions) that precludes appropriate comparisons (Boertien et al., 2019; Romano et al., 2021). Another major difficulty is the roles of confounding variables such as medication use (e.g., L-DOPA), diet, geography, and age, all of which may independently shape gut microbiota apart from PD (Hill-Burns et al., 2017). Unfortunately, only a limited number of studies evaluated drug-naïve or early-stage PD patients, which are of utmost importance in order to understand the microbial signature of disease rather than the microbial signature associated with therapeutic effects (Bedarf et al., 2017; Scheperjans et al., 2015).

The Review's Strengths

The review presents the evidence across a large variety of study designs (human observational studies, randomized trials, animal studies, mechanistic reviews) for a comprehensive presentation of the ways in which gut microbiota may influence PD further continues with recent developments on microbiome-targeted interventions that can provide a translational angle.

Future Areas of Research

To move this field forward, future studies could focus on the following priorities:

• Longitudinal cohort study design to assess how microbial characteristics change over time.

• Standardized protocols for microbiome study utilization (e.g., sample collection, sequencing, and taxonomic categorization).

• Larger multi-centre clinical randomized trials to improve our understanding of microbiome- centered therapies like next-generation probiotics or FMT.

• Multi-omics study designs (i.e., metagenomics integrated with metabolomics, transcriptomics, clinical phenotyping) to identify exact mechanistic connections between microbiota and PD (Cryan et al., 2019).

Conclusion

This systematic review displays an ongoing trend for many researchers to provide evidence that a gut microbiome dysbiosis is definitively associated with Parkinson's disease (PD). Evidence from human and animal research consistently presented similar patterns of microbial profiles, lower abundance of beneficial taxa, and compromised metabolic output with an emphasis in short-chain fatty acids for PD patients compared to healthy controls. Alterations in microbial profiles are likely influencing pathogenic processes in the gut and systemic neuroinflammation, including increased intestinal permeability, systemic and neuroinflammation, and a-synuclein fibrillation with collective contribution to the neurodegenerative processes associated with PD (Claudino dos Santos et al., 2023; Sampson et al., 2016; Houser & Tansey, 2017).

In addition, the review presents the potential role of some microbiome-targeted interventions, including probiotics, dietary interventions, and fecal microbiota transplantation (FMT) as adjunct approaches in the management of PD. While the initial trials seem promising, particularly, in symptom relief measures and improving microbiome factors, larger randomized controlled trials on these microbiome-based therapies are warranted to establish their therapeutic potential and safety (Tan et al., 2022; Bedarf et al., 2017; Bonaz, 2024)

Some hurdles remain, such as different methodologies utilized in the studies that made up our review, no follow-up data whether longitudinally or wait list/delayed and limited inclusion of early- stage PD or drug-naïve patients. Addressing these limitations is important for establishing causal relationships between various microbiome changes and PD presentation and then exploring whether personalized microbiome-based therapies may help.

To summarize, the gut microbiome is one of the new, exciting areas of PD research and potential treatment, and continued investigation into the microbiota-gut-brain axis may not only further our understanding of PD pathogenesis but will likely give way to new diagnostics and therapeutic agents aimed at changing disease course and improving quality of life (Cryan et al., 2019; Tan et al., 2022).

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