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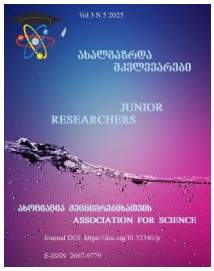

# The Role of Gut Microbiota Alterations in Modulating Neuroinflammation and Disease Progression in Alzheimer's and Parkinson's Disease

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Abstract

Background: Alzheimer's disease (AD) and Parkinson's disease (PD) are the two leading neurodegenerative disorders worldwide. Growing evidence highlights gut microbiota dysbiosis as a critical factor influencing neuroinflammation, pathological protein aggregation, and clinical progression.

Objective: To synthesise current evidence on the role of gut microbiota alterations in modulating neuroinflammation and disease progression in AD and PD.

Methods: A narrative review was conducted, integrating data from human observational studies, meta-analyses, animal models, and interventional trials. Microbial taxa shifts, metabolite changes, and mechanistic pathways were systematically examined.

Results: Both AD and PD are characterised by reduced microbial diversity, depletion of short-chain fatty acid–producing bacteria, and enrichment of pro-inflammatory taxa. In PD, dysbiosis strongly correlates with α-synuclein aggregation, gastrointestinal prodromes, and motor dysfunction. In AD, altered tryptophan metabolism, amyloid deposition, and tau pathology have been linked to microbial and metabolic disturbances. Animal models provide causal evidence, while human studies remain largely associative. Early interventions such as dietary modulation, probiotics, and fecal microbiota transplantation show promise, but long-term neurological benefits are unproven.

Conclusion: Gut microbiota dysbiosis emerges as both a potential biomarker and therapeutic target in AD and PD. Although mechanistic insights are compelling, robust longitudinal studies and well-powered clinical trials are needed to establish causality and evaluate the translational potential of microbiome-targeted therapies.

## Introduction

### Epidemiological Burden of Neurodegenerative Diseases Globally

Parkinson's disease (PD) and Alzheimer's disease (AD) are the two most prevalent neurodegenerative disorders, disproportionately affecting aging populations worldwide.Their steadily increasing incidence contributes to significant disability, morbidity, and socioeconomic burden.

In 2023, Alzheimer's disease was estimated to account for 60–70% of dementia cases, affecting approximately 55 million individuals globally a figure projected to rise to 139 million by 2050 due to demographic aging. Similarly, the current 8.5 million individuals with PD are expected to double by 2040. These numbers underscore the urgent need for more effective therapeutic strategies.

The limited availability of only symptomatic interventions, coupled with longer life expectancy, will likely exacerbate disease burden. Hence, there is a pressing need for disease-modifying and potentially curative therapies to halt or reverse neurodegeneration.

Given the lack of success with conventional pharmacotherapies, research has increasingly shifted toward unconventional drivers of disease. Among them, the gut microbiota has emerged as a promising factor implicated in the pathogenesis of PD and AD.Understanding gut–brain interactions may provide mechanistic insights into disease onset and progression, ultimately shaping new therapeutic and diagnostic avenues.

### Bidirectional Crosstalk of the Gut–Brain Axis

The gut–brain axis represents a bidirectional communication network between the central nervous system (CNS) and the enteric nervous system (ENS), mediated through neural, endocrine, and immune pathways.[] Gut microbial metabolites including tryptophan derivatives, bile acids, and short-chain fatty acids (SCFAs)—modulate neurotransmission, blood–brain barrier permeability, and microglial activity.Conversely, CNS dysfunction can impair gastrointestinal homeostasis, reinforcing a pathogenic cycle.

The dynamic interplay of this axis highlights how microbial dysregulation may drive neuroinflammation and neurodegeneration in PD and AD.[] These insights emphasize the potential of microbiota-based biomarkers and therapeutic manipulation to preserve CNS integrity. Emerging Evidence of Microbial Dysbiosis in Parkinson's and Alzheimer's Disease. Accumulating evidence links gut microbial dysbiosis—an altered composition of gut microbiota—with PD and AD pathogenesis. Clinical and preclinical studies report decreased microbial diversity and characteristic shifts in specific taxa in affected patients compared with healthy controls.[5,11–13]

For example, PD cohorts often show an overrepresentation of proinflammatory Enterobacteriaceae and reduced levels of SCFA-producing Faecalibacterium.[14–16] Similarly, AD patients exhibit decreased butyrate-producing bacteria and increased proinflammatory taxa, correlating with cognitive decline. These microbial signatures are increasingly studied as potential biomarkers for early detection and therapeutic targets for intervention.

### Mechanistic Insights on Gut Dysbiosis and Neurodegeneration

Several mechanisms have been implicated in gut–brain–mediated neuropathology:

1. Curli protein from E. coli promotes aggregation and misfolding of amyloid-β and α-synuclein in AD and PD.

2. Elevated lipopolysaccharides (LPS) from Gram-negative bacteria induce systemic neuroinflammation, impairing synaptic and microglial function.
3. Reduced SCFAs weaken gut barrier integrity, enabling microbial metabolites to enter circulation and trigger CNS inflammation.
4. The vagus nerve serves as a neural conduit for transmitting pathological protein signals.

These findings suggest that microbial alterations may be plausible triggers of neurodegeneration through immune and neuronal disruptions.

Unaddressed Knowledge Gaps

Despite growing evidence, significant gaps remain. Current studies are largely associative, limiting conclusions about causality between gut dysbiosis and neurodegeneration. Methodological variability (e.g., shotgun metagenomics vs. 16S rRNA sequencing) and inconsistent findings across cohorts hinder reproducibility. Furthermore, the functional roles of certain taxa (e.g., Bacteroides, Akkermansia) remain ambiguous. The dual roles of SCFAs—anti- or pro-inflammatory depending on concentration—add complexity.

Another limitation is the lack of longitudinal studies to establish whether dysbiosis precedes or follows disease onset. Clarifying this timeline is critical for developing microbiota-based diagnostics and therapies.

Thus, while gut–brain communication is well recognized, the precise role of gut microbiota as a cause, modulator, or consequence in PD and AD remains unresolved. Bridging these gaps could translate into novel interventions, such as probiotics, dietary modulation, or fecal microbiota transplantation (FMT), though their safety and long-term efficacy require validation through robust clinical trials.

Methodology

Study Design

This study is a narrative review aimed at synthesising and critically evaluating the current literature regarding the influence of gut microbiota alterations on neuroinflammation and disease progression in Alzheimer's Disease (AD) and Parkinson's Disease (PD). The methodological framework is grounded in established approaches to narrative reviews, focusing on a comprehensive and interpretive synthesis of knowledge. The design follows established research protocols, with particular emphasis on microbial taxa, metabolites, and signalling pathways linking gut dysbiosis to the pathophysiology of neurodegenerative disorders. The central study question is: "Do modifications in gut microbiota facilitate neuroinflammation and accelerate disease progression in AD and PD?"

To ensure comprehensive coverage, the review integrates results from preclinical animal models, human observational case-control studies, and clinical trials. This triangulation facilitates a critical comparison, linking mechanistic research with clinical observations. Comparative analysis between AD and PD remains a key feature, highlighting both shared and distinct microbial signatures and mechanistic pathways.

Literature Search Strategy

A systematic literature search was conducted for studies published between January 2012 and September 2024 across MEDLINE (via PubMed), Scopus, and Web of Science. The search strategy incorporated both MeSH terms and free-text keywords to maximise sensitivity, e.g.:
("Alzheimer's Disease" OR "Parkinson's Disease" OR neurodegeneration) AND ("gut microbiota" OR microbiome OR dysbiosis OR "gut–brain axis") AND (neuroinflammation OR inflammation OR microglia OR astrocytes OR cytokines).
Reference lists of retrieved articles and relevant reviews were hand-searched to identify additional eligible studies.
Inclusion and Exclusion Criteria
Inclusion criteria:[1–4]

- Original research articles, including animal studies, observational human studies, and clinical trials.
- Focus on gut microbiota in AD or PD.
- Explicit evaluation of neuroinflammation, immune modulation, or molecular pathways.
- Peer-reviewed publications in English.

Exclusion criteria:

- Case reports, editorials, letters, or abstracts lacking data.
- Studies outside AD/PD scope (e.g., psychiatric disorders).
- Basic science literature without translational relevance.
- Two independent reviewers screened titles and abstracts, followed by full-text assessment. Disagreements were resolved by consensus.

Data Extraction and Synthesis
Key data extracted included: study design, participant/animal characteristics, microbiota analysis methods (e.g., 16S rRNA sequencing, metagenomics), findings on microbial diversity and taxa, metabolites (e.g., SCFAs, LPS), and neuroinflammatory markers (e.g., cytokines, microglial activation).
A narrative synthesis approach was utilized to integrate findings across the reviewed studies, facilitating the identification of both convergent and divergent patterns. The results were organized thematically, encompassing alterations in gut microbiota composition in Alzheimer's disease (AD) compared to Parkinson's disease (PD), the mechanistic pathways linking microbial dysbiosis to neuroinflammation and disease progression, and a critical evaluation of methodological strengths and limitations. This approach enabled a nuanced interpretation that transcended individual study outcomes, thereby providing a cohesive and comprehensive understanding of gut–brain interactions in neurodegenerative disorders.

Primary outcomes:

- Gut microbiota diversity indices (e.g., Shannon index for alpha-diversity; Bray–Curtis dissimilarity for beta-diversity).
- Differential abundance of microbial taxa.

Secondary outcomes:

- Metabolite shifts (SCFAs, LPS, tryptophan derivatives).
- Inflammatory markers (IL-1β, TNF-α, IL-6).
- Clinical correlations with MMSE (AD) and UPDRS (PD).

Statistical Analysis

No original statistical analyses were performed due to the narrative review design. Instead, statistical methodologies reported in the included studies were summarized. These encompassed assessments of alpha-diversity using Kruskal–Wallis tests, beta-diversity through PERMANOVA, differential taxa analyses employing DESeq2 or comparable tools, and correlation analyses utilizing Spearman's or Pearson's coefficients to explore associations between microbiota composition, metabolite profiles, inflammatory markers, and clinical parameters.

Ethical Considerations

As a secondary analysis of published data, this review required no new IRB approval. However, included primary studies were required to report IRB approval and informed consent for human participants.

Results

Key Findings

1. Gut Dysbiosis and Neuroinflammation in PD and AD

Research indicates that gut microbiota dysbiosis contributes to neuroinflammation and disease progression in both Parkinson's Disease (PD) and Alzheimer's Disease (AD).[1–3] Human case–control studies and meta-analyses consistently demonstrate reduced microbial diversity and reproducible shifts in microbial community composition in both disorders. Animal studies further support these findings by establishing mechanistic pathways linking microbial alterations to central nervous system (CNS) immune activation.

2. Parkinson's Disease

PD cohorts show a reduction of SCFA-producing bacteria (e.g., Firmicutes genera) and expansion of pro-inflammatory taxa. Biomarkers of gut permeability (e.g., fecal calprotectin, zonulin) support the leaky gut hypothesis, where bacterial products translocate into circulation, cross the blood–brain barrier, and trigger CNS inflammation. Germ-free and antibiotic-treated animal models demonstrate that PD-associated microbiota and metabolites can trigger microglial activation and worsen motor dysfunction, strengthening causal links.

3. Alzheimer's Disease

In AD, altered microbial composition is characterised by decreased SCFA-producing bacteria and disrupted tryptophan metabolism, associated with increased systemic inflammation and blood–brain barrier dysfunction. Animal models reveal that microbiota modulation (antibiotics, probiotics, fecal microbiota transplantation) influences amyloid deposition and microglial activation, suggesting the gut

microbiome directly impacts hallmark AD pathology. Human studies remain inconsistent across populations, underlining the need for longitudinal, standardised cohorts.

4. Microbiota to neuroinflammation:[10–12]

Microbial metabolites (e.g., SCFAs) regulate microglial development and systemic immune tone. Pro-inflammatory microbial products (e.g., LPS) activate Toll-like receptors and cytokine cascades. Barrier dysfunction (gut and blood–brain barrier) permits peripheral immune factor entry to the CNS. Neural pathways (vagal and enteric) transmit inflammatory and misfolded protein signals between gut and brain. Evidence for these mechanisms comes primarily from animal studies, with human biomarker data increasingly supportive.

5. Therapeutic Insights

Early PD clinical interventions (diet, probiotics, prebiotics, fecal microbiota transplantation) show symptomatic benefits for gastrointestinal and non-motor symptoms. However, trials remain small, heterogeneous, and underpowered. Long-term neurological outcomes and disease-modifying effects are not yet established. For AD, evidence is less consistent; microbiome modulation remains experimental but promising.

6. Overall Model

Gut microbiota alterations contribute to a pro-inflammatory systemic milieu and modulate CNS immune responses, influencing disease pathology in both PD and AD. Evidence for PD is stronger due to more consistent taxonomic findings, early GI prodromes, and mechanistic links to $\alpha$-synuclein. For AD, evidence is emerging but more heterogeneous across populations. Causality in humans remains unproven; robust interventional trials with standardised endpoints and multi-omics profiling are urgently needed.

Discussion

An extensive body of evidence now suggests that the gut microbiome is an essential mediator of neuroinflammation and neurodegeneration, reshaping our understanding of Alzheimer's disease (AD) and Parkinson's disease (PD). The findings strongly support the concept that gut microbiota dysbiosis is not merely a byproduct of neurodegenerative states but an active contributor to their onset and progression. This discussion analyses the primary findings on the microbiota–gut–brain axis, evaluates shared and distinct microbial pathways in AD and PD, and considers their clinical and therapeutic implications.

The most consistent finding across studies is gut dysbiosis in both AD and PD compared with age-matched healthy controls. This manifests as reduced microbial diversity and compositional shifts favouring pro-inflammatory taxa while reducing beneficial butyrate-producing populations.[1–3] In PD, reduced Prevotella and increased Lactobacillus and Bifidobacterium are frequently observed.[] Correlations between these microbial changes and inflammatory markers (e.g., TNF-$\alpha$, IFN-$\gamma$) highlight the immune-modulatory role of the microbiota.Importantly, higher prevalence of Bacteroides correlates with the non-tremor PD subtype and worse motor severity, linking microbial shifts to clinical phenotype. In AD, fecal microbiota transplantation from patients into germ-free transgenic mice exacerbated A$\beta$ plaques and neurofibrillary tangles, alongside cognitive deficits. These changes were associated with elevated Bacteroides, which metabolise pro-inflammatory PUFAs,

linking microbial metabolism directly with AD pathology. Thus, dysbiotic microbiota actively promote systemic inflammation that sustains neurodegeneration.

Multiple interrelated mechanisms explain how gut dysbiosis accelerates neurodegeneration:

1. Leaky Gut and Neuroinflammation
   Dysbiosis increases intestinal permeability, enabling bacterial products such as lipopolysaccharides (LPS) to enter systemic circulation. LPS cross a compromised blood–brain barrier, activating microglia and astrocytes to trigger neuroinflammation.
2. Metabolic Shifts
   Reduced short-chain fatty acids (SCFAs) remove anti-inflammatory and neuroprotective influences, while elevated harmful metabolites (PUFA derivatives, trimethylamine N-oxide) enhance glial activation and amyloid pathology.
3. Amyloid Cross-Seeding
   Gut bacteria such as E. coli produce functional amyloids (e.g., curli) that stimulate immune responses cross-reactive with neuronal amyloids like $\alpha$-synuclein. This promotes $\alpha$-synuclein aggregation in the enteric nervous system, with propagation to the brain via the vagus nerve, consistent with Braak's hypothesis.

## Limitations and Future Directions

Future research should prioritise longitudinal, multi-omic studies integrating microbiome, metabolome, and immune data over time. Interventional clinical trials are urgently needed to evaluate microbiome-targeted therapies, ideally stratifying patients by dysbiosis profiles for personalised medicine. Additionally, further exploration of bidirectional interactions between neurodegeneration and gut alterations via the autonomic nervous system represents a critical research frontier.

## Conclusion

This review of current evidence demonstrates that gut microbiota dysbiosis plays a pivotal role in modulating neuroinflammation and shaping the trajectory of neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD). Both conditions share common microbial signatures, notably the loss of short-chain fatty acid–producing bacteria and enrichment of pro-inflammatory taxa, yet they diverge in mechanistic emphasis: PD is more strongly associated with $\alpha$-synuclein aggregation and gastrointestinal prodromes, whereas AD reflects altered tryptophan metabolism and amyloid pathology.

Animal models provide compelling causal evidence that gut microbiota can drive microglial activation, barrier dysfunction, and pathological protein aggregation, while human studies remain largely associative but consistent across multiple cohorts. Early therapeutic strategies, including probiotics, dietary interventions, and fecal microbiota transplantation, show promise in alleviating non-motor symptoms and modifying pathological processes, though robust clinical validation is still lacking.

Taken together, these findings highlight the gut microbiome as both a biomarker reservoir for early detection and a therapeutic target for disease modification. However, the current evidence base is heterogeneous, and causality in humans remains unproven. Future longitudinal, multi-omics studies and rigorously designed interventional trials are urgently needed to clarify the translational potential of microbiome-targeted therapies in slowing or preventing neurodegenerative disease progression.

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