UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

Gut-Brain Axis Dysfunction in Alzheimer's and Parkinson's Diseases: The Role of Dysbiosis, Inflammation, and Therapeutic Targets — A Literature Review

Paniz Abadi, BSc Student [1], Savita Perera, BSc Student [2]

[1] Department of Kinesiology & Health Science, York University, Toronto, Ontario, Canada M3J 1P3
[2] Department of Biology, McMaster University, Hamilton, Ontario, Canada, L8S 4L8

Corresponding Author: panizaba@my.yorku.ca

Abstract
Introduction: Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders, causing progressive cognitive and motor decline. High rates of new diagnoses, coupled with increasing evidence linking gastrointestinal (GI) dysfunction to neurodegeneration, highlight the significance of understanding the gut-brain axis (GBA). Changes in gut microbiota composition are associated with amyloid-beta accumulation in AD and α-synuclein aggregation in PD, suggesting that gut dysbiosis and inflammation may worsen disease pathology.
Methods: A systematic literature review was conducted using peer-reviewed primary research articles published between 2014 and 2025. Articles were selected based on their relevance to GI inflammation, gut microbiota dysbiosis, and neurodegenerative diseases. Studies involving human participants and relevant animal models were prioritized. Databases searched included PubMed, Google Scholar, ScienceDirect, JSTOR, and SpringerLink.
Results: Gut dysbiosis was consistently associated with increased intestinal permeability, systemic inflammation, and neuroinflammatory responses in AD and PD. Specific microbial imbalances correlated with accelerated disease progression and cognitive decline. Animal studies demonstrated that fecal microbiota transplantation from diseased individuals worsened motor and mental symptoms, while interventions targeting gut health, such as probiotics and dietary modifications, reduced neuroinflammation and improved outcomes.
Discussion: Findings support the GBA's critical role in mediating neurodegeneration through immune activation and inflammatory pathways. Dysbiosis-induced changes in microbial metabolite production, including short-chain fatty acids (SCFAs) and tryptophan derivatives, further contribute to neuroinflammatory processes. Despite promising preclinical results, challenges remain in translating gut-targeted therapies to clinical use due to variability in individual microbiomes and limited longitudinal human data.
Conclusion: This review emphasizes the gut microbiota as a modifiable factor in the pathogenesis of AD and PD. Targeting GI inflammation and restoring microbial balance may offer novel therapeutic strategies for slowing disease progression. Future research should focus on validating gut-derived biomarkers, personalizing microbiome-based treatments, and conducting longitudinal clinical trials to optimize gut-brain interventions in neurodegenerative diseases.

Keywords: Alzheimer's disease; Parkinson's disease; gut-brain axis; gut dysbiosis; neurodegenerative diseases; neuroinflammation; Parkinson's pathology; Alzheimer's pathology; gut-brain signaling; gut microbiome

Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative disorders [1]. Between 2022 and 2023, approximately 98,695 Canadians aged 65 and older were newly diagnosed with dementia, including AD, with a higher incidence among females. During the same period, approximately 13,875 Canadians aged 40 and older were newly diagnosed with Parkinsonism, including PD, with a higher incidence among males [1].

AD, the leading cause of dementia, is characterized by progressive memory loss, cognitive decline, and behavioural changes, driven by β-amyloid plaques and neurofibrillary tangles [1, 2]. PD is characterized by a gradual loss of dopaminergic neurons in the substantia nigra pars compacta and abnormal a-synuclein aggregation, forming Lewy bodies and neurites [3, 4]. This results in motor symptoms such as bradykinesia, tremors, muscle stiffness, and impaired body movement, as well as non-motor symptoms, including gastrointestinal (GI) dysfunction [5]. In 2019, approximately 60 million people worldwide lived with AD or PD, highlighting their significant impact on healthcare systems and quality of life [6].

GI dysfunction is increasingly recognized as a contributor to neurodegenerative diseases. Constipation, a common non-motor symptom in PD, leads to reduced quality of life, disability, and treatment challenges [7]. Similarly, chronic constipation in people with AD is linked to gut dysbiosis, an unhealthy shift in gut microbes characterized by reduced diversity, loss of beneficial species, or overgrowth of harmful bacteria that can trigger inflammation and intestinal barrier dysfunction [8]. Addressing GI problems is therefore critical for improving health outcomes in both diseases.

Recent research has established a strong connection between GI dysfunction and neurodegenerative diseases [1]. The gut-brain axis (GBA) enables communication between gut microbiota and the central nervous system (CNS), influencing neuroinflammation and cognitive health [1]. The GBA also connects gut function with emotional and cognitive processes such as memory and learning, and research shows that alterations in gut microbiota can negatively affect these functions, while probiotics may help enhance them [9]. This system also involves the immune response, where gut dysbiosis can trigger systemic inflammation and contribute to the development of neurodegenerative diseases [9].

Inflammation, particularly chronic low-grade inflammation associated with aging (inflammaging), primarily results from immune system dysregulation [10]. Elevated proinflammatory cytokines like IL-1, IL-6, and TNF-α contribute to tissue damage and age-related functional decline [10]. Gut dysbiosis has also been linked to inflammaging, AD, PD, anxiety, depression, cognitive dysfunction, and altered social and behavioural regulation [11]. Building on what is currently known, this narrative review investigates how GI inflammation and gut dysbiosis contribute to the onset and progression of neurodegenerative diseases like AD and PD.

Methods

Peer-reviewed primary research articles published between 2014-2025 that examined GI inflammation, gut dysbiosis, intestinal permeability, and neurodegenerative diseases such as AD or PD were systematically reviewed. Eligibility and exclusion criteria were summarized in Table 1. A total of 18 studies met these criteria (8 human, 10 animal). Methodological rigor was evaluated based on sample size, controls, validated measures, and statistical analysis, focusing on randomization/blinding in animal studies and standardized scales or biomarkers in human studies.

The keywords used for the literature search include "Alzheimer’s disease," "Parkinson’s disease," "gut-brain axis," "gut dysbiosis," "neurodegenerative diseases," "neuroinflammation," "Parkinson’s pathology," "Alzheimer’s pathology," "gut-brain signaling," and "gut microbiome." Boolean operators were also used. The databases used were PubMed, PubMed Central, Google Scholar, ScienceDirect, JSTOR, and SpringerLink.

Table 1. Inclusion Criteria for Article Selection

Criteria	Inclusion	Exclusion
Publication Date	Articles published between 2014 and 2025	Articles published before 2014 or after 2025
Article Type	Peer-reviewed primary research articles with original experimental or clinical data	Reviews, meta-analyses, editorials, conference abstracts
Study Focus	Research on GI inflammation, gut dysbiosis, intestinal permeability, or neurodegenerative diseases	Articles unrelated to GI health or neurodegenerative diseases
Study Participants	Human participants or relevant mammalian models	In vitro studies, non-mammalian species
Methodological Rigour	Studies with clear methodology, data analysis, and statistical validation	Studies with unclear or incomplete methods
Language	Articles only in English	Articles in languages other than English
Total Studies Included	18 studies (8 human, 10 animal model)	—
Quality Appraisal	Studies assessed for sample size, control/comparison groups, validated measures, and statistical analysis	—

Results

Role of Gut Dysbiosis in Alzheimer's Disease Pathology

A key study demonstrated a mechanistic link between gut microbiota and AD pathology [12]. Using APP/PS1 transgenic mice, the researchers transplanted fecal microbiota from people with AD and assessed cognition through the Morris water maze, and found impaired memory performance. Molecular analyses (IHC, Western blot, ELISA) further revealed activation of the NLRP3 inflammasome and microglial inflammation in the hippocampus. These effects were reversed by healthy donor FMT or minocycline treatment; direct experimental evidence that gut dysbiosis contributes to AD pathology by promoting neuroinflammation through inflammasome activation [12]. In people with AD, increased intestinal inflammation was consistently associated with AD progression. For example, increased fecal calprotectin levels, a marker of intestinal inflammation, were positively associated with amyloid burden [13]. Also, imbalances in gut microbiota may accelerate amyloid-beta accumulation and disease progression, supported by experimental findings in transgenic mice [1].

Other studies have reported alterations in gut microflora composition that impact inflammatory pathways, along with the release of pro-inflammatory metabolites in both the gut and brain [14]. Gut inflammation was further associated with aging and correlates with neuropathological changes observed in individuals with AD [13]. Experimental findings suggest that microbial dysbiosis triggers the release of pro-inflammatory cytokines, which aggravate neurodegeneration and intensify GBA dysfunction [12]. Moreover, evidence showed that dysbiosis frequently precedes clinical symptoms, linking microbial imbalance with psychiatric disorders and early stages of neurodegeneration in both AD and PD [15].

Bidirectional Gut-Brain Axis Dysfunction in Parkinson's Disease

PD also exhibits a well-established bi-directional relationship between intestinal and neuro-inflammation, with pathological changes in one system influencing the other [5]. Key features of PD pathology include increased gut permeability, allowing lipopolysaccharides (LPS) from Gram-negative bacteria to enter systemic circulation and stimulate inflammatory cytokine production (eg., TNF-α, IL-1β, IL-6) [5, 16]. A study utilized a germ-free mouse model that overexpresses human α-synuclein, a hallmark protein associated with PD. These mice were raised in sterile conditions to eliminate gut microbiota, and were compared with conventionally colonized counterparts [17]. The germ-free α-synuclein mice showed significantly reduced motor impairments and lower levels of neuroinflammation. Motor deficits were measured using the beam traversal test, which assesses balance and coordination, the pole descent test, which tests bradykinesia, the adhesive removal test, which tests sensorimotor function, and hindlimb clasping, which assesses neurological integrity [17]. Reintroducing gut microbiota from either people with PD or specific short-chain fatty acids (SCFAs) into the germ-free mice resulted in the reappearance of motor symptoms and increased microglial activation in the brain [17]. These findings highlight that the gut microbiota directly regulate motor deficits and neuroinflammation associated with PD. Human studies also show elevated LPS levels and imbalances in microbiota, such as increased Akkermansia and decreased Prevotella in people with PD, further supporting this connection [5]. Additionally, people with inflammatory bowel disease (IBD) have an increased risk of developing PD, suggesting that chronic gut inflammation has a role in causing it [8]. Vagotomy, or the surgical cutting of the vagus nerve, is also associated with a reduced risk of PD, reinforcing the role of gut-brain transmission of α-synuclein pathology [7]. Neuroinflammation exacerbates GI dysfunction, as microglial activation and persistent cytokine release in people with PD interfere with autonomic control of gut motility and permeability, resulting in a cycle of gut dysbiosis [18]. Animal studies show that chronic gut inflammation reduces activity in the hippocampus and impairs memory in mice [19]. In these studies, manganese-enhanced MRI revealed suppressed activity in the hippocampus, and behavioural tests demonstrated poor memory performance. Elevated IL-1β and an increased blood-brain barrier permeability further confirmed a strong neuroinflammatory response [19, 20].

Recent findings indicate that inflammatory molecules are linked to disturbances in gut health and brain pathology. Gut inflammation can increase intestinal permeability, allowing endotoxins like LPS to translocate into systemic circulation [16]. LPS, produced by gram-negative bacteria such as Enterobacteriaceae and Proteobacteria, promotes neuroinflammation and α-synuclein aggregation in people with PD [5]. Additionally, individuals with IBD are at a higher risk of developing PD, reinforcing the critical role of gut health in neurodegeneration [8]. In PD, however, evidence suggests that misfolded alpha-synuclein proteins may originate in the gut and spread to the brain through the vagus nerve, initiating neurodegeneration [7]. A lower risk of PD has been observed in individuals who have undergone vagotomy [7]. Microbial imbalances, such as reduced Prevotella and increased Akkermansia species, are common in people with PD.

Neuroinflammation further intensifies GI dysfunction in PD. The CNS regulates gut motility, permeability, and immune function via the autonomic nervous system. Neuroinflammatory processes in PD, characterized by microglial activation and sustained cytokine release, disrupt these regulatory pathways, leading to impaired intestinal barrier function and persistent gut dysbiosis [18]. Studies have shown that people with PD exhibit a significant decrease in beneficial gut microbiota and an increase in pro-inflammatory bacteria, reinforcing the cycle of inflammation [18].

In PD models, removing pro-inflammatory gut bacteria alleviated motor symptoms, while in AD models, an unhealthy microbiome triggered inflammation and cognitive decline. The vagus nerve serves as an important channel for this bidirectional communication, supported by findings of a reduced risk for PD in individuals who have undergone a vagotomy [7]. Additionally, the activation of the NLRP3 inflammasome, a key component of the immune response, has been linked to both intestinal and CNS inflammation, further highlighting the interconnected nature of these inflammatory processes [12].

In a mouse model of chronic colitis, chronic intestinal inflammation was shown to suppress hippocampal activity and impair memory, providing direct evidence of a gut–brain link [19]. Neuroinflammation triggered by signals from the gut has been recognized as a vital mediator in this process [19]. The high-mobility group box 1 release, which is a damage-associated molecular pattern, from the inflamed gut activates inflammatory pathways in the brain, including the caspase-1 and caspase-11 pathways, associated with neurodegeneration and neuroinflammation [19]. In a mouse model of chronic colitis, MEMRI revealed reduced hippocampal activity compared to controls, and behavioural testing showed significantly poorer memory performance [19]. Moreover, mice with chronic colitis exhibited elevated levels of interleukin-1 beta (IL-1β) and increased blood-brain barrier permeability, indicating a strong neuroinflammatory response [20]. Morin's neuroprotective effects were demonstrated in a rotenone-induced PD model, emphasizing the impact of environmental gut-derived signals on worsening neurodegenerative processes [20]. Elevated inflammatory markers, including caspase-11 and glial fibrillary acidic protein in colitis-afflicted mice brains, indicate that chronic gut inflammation significantly contributes to neuroinflammatory brain changes [19].

Gut-Derived Metabolites as Modulators of Neuroinflammation

According to recent research, gut microbiota has an important role in the production of anti-inflammatory metabolites that regulate neuroinflammation in both AD and PD. SCFAs, such as butyrate, propionate, and acetate, are fermentation byproducts of gut bacteria, including *Faecalibacterium prausnitzii* and *Roseburia*, which regulate immune responses, maintain gut barrier integrity, and suppress microglial activation [21]. Butyrate, known for its anti-inflammatory and neuroprotective properties, has been shown to reduce the production of pro-inflammatory cytokines and provide neuroprotection [21].

However, studies show that both people with AD and PD exhibit a significant depletion of SCFA-producing bacteria, correlating with increased intestinal permeability and systemic inflammation [21]. Furthermore, alterations in microbial tryptophan metabolism disturb the balance between neuroprotective (kynurenic acid) and neurotoxic (quinolinic acid) metabolites, contributing to disease progression [22]. The ability of gut bacteria to metabolize dietary polyphenols into anti-inflammatory compounds is also impaired in dysbiosis. For example, impaired polyphenol metabolism in individuals with AD and PD resulted in reduced neuroprotective metabolites, emphasizing the need to restore microbial diversity to enhance neuroprotection [23]. These findings emphasize the critical role of gut-derived metabolites in modulating neuroinflammation across AD and PD.

Table 2. Comparison of Studies Investigating the Role of Gut Microbiota and Inflammation in Alzheimer's Disease

Study	Focus	Methodology	Key Findings	Implications for AD
[14]	Gut microbiota composition and inflammatory factors	Human cohort study	Identified microbiota alterations linked to inflammation	Suggests microbiota-targeted therapies for AD
[12]	Microbiota-driven inflammasome activation	Animal Model	Found that gut bacteria activate NLRP3 inflammasome, worsening neuroinflammation	Highlights gut dysbiosis in AD pathology
[13]	Gut inflammation and AD pathology	Human cohort study	Recognized correlation between gut inflammation and AD progression	Supports brain axis theory in AD
[17]	Gut microbiota's impact on motor deficits and neuroinflammation in PD	Animal model (gut microbiota transfer)	Microbiota transferred worsened symptoms and increased microglial activation	Supports gut microbiota's role in PD progression

Study	Focus	Methodology	Key Findings	Implications for AD
[16]	LPS and cytokine production in PD	Human biomarker study	LPS levels elevated; linked to TNF-α, IL-1β, IL-6 expression	Links gut inflammation to dopaminergic neuron loss in PD
[7]	α-synuclein origin in gut; vagotomy link to PD	Observational study in humans	Early misfolded alpha-synuclein proteins found in gut; vagotomy reduces PD risk	Supports gut-brain transmission of PD pathology
[19]	Chronic colitis, hippocampal dysfunction, and memory loss in mice	MEMRI and behavioural tests in mice	Chronic colitis led to memory deficits and hippocampal dysfunction	Links GI inflammation to functional brain deficits
[20]	Morin neuroprotective effects in rotenone-induced PD model	PD mouse model with morin intervention	Morin reduced neuroinflammation and dopaminergic neuron loss	Suggests antioxidant interventions for gut-induced PD
[21]	SCFA depletion in AD and PD	Gut microbiota analysis	SCFA-producing bacteria depleted in neurodegenerative diseases	Reinforces inflammation's role in AD/PD progression
[22]	Tryptophan metabolism and neuroinflammatory imbalance	Biochemical pathway analysis	Kynurenine pathway altered; neurotoxic vs. neuroprotective metabolite imbalance	Reveals metabolic target for regulating inflammation
[23]	Impaired polyphenol metabolism in gut dysbiosis	Gut microbiota and metabolic pathway analysis	Dysbiosis impaired polyphenol metabolism; reduced neuroprotection	Suggests restoring microbial metabolism for neuroprotection

Discussion

Gaps in Current Research

Increasing evidence links gut inflammation and dysbiosis to neurodegenerative conditions such as AD and PD. Still, significant research gaps remain, particularly the lack of longitudinal human studies that can clarify causal relationships between gut-derived inflammation. For example, while constipation and other GI symptoms are more prevalent in individuals with dementia and mild cognitive impairment [14], cross-sectional designs cannot determine whether gut dysfunction occurs before, after, or contributes causally to neurodegeneration. This uncertainty highlights the need for longitudinal research. In PD, microbiota profiles appear relatively stable over time, but it remains uncertain how these patterns relate to disease onset or progression [18].

Therapeutic Gaps and Need for Gut-Targeted Approaches

Another gap is regarding the clarity of how mechanisms of gut-derived inflammation and microbial metabolites affect the CNS. Current treatments primarily focus on symptom management, rather than targeting the underlying causes of gut dysbiosis and neuroinflammation [24]. Preclinical studies demonstrated that PD-associated gut microbiota can drive neuroinflammation and motor impairments [17], but translating these findings into human therapies remains a significant challenge. These findings highlight the need for translational research to determine whether microbiota-targeted interventions, such as probiotics, dietary modifications, or anti-inflammatory agents, can prevent or slow neurodegeneration [8]. Despite such recommendations, few clinical trials have directly tested how improvement in gut health affects outcomes in PD or AD.

Gut-Derived Metabolites as Biomarkers

Current research suggests that pro-inflammatory metabolites produced by gut bacteria, like LPS, play a role in systemic inflammation and neurodegeneration in AD and PD [25]. These molecules show promise as early biomarkers, but their clinical reliability must be validated. In PD, elevated LPS levels highlight the role of gut-derived inflammatory molecules in promoting intestinal barrier dysfunction and α-synuclein aggregation, while in AD, increased fecal calprotectin levels suggest a measurable biomarker of amyloid burden [21]. Standardizing detection methods remains challenging due to individual variability

DOI Link: https://doi.org/10.26685/urncst.907

in the gut microbiome, as diet can rapidly reshape microbial composition, while antibiotics may cause long-term disruptions that differ between individuals [26]. However, further research on gut-derived metabolites could lead to reliable, non-invasive biomarkers for neurodegenerative diseases. Thus, metabolite-based biomarkers represent a promising but still developing tool for early detection and monitoring.

Table 3. Feasibility of Interventions for AD and PD in Preclinical Models

Study (Year)	Disease Focus	Intervention/Focus	Key Results	Conclusion on Feasibility
[22]	AD	Tetramethylpyrazine (TMP, herbal alkaloid)	TMP treatment in AD transgenic mice improved memory, reduced β-amyloid and tau phosphorylation, and altered mitochondrial and synaptic proteins, leading to less Alzheimer's pathology.	A multi-target approach shows promise in alleviating Alzheimer's symptoms and neurodegeneration, suggesting that natural therapies may offer neuroprotective benefits for Parkinson's disease as well.
[20]	PD	"Double Stem Cell" (DSC) plant extract (apple & grape stem cells)	DSC supplementation improved motor and cognitive functions in MPTP-induced PD mice and fruit flies, enhancing performance in tests and increasing lifespan. It reduced oxidative stress and neuroinflammation, leading to less dopaminergic neuron loss.	DSC supplementation shows promise as a treatment for Parkinson's disease by improving motor and cognitive functions, reducing oxidative stress and neuroinflammation, and protecting neurons in both mice and fruit flies. Its consistent benefits suggest it warrants further research in clinical studies.
[12]	AD	Gut microbiota transfer (FMT from people with AD)	This study explored the gut-brain axis by transplanting fecal microbiota from people with AD into mice, causing inflammation and cognitive decline, while healthy microbiota reduced this inflammation.	Gut dysbiosis may worsen Alzheimer's disease and inflammation, indicating that the gut microbiome could be a target for intervention to alleviate symptoms and slow neurodegeneration.
[17]	PD	Gut microbiota modulation (antibiotics, SCFAs, human FMT)	A PD mice study found gut microbes crucial for symptoms; germ-free or antibiotic-treated mice showed fewer motor deficits, while transplants from people with PD worsened symptoms.	Modifying the gut microbiome may alleviate Parkinson's symptoms; reducing harmful bacteria improved motor deficits and neuroinflammation in mice, suggesting potential benefits for patients.

Multi-Target Interventions and Symptom Mitigation

As shown in Table 3, these studies provide promising evidence that multi-target interventions can mitigate the symptoms of neurodegeneration in AD and PD models. A common theme is reducing *inflammation and pathogenic protein burden* through unconventional avenues beyond classic neurotransmitter therapies. For example, modulating the gut microbiome has shown profound effects in AD and PD: altering gut flora composition can worsen or ameliorate brain pathology.

The relationship between gut and brain inflammation appears to create a continuous feedback loop that may accelerate PD progression. Gut-derived inflammatory mediators amplify neurodegeneration, while CNS inflammation further disrupts gut function, compounding GI symptoms and systemic immune activation. These findings suggest that GBA interventions (such as probiotics, dietary changes, or fecal transplants) are a feasible approach to reduce neuroinflammation and slow symptom progression in neurodegenerative diseases. In PD, gut–brain dysfunction may initiate pathology, while in AD it more often accelerates progression, stressing the need for disorder-specific strategies. Interventions such as probiotics, dietary modifications, and microbiome-based treatments may also support healthy aging by mitigating inflammaging [1, 8]. However, further research is needed to clarify mechanisms and develop targeted therapies that address both intestinal and neuroinflammation in AD and PD.

Beyond Gut Therapies: Immunological and Antioxidant Interventions

Similarly, targeting neuroinflammation and neuronal survival pathways has proven beneficial. Approaches like antioxidant-rich nutraceuticals (e.g., plant stem cell extracts) and traditional herbal compounds like tetramethylpyrazine enhance cognitive and motor function by *blunting oxidative stress and protecting neurons*. On the immunological front, suppressing *peripheral immune cell attacks on the brain* (as with $CD4^+$ T-cell inhibition) protected dopamine neurons in PD, pointing to the feasibility of immunotherapy to reduce neurodegenerative damage. These cytokines, including TNF-α, IL-1β, and IL-6, are thought to promote neuroinflammation by activating microglia in the CNS, contributing to dopaminergic neuronal degeneration [5, 16]. Across all reviewed studies, the evidence strongly supports the feasibility of attenuating AD and PD symptoms through strategies that reduce inflammation (gut-driven or immune cell-driven) and bolster neuroprotective mechanisms. While most findings are preclinical, they open promising avenues for developing multi-faceted treatments that modify disease processes, rather than merely managing symptoms. Continued research and clinical trials will be crucial to translating these insights into effective patient therapies.

Personalized Microbiome Medicine and Future Challenges

The growing understanding of the GBA and its relationship with neurological disorders highlights the potential for personalized medicine approaches, which involve tailoring interventions to individual microbiome profiles. Variations in gut microbiota composition influence neuroinflammation, intestinal permeability, and the production of metabolites that either exacerbate or mitigate neurodegenerative processes [27]. For example, reduced levels of beneficial bacteria in people with PD and increased gut inflammation in people with AD suggest that microbiome-targeted therapies, including probiotics, prebiotics, and dietary interventions, could be optimally utilized for each individual. Personalized gut microbiome analyses could enable early disease risk assessment, customized therapeutic strategies, and enhanced patient outcomes [28]. These findings highlight the importance of implementing strategies to restore beneficial microbial metabolites and mitigate neuroinflammation in neurodegenerative diseases. However, challenges such as microbiome variability across populations, environmental influences, and the need for standardized diagnostic tools must be addressed before implementing these strategies [29]. Future research should focus on refining microbiome-based interventions and integrating them with conventional treatments to enhance their effectiveness in the management of AD and PD.

Future Research Directions

Future research should prioritize longitudinal and multi-omic studies to clarify the causality between gut microbiota changes and neurodegeneration [13]. Furthermore, the identification of pathways that connect gut inflammation to brain pathology is significant [14]. Validating microbial biomarkers across diverse populations could support earlier AD detection and more targeted prevention strategies [12]. Finally, the development and testing of gut-targeted therapies in human trials can effectively bring these treatments into clinical use.

Conclusions

Growing recognition of the GBA emphasizes its crucial role in the development and progression of neurodegenerative diseases such as AD and PD. This review highlights how gut dysbiosis, GI inflammation, and the production of altered microbial metabolites significantly contribute to systemic and neuroinflammatory processes that drive disease pathology. Gut microbiota dysbiosis can cause increased intestinal permeability, allowing endotoxins like LPS to enter circulation and promote neurodegeneration due to prolonged immune activation.

Increasing evidence supports the potential of gut-targeted treatments, such as probiotics, dietary modification, anti-inflammatory medications, and microbiome reconstitution therapies, as strategies for mitigating neurodegenerative disease progression. Preclinical studies consistently demonstrate that modifying the gut microbiota can reduce motor and cognitive dysfunction, reinforcing the gut as a promising therapeutic target. Furthermore, gut-derived metabolites have emerged as promising biomarker targets for early diagnosis and disease monitoring.

Despite such progress, various gaps in the research remain. Causal connections between gut dysbiosis and neurodegeneration must be defined through longitudinal studies. Additionally, the considerable variability of individual microbiomes complicates the development of standardized therapies, suggesting a future need for personalized microbiome-based approaches in medicine. Future studies should focus on validating gut-based biomarkers, improving microbiome-targeted treatments, and integrating these strategies into mainstream clinical practice.Overall, the GBA presents a promising and multifaceted approach for preventing or delaying the onset of neurodegenerative diseases. Continued research into gut-mediated neuroinflammatory processes and the translation of this knowledge into clinical applications will advance the development of new treatments that address the root causes, rather than just the symptoms, of neurodegenerative diseases such as AD and PD.

List of Abbreviations
AD: Alzheimer's disease
CNS: central nervous system
GBA: gut-brain axis
GI: gastrointestinal
IBD: inflammatory bowel disease(s)
IL-1β: interleukin-1 beta
LPS: lipopolysaccharides
MEMRI: manganese-enhanced magnetic resonance imaging
PD: Parkinson's disease
SCFAs: short-chain fatty acids

Conflicts of Interest
The authors declare no conflicts of interest.

Ethics Approval and/or Participant Consent
Not applicable. This study is a literature review and did not involve human participants or animal subjects.

Authors' Contributions
PA: Made substantial contributions to the study's design, collecting and analyzing data, drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.
SP: Made substantial contributions to the study's design, collecting and analyzing data, drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Acknowledgements
We would like to express our sincere gratitude to our mentor, Mikayala Hall-Bruce, for her invaluable guidance, encouragement, and support throughout the course of this project.

Funding
No specific funding was received for this work.

References
[1] Giau VV, Wu SY, Jamerlan A, An SSA, Kim SY, Hulme J. Gut microbiota and their neuroinflammatory implications in Alzheimer's disease. Nutrients. 2018;10(11):1765. Available from: https://doi.org/10.3390/nu10111765
[2] Megur A, Baltriukienė D, Bukelskienė V, Burokas A. The microbiota–gut–brain axis and Alzheimer's disease: neuroinflammation is to blame? Nutrients. 2020 Dec 24;13(1):37. Available from: https://doi.org/10.3390/nu13010037
[3] Klingelhoefer L, Reichmann H. Pathogenesis of Parkinson disease—the gut–brain axis and environmental factors. Nat Rev Neurol. 2015 Nov;11(11):625–636. Available from: https://doi.org/10.1038/nrneurol.2015.197
[4] Menozzi E, Macnaughtan J, Schapira AHV. The gut-brain axis and Parkinson disease: clinical and pathogenetic relevance. Ann Med. 2021 Apr 16;53(1):611–625. Available from: https://doi.org/10.1080/07853890.2021.1890330
[5] Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? NPJ Parkinsons Dis. 2017 Jan 11;3:3. Available from: https://doi.org/10.1038/s41531-016-0002-0
[6] Ji Z, Chen Q, Yang J, Hou J, Wu H, Zhang L. Global, regional, and national health inequalities of Alzheimer's disease and Parkinson's disease in 204 countries, 1990–2019. Int J Equity Health. 2024 Jun 19;23:125. Available from: https://doi.org/10.1186/s12939-024-02212-5
[7] Gorecki AM, McManus RM, O'Neill LAJ. The gut-brain axis and gut inflammation in Parkinson's disease: stopping neurodegeneration at the toll gate. Expert Opin Ther Targets. 2020 Jul;24(7):601–4. Available from: https://doi.org/10.1080/14728222.2020.1763956
[8] Chen SJ, Lin CH. Gut microenvironmental changes as a potential trigger in Parkinson's disease through the gut–brain axis. J Biomed Sci. 2022 Jul 27;29(1):54. Available from: https://doi.org/10.1186/s12929-022-00839-6
[9] Kesika P, Suganthy N, Sivamaruthi BS, Chaiyasut C. Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease. Life Sci. 2021 Jan;264:118627. Available from: http://doi.org/10.1016/j.lfs.2020.118627
[10] Fülöp T, Larbi A, Witkowski JM. Human inflammaging. Gerontology. 2019;65(5):495–504. Available from: https://doi.org/10.1159/000497375
[11] DeGruttola AK, Low D, Mizoguchi A, Mizoguchi EM. Current understanding of dysbiosis in disease in human and animal models. Inflamm Bowel Dis. 2016 May;22(5):1137–1150. Available from: https://doi.org/10.1097/MIB.0000000000000750
[12] Shen H, Guan Q, Zhang X, Yuan C, Tan Z, Zhai L, et al. New mechanism of neuroinflammation in Alzheimer's disease: The activation of NLRP3 inflammasome mediated by gut microbiota. Prog Neuropsychopharmacol Biol Psychiatry. 2020 Jun;100:109884. Available from: https://doi.org/10.1016/j.pnpbp.2020.109884
[13] Heston MB, Hanslik KL, Zarbock KR, et al. Gut inflammation associated with age and Alzheimer's disease pathology: a human cohort study. Sci Rep. 2023 Nov 14;13(1):18924. Available from: https://doi.org/10.1038/s41598-023-45929-z
[14] Wang F, Fei M, Hu WZ, Wang XD, Liu S, Zeng Y, et al. Prevalence of constipation in elderly and its association with dementia and mild cognitive impairment: A cross-sectional study. Front Neurosci. 2022 Jan 24;15:821654. Available from: https://doi.org/10.3389/fnins.2021.821654

[15] Denman CR, Park SM, Jo J. Gut-brain axis: Gut dysbiosis and psychiatric disorders in Alzheimer's and Parkinson's disease. Front Neurosci. 2023;17:1268419. Available from: https://doi.org/10.3389/fnins.2023.1268419
[16] Gorecki AM, Preskey L, Bakeberg MC, Kenna JE, Gildenhuys C, MacDougall G, et al. Altered gut microbiome in Parkinson's disease and the influence of lipopolysaccharide in a human α-synuclein over-expressing mouse model. Front Neurosci. 2019;13:839. Available from: https://doi.org/10.3389/fnins.2019.00839
[17] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell. 2016 Dec 1;167(6):1469–1480.e12. Available from: https://doi.org/10.1016/j.cell.2016.11.018
[18] Aho VTE, Pereira PAB, Voutilainen S, Paulin L, Pekkonen E, Auvinen P, et al. Gut microbiota in Parkinson's disease: Temporal stability and relations to disease progression. EBioMedicine. 2019 Jun;44:691–707. Available from: https://doi.org/10.1016/j.ebiom.2019.05.064
[19] Mitchell J, Kim SJ, Howe C, Lee S, Her JY, Patel M, et al. Chronic intestinal inflammation suppresses brain activity by inducing neuroinflammation in mice. Am J Pathol. 2022 Jan;192(1):72–86. Available from: https://doi.org/10.1016/j.ajpath.2021.09.006
[20] Ishola IO, Awogbindin IO, Olubodun-Obadun TG, Oluwafemi OA, Onuelu JE, Adeyemi OO. Morin ameliorates rotenone-induced Parkinson's disease in mice through antioxidation and anti-neuroinflammation: Gut-brain axis involvement. Brain Res. 2022 Aug;1789:147958. Available from: https://doi.org/10.1016/j.brainres.2022.147958
[21] Zhu M, Liu X, Ye Y, Yan X, Cheng Y, Zhao L, et al. Gut microbiota: A novel therapeutic target for Parkinson's disease. Front Immunol. 2022 Jun 24;13:937555. Available from: https://doi.org/10.3389/fimmu.2022.937555
[22] Huang S, Chen Z, Fan B, Chen Y, Zhou L, Jiang B, et al. A selective NLRP3 inflammasome inhibitor attenuates behavioral deficits and neuroinflammation in a mouse model of Parkinson's disease. J Neuroimmunol. 2021 May;354:577543. Available from: https://doi.org/10.1016/j.jneuroim.2021.577543
[23] Pasinetti GM, Singh R, Westfall S, Herman F, Faith J, Ho L. The role of the gut microbiota in the metabolism of polyphenols as characterized by gnotobiotic mice. J Alzheimers Dis. 2018;63(2):409–421. Available from: https://doi.org/10.3233/JAD-171151
[24] Boehme M, Guzzetta KE, Wasén C, Cox LM. The gut microbiota is an emerging target for improving brain health during ageing. Gut Microbiome (Camb). 2023;4:e2. Available from: https://doi.org/10.1017/gmb.2022.11
[25] Kalyan M, Tousif AH, Sonali S, Vichitra C, Sunanda T, Praveenraj SS, et al. Role of endogenous lipopolysaccharides in neurological disorders. Cells. 2022 Dec 14;11(24):4038. Available from: https://doi.org/10.3390/cells11244038
[26] Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. Nat Med. 2018 Apr;24(4):392–400. Available from: https://doi.org/10.1038/nm.4517
[27] Solanki R, Karande A, Ranganathan P. Emerging role of gut microbiota dysbiosis in neuroinflammation and neurodegeneration. Front Neurol. 2023 May 15;14:1149618. Available from: https://doi.org/10.3389/fneur.2023.1149618
[28] Loh JS, Mak WQ, Tan LK, Ng CX, Chan HH, Yeow SH, et al. Microbiota–gut–brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduct Target Ther. 2024 Feb 16;9(1):123. Available from: https://doi.org/10.1038/s41392-024-01743-1
[29] Seo D, Holtzman DM. Current understanding of the Alzheimer's disease-associated microbiome and therapeutic strategies. Exp Mol Med. 2024 Jan 4;56(1):86–94. Available from: https://doi.org/10.1038/s12276-023-01146-2

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Mikayla Hall-Bruce, Ricky Chow
Article Dates: Received Apr 27 25; Accepted Sep 05 25; Published Nov 06 25

Citation
Please cite this article as follows:
Abadi P, Perera S. Gut-brain axis dysfunction in Alzheimer's and Parkinson's diseases: The role of dysbiosis, inflammation, and therapeutic targets — A literature review. URNCST Journal. 2025 Nov 06: 9(10). https://urncst.com/index.php/urncst/article/view/907
DOI Link: https://doi.org/10.26685/urncst.907