



Brain–Gut–Microbiota Axis in Parkinson’s Disease: Gut Dysbiosis, Pathophysiological Mechanisms and Therapeutic Perspectives

Rohini. N^[1], Dr. S. Swarnalatha^[2], Dr. J.Karthi^[3], Vignesh M^[4]

^[1] Department of pharmacology – Pallavan pharmacy college, Kanchipuram, E. Mail: rohininatarajan1101@gmail.com

^[2] Department of pharmacology, Head of the Department – Pallavan pharmacy college, Kanchipuram

^[3] Department of Pharmacognosy – Principal of Pallavan Pharmacy College, Kanchipuram

^[4] Department of Pharmacology – Assistant Professor, Pallavan Pharmacy College, Kanchipuram. E. Mail: vigneshjee2202@gmail.com

ABSTRACT

Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor manifestations. Although its major pathological features include degeneration of dopaminergic neurons and accumulation of abnormal alpha-synuclein, increasing research has examined the possible involvement of the gastrointestinal tract and gut microbiota. The brain–gut–microbiota axis represents a bidirectional communication network linking the gastrointestinal tract and central nervous system through neural, immune, endocrine and metabolic pathways. Alterations in gut microbial composition and function, commonly referred to as gut dysbiosis, have been reported in individuals with PD. Proposed mechanisms connecting intestinal changes with neurological processes include altered intestinal barrier function, immune activation, microbial metabolites, enteroendocrine signalling and alpha-synuclein-related processes. The body-first hypothesis suggests that disease-related pathology may begin outside the central nervous system in a subgroup of patients, whereas the brain-first hypothesis proposes an initial central nervous system origin. These concepts may help explain clinical heterogeneity but remain under investigation. Microbiota-directed interventions, including dietary approaches, probiotics, prebiotics and faecal microbiota transplantation, are being explored as potential therapeutic strategies. However, the current evidence does not establish gut dysbiosis as a direct cause of PD, and the clinical effectiveness of microbiota-targeted treatments remains uncertain. This review discusses the brain–gut–microbiota axis in PD, with emphasis on gut dysbiosis, proposed pathophysiological mechanisms, therapeutic perspectives and future research directions.

Keywords: Parkinson’s disease; gut microbiota; gut dysbiosis; brain–gut–microbiota axis; alpha-synuclein; neuroinflammation; intestinal barrier.

INTRODUCTION

Parkinson’s disease (PD) is a progressive neurodegenerative disorder associated with motor symptoms such as bradykinesia, rigidity and resting tremor. Non-motor manifestations, including constipation, sleep disturbances, autonomic dysfunction and mood changes, also contribute to the clinical burden of the disease. The principal pathological features of PD include degeneration of dopaminergic neurons in the substantia nigra and the accumulation of abnormal alpha-synuclein. Although PD has traditionally been studied as a disorder of the central nervous system, increasing attention has been directed towards the gastrointestinal tract and its possible involvement in disease-related processes.

The gastrointestinal tract contains a diverse community of microorganisms, collectively known as the gut microbiota. These microorganisms participate in digestion, metabolism, intestinal barrier maintenance and immune regulation. Communication between the gut and the brain occurs through the brain–gut–microbiota axis, a bidirectional network involving neural, immune, endocrine and metabolic pathways. Research has suggested that changes in gut microbial composition or function may be associated with PD. However, microbial findings differ across studies, and it remains uncertain whether these alterations contribute to disease development, result from the disease, or are influenced by factors such as diet, medication and gastrointestinal dysfunction.

Gastrointestinal symptoms, particularly constipation, may occur before the appearance of motor symptoms in some individuals with PD. This observation has contributed to interest in the possibility that disease-related processes may involve the gastrointestinal tract during early stages. Researchers have proposed that intestinal barrier changes, immune signalling, microbial metabolites and alpha-synuclein-related processes may participate in communication between the gut and brain. The enteric nervous system and vagus nerve have also been investigated as potential pathways connecting intestinal events with central nervous system processes. Nevertheless, these mechanisms are not established as a universal sequence of disease development.

The body-first and brain-first hypotheses have been proposed to explain differences in the possible origin and progression of PD. The body-first hypothesis suggests that pathology may begin in peripheral sites, potentially including the gastrointestinal tract, before involving the brain. In contrast, the brain-

first hypothesis proposes that disease-related changes may initially arise within the central nervous system. These concepts may help explain differences in clinical presentation, but they remain hypotheses and may not account for all patients.

Interest in the brain–gut–microbiota axis has also encouraged research into microbiota-directed therapeutic approaches. Dietary interventions, probiotics, prebiotics, faecal microbiota transplantation and other strategies are being investigated for their potential to influence gut microbial composition and gut–host communication. However, their ability to prevent PD or modify its progression has not been established.

Therefore, this review discusses the brain–gut–microbiota axis in PD, focusing on gut dysbiosis, proposed mechanisms connecting intestinal changes with neurological processes, emerging therapeutic approaches and current research limitations.

OVERVIEW OF PARKINSON'S DISEASE

Parkinson's disease is a multisystem neurological disorder with a variable clinical presentation. Its motor features are commonly associated with dysfunction of dopaminergic pathways, particularly those involving the substantia nigra and striatum. The loss of dopaminergic neurons contributes to impaired movement control and the development of characteristic motor symptoms.

Alpha-synuclein is a neuronal protein that has been implicated in PD pathology. Abnormal accumulation and aggregation of alpha-synuclein are associated with Lewy pathology. Although the precise sequence of events leading to neuronal degeneration remains incompletely understood, alpha-synuclein-related processes are central to current models of PD pathophysiology.

PD also involves non-motor systems, including the autonomic and gastrointestinal systems. Constipation and other gastrointestinal symptoms are important because they may occur early in the disease course and can affect quality of life. The presence of gastrointestinal manifestations has encouraged investigation into possible interactions between intestinal physiology, microbial communities and neurological processes.

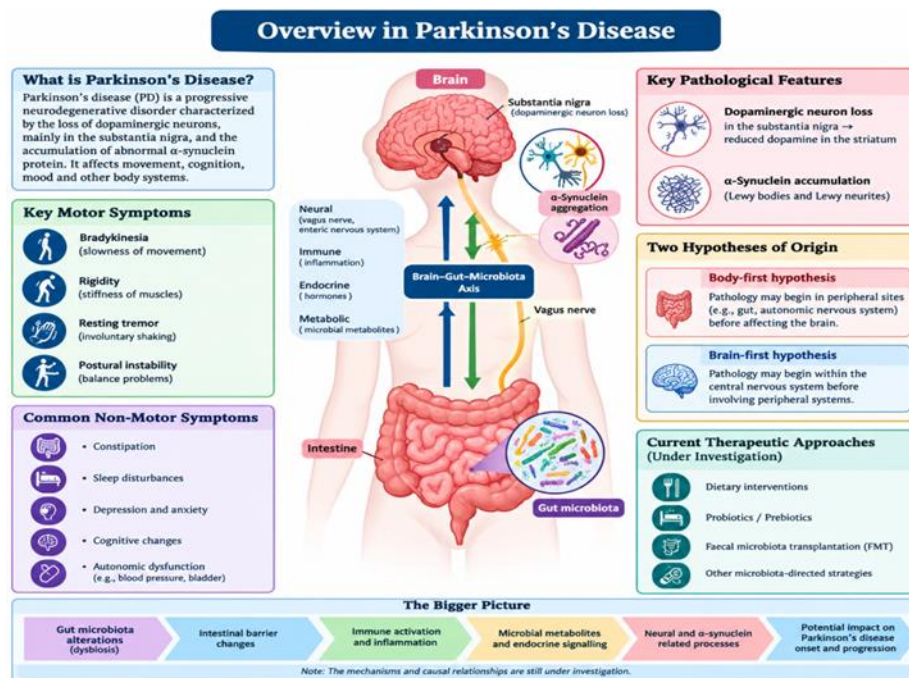


Fig no.01: Overview In Parkinson's Disease

THE BRAIN–GUT–MICROBIOTA AXIS

The brain–gut–microbiota axis describes communication among the central nervous system, gastrointestinal tract and gut microorganisms. This communication is bidirectional: signals from the brain can influence intestinal function, while intestinal signals may affect neural, immune and metabolic processes.

Neural communication

The enteric nervous system regulates several gastrointestinal functions, including motility and secretion. It communicates with the central nervous system through autonomic pathways, including the vagus nerve. These connections have been investigated as possible routes through which gut-related signals may influence the brain.

In PD research, neural communication is relevant to the hypothesis that alpha-synuclein-related pathology may involve the enteric nervous system and potentially spread through connected neural pathways. However, the extent and direction of such processes in humans remain uncertain.

Immune communication

The intestinal immune system interacts with gut microorganisms and their products. Changes in microbial composition or intestinal barrier function may influence immune activity and inflammatory signalling. Researchers are investigating whether these signals contribute to systemic inflammation or processes relevant to neuroinflammation in PD.

The relationship between intestinal immune activity and brain inflammation is complex. Current evidence supports further investigation of this pathway but does not establish that intestinal inflammation is a necessary or sufficient cause of PD.

Endocrine communication

The gastrointestinal tract contains enteroendocrine cells that release signalling molecules in response to nutrients and other intestinal stimuli. These cells may interact with neural and metabolic pathways and have received increasing attention in PD research.

Altered enteroendocrine signalling has been proposed as one possible link between the intestinal environment and neurological processes. Further research is required to clarify its contribution to disease initiation or progression.

Microbial and metabolic communication

Gut microorganisms produce and modify a variety of metabolites that may influence intestinal function, immune activity and host metabolism. These metabolites provide one possible route through which the microbiota may affect gut–brain communication.

The biological effects of microbial metabolites depend on their type, concentration, location and interaction with the host. Therefore, changes in microbial abundance alone may not fully explain functional changes in the gut–brain axis.

GUT DYSBIOSIS IN PARKINSON'S DISEASE

Gut dysbiosis generally refers to an alteration in the composition or function of the gut microbial community. In PD, researchers have investigated whether microbial changes are associated with gastrointestinal symptoms, disease characteristics or biological processes relevant to neurodegeneration.

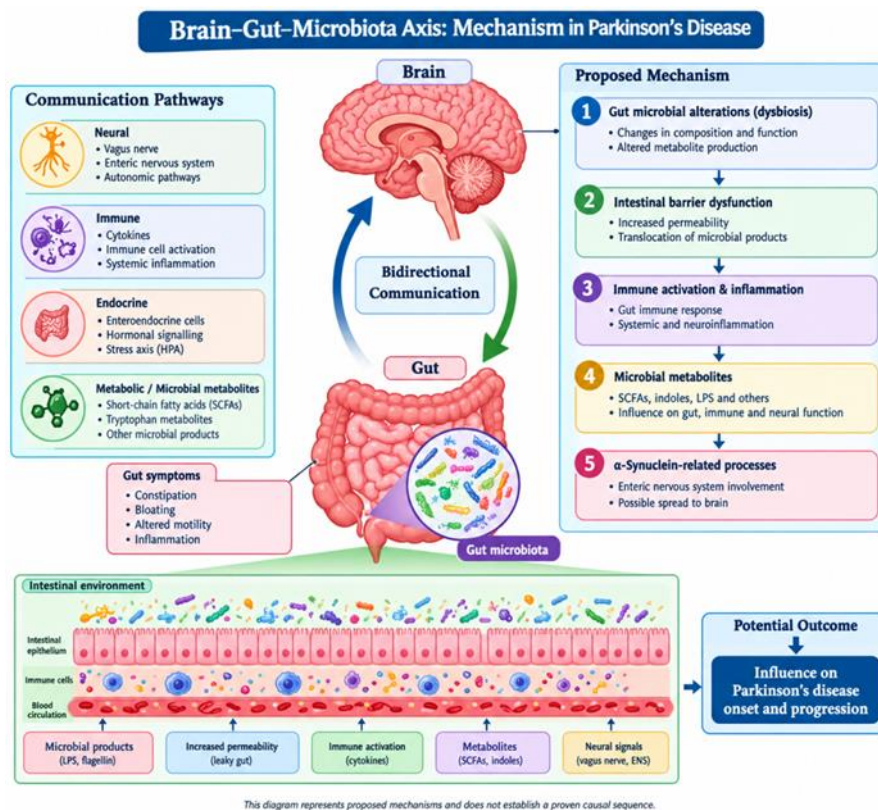


Fig no.02: Brain gut microbiota axis: Mechanism in Parkinsons Disease

Clinical studies have reported differences in gut microbial composition between people with PD and control groups. However, the findings are not fully consistent across studies. Differences in study populations, dietary habits, medication exposure, constipation, sample collection and analytical methods may contribute to variation in reported results.

It is also important to distinguish between microbial composition and microbial function. Two individuals may have different microbial communities but similar functional capacities, while similar microbial profiles may produce different metabolic outputs under different conditions. Consequently, studies examining microbial genes, metabolites and host responses may provide additional information beyond taxonomic measurements.

At present, the evidence supports an association between gut microbial alterations and PD in at least some study populations. It does not establish that a single microbial pattern is present in all patients or that dysbiosis directly causes the disease.

PROPOSED PATHOPHYSIOLOGICAL MECHANISMS

Several mechanisms have been proposed to explain how gut-related changes might interact with neurological processes in PD. These mechanisms may overlap and should not be interpreted as a confirmed step-by-step sequence.

Intestinal barrier dysfunction

The intestinal barrier regulates the movement of substances between the intestinal lumen and the body. It includes epithelial cells, intercellular junctions, mucus and immune components. Alterations in barrier function may affect exposure to microbial products and influence local immune responses.

In PD research, intestinal barrier changes have been investigated as a possible factor linking gut microbial alterations with inflammation and neurological processes. However, the extent to which barrier dysfunction contributes to disease development or progression remains uncertain.

Immune activation and inflammation

The gut microbiota interacts with intestinal immune cells and may influence inflammatory signalling. Changes in microbial composition, microbial products or intestinal barrier function could affect immune responses.

Researchers have proposed that inflammatory signals originating in the gut may interact with systemic and central nervous system immune pathways. Neuroinflammation is also relevant to PD pathology, but the precise contribution of gut-derived inflammation to human disease remains under investigation.

Microbial metabolites

Gut microorganisms produce metabolites that may influence host physiology. These include short-chain fatty acids and other compounds involved in metabolic and immune signalling. Such metabolites may affect intestinal function and provide communication between the microbiota and host tissues.

The relationship between microbial metabolites and PD is complex. A metabolite may have different effects depending on its concentration, tissue location and biological context. Further studies are needed to determine which microbial metabolites are consistently altered in PD and whether modifying them produces meaningful clinical effects.

Alpha-synuclein-related processes

Alpha-synuclein pathology has been observed in both central and peripheral nervous system structures. This has led to the hypothesis that pathological alpha-synuclein-related processes may involve the enteric nervous system in some patients.

The proposed body-first model suggests that pathology may begin in peripheral sites and spread towards the brain through connected neural pathways. However, the presence of gastrointestinal symptoms or intestinal alpha-synuclein-related findings does not by itself prove that the disease originated in the gut. The relevance of this mechanism may differ among patients.

Enteroendocrine cell signalling

Enteroendocrine cells detect signals within the intestinal environment and release molecules that participate in gut–host communication. Their potential interaction with alpha-synuclein-related processes and neural pathways has become an area of interest in PD research.

Although this pathway may provide additional insight into interactions between intestinal physiology and the nervous system, its precise role in human PD requires further investigation.

THERAPEUTIC PERSPECTIVES

The brain–gut–microbiota axis has become a potential research target in PD. Several interventions are being investigated for their ability to influence gut microbial composition, intestinal function or gut–host signalling.

Dietary approaches

Diet can influence the composition and metabolic activity of gut microorganisms. Dietary interventions are therefore being studied as possible ways to support gastrointestinal health and modify microbial function.

However, the effects of dietary approaches may vary according to individual characteristics, nutritional patterns and disease status. Their ability to alter the course of PD has not been established.

Probiotics and prebiotics

Probiotics are live microorganisms intended to provide a health benefit when administered in adequate amounts. Prebiotics are substrates selectively used by host microorganisms that may provide a health benefit. Both approaches have been investigated in relation to gastrointestinal symptoms and gut microbial function.

Their potential role in PD requires further evaluation, particularly regarding strain selection, dose, treatment duration, clinical outcomes and long-term safety.

Faecal microbiota transplantation

Faecal microbiota transplantation (FMT) involves transferring a processed microbial community from a donor to a recipient. It has been investigated as a method of altering the gut microbiota.

FMT remains an investigational approach for PD. Questions remain regarding patient selection, donor screening, treatment protocols, durability of microbial changes, safety and clinically meaningful outcomes. It should not be described as an established treatment for preventing or modifying PD progression.

Other microbiota-directed approaches

Additional approaches under investigation include interventions targeting microbial activity, intestinal signalling and related metabolic pathways. The therapeutic rationale is to modify specific biological processes rather than assume that all microbial changes are harmful.

Future studies should determine whether microbiota-directed interventions produce reproducible clinical benefits and identify which patient groups, if any, may benefit.

LIMITATIONS AND RESEARCH GAPS

Despite growing interest in the brain–gut–microbiota axis, several limitations affect interpretation of the current evidence.

First, many human studies are observational and cannot establish whether microbial alterations precede or follow PD. Second, differences in study populations and methods make comparisons difficult. Third, medication use, diet, constipation and other gastrointestinal symptoms may influence microbiome findings. Fourth, animal models can help investigate mechanisms but may not fully reproduce the complexity of human PD.

There is also a need to distinguish microbial associations from functional effects. Future research should combine microbial profiling with metabolomic, immune, intestinal and clinical measurements. Longitudinal studies may help determine whether changes in the gut microbiota occur before disease onset, accompany disease progression or reflect treatment and lifestyle factors.

Clinical trials of microbiota-directed therapies should use appropriate control groups, standardized intervention protocols and clearly defined outcomes. Studies should also assess safety and determine whether observed changes are sustained over time.

FUTURE PERSPECTIVES

Future research should focus on identifying reproducible microbial and metabolic patterns associated with PD and understanding how these patterns relate to clinical characteristics. Longitudinal studies involving individuals at different disease stages may help clarify the timing of gut-related changes.

Integrated approaches combining microbiome analysis, metabolomics, immune markers and clinical assessment may provide a more complete understanding of gut–brain communication. Researchers should also investigate whether differences in gastrointestinal symptoms or clinical phenotype are associated with distinct gut-related mechanisms.

Therapeutic research should move beyond demonstrating changes in microbial composition and determine whether interventions produce meaningful benefits for patients. Carefully designed clinical trials are required before microbiota-directed approaches can be recommended as disease-modifying treatments.

CONCLUSION

The brain–gut–microbiota axis is an important emerging area of Parkinson's disease research. Studies have reported gut microbial alterations and have proposed several mechanisms connecting the gastrointestinal tract with neurological processes, including intestinal barrier changes, immune signalling, microbial metabolites, enteroendocrine pathways and alpha-synuclein-related processes. The body-first and brain-first hypotheses provide possible frameworks for understanding differences among patients, but neither explains all cases of PD.

Microbiota-directed interventions, including dietary approaches, probiotics, prebiotics and faecal microbiota transplantation, are being investigated as potential therapeutic strategies. However, the causal role of gut dysbiosis and the clinical effectiveness of these interventions remain uncertain. Further

longitudinal, mechanistic and clinical studies are necessary to establish the relevance of the brain–gut–microbiota axis to PD development, progression and treatment.

REFERENCES

1. Tan AH, Lim SY, Lang AE. The microbiome–gut–brain axis in Parkinson disease—from basic research to the clinic. *Nat Rev Neurol*. 2022;18(8):476–495. doi:10.1038/s41582-022-00681-2. PMID: 35750883.
2. Menozzi E, Schapira AHV, Borghammer P. The Gut-Brain Axis in Parkinson disease: Emerging Concepts and Therapeutic Implications. *Mov Disord Clin Pract*. 2025;12(7):904–916. doi:10.1002/mdc3.70029. PMID: 40079755.
3. Chen SJ, Lin CH. Gut microenvironmental changes as a potential trigger in Parkinson's disease through the gut–brain axis. *J Biomed Sci*. 2022;29:54. doi:10.1186/s12929-022-00839-6.
4. Nishiwaki H, Ueyama J, Ito M, Hamaguchi T, Takimoto K, Maeda T, et al. Meta-analysis of shotgun sequencing of gut microbiota in Parkinson's disease. *NPJ Parkinsons Dis*. 2024;10:106. doi:10.1038/s41531-024-00724-z. Nature
5. Rajkovaca Latic I, et al. Association of intestinal inflammation and permeability markers with clinical manifestations of Parkinson's disease. *Parkinsonism Relat Disord*. 2024;123:106948. doi:10.1016/j.parkreldis.2024.106948. ScienceDirect
6. Rusch C, Beke M, Nieves C Jr, Mai V, Stiep T, Tholanikunnel T, et al. Promotion of a Mediterranean diet alters constipation symptoms and fecal calprotectin in people with Parkinson's disease: a randomized controlled trial. *Nutrients*. 2024;16(17):2946. doi:10.3390/nu16172946. PubMed Central (PMC)
7. Gut microbial metabolites and future risk of Parkinson's disease: a metabolome-wide association study. *Mov Disord*. 2024. PubMed Central (PMC)
8. Recent human microbiome research in Parkinson's disease: gut/oral microbiome profiling and candidate microbial signatures. 2024.
9. Use this as a supporting recent microbiome study in your biomarker section; if you want, I can identify the exact full citation from the specific paper you selected rather than inserting an incomplete reference.
10. Gut microbiota modulation via repeated donor fecal transplantation improves motor and gastrointestinal symptoms in drug-naïve Parkinson's disease: a randomized phase 2 trial. 2026.
11. This is a particularly recent human intervention study: 72 participants were randomized, with improvements reported in motor and constipation outcomes after donor FMT. PubMed
12. Human gut–brain–microbiota axis research in Parkinson's disease: emerging evidence for body-first/brain-first mechanisms, α -synuclein propagation, intestinal inflammation and microbiota-directed therapies. 2025.
13. Menozzi et al. is the key source for this section and should be cited directly rather than relying on a secondary summary. Movement Disorder Society.
14. Scheperjans F, Levo R, Bosch B, Lääperi M, Pereira PAB, Smolander OP, et al. Fecal microbiota transplantation for treatment of Parkinson disease: a randomized clinical trial. *JAMA Neurol*. 2024;81(9):925–938. doi:10.1001/jamaneurol.2024.2305. PubMed
15. Cassani E, et al. Safety and efficacy of faecal microbiota transplantation in patients with mild to moderate Parkinson's disease (GUT-PARFECT): a double-blind, placebo-controlled, randomised, phase 2 trial. *EClinicalMedicine*. 2024;71:102563. doi:10.1016/j.eclinm.2024.102563. PubMed Central (PMC)
16. Benvenuti L, Di Salvo C, Bellini G, Seguella L, Rettura F, Esposito G, et al. Gut-directed therapy in Parkinson's disease. *Front Pharmacol*. 2024;15:1407925. doi:10.3389/fphar.2024.1407925. Frontiers
17. De Sciscio M, Bryant RV, Haylock-Jacobs S, Day AS, Pitchers W, Iansek R, et al. Faecal microbiota transplant in Parkinson's disease: pilot study to establish safety & tolerability. *NPJ Parkinsons Dis*. 2025;11:203. doi:10.1038/s41531-025-01061-5. Nature
18. Leta V, et al. Effects of a four-strain probiotic on gut microbiota, inflammation, and symptoms in Parkinson's disease: a randomized clinical trial. *Mov Disord*. 2025;40(12):2710–2721. doi:10.1002/mds.70047. Movement Disorder Society
19. A prebiotic dietary pilot intervention restores faecal metabolites and may be neuroprotective in Parkinson's disease. *NPJ Parkinsons Dis*. 2025;11:66. doi:10.1038/s41531-025-00885-5. DOI
20. Gut microbiota modulation via repeated donor fecal transplantation improves motor and gastrointestinal symptoms in drug-naïve Parkinson's disease: a randomized phase 2 trial. [2026]. PubMed