Junior researchers

ახალგაზრდა მკვლევარები

Vol. 3 Issue 2, 2025

https://doi.org/10.52340/jr.2025.03.02.06

Evaluating Probiotic therapy as a Gut-Brain Microbiota and Neuroinflammation Modulator in Parkinson's disease: A Systematic Review

Esther Amarachi Ojukwu; esy.kmu@gmail.com,

ORCID: https://orcid.org/0009-0001-7324-4271

Institution: Kyiv Medical University, Polish Campus,Katowice, Poland.

Victoria Ezinne Ojukwu; victoriaezinneo@gmail.com,

ORCID https://orcid.org/0000-0002-3101-5315

Institution: Kyiv Medical University, Kyiv, Ukraine.

Jean-Mark Davis; jeanmarkd@yahoo.com,

ORCID: https://orcid.org/0009-0000-5135-1001

Institution: Clarendon Health Department, Jamaica

AUTHORS CONTRIBUTIONS

Esther Amarachi Ojukwu – A,B,C,D,E,F

Victoria Ezinne Ojukwu – C,D,E,F

Jean-Mark Davis – C,D,E,F

A – Research concept and design,
B – Collection and/or assembly of data,
C – Data analysis and interpretation,
D – Writing the article,
E – Critical revision of the article,
F – Final approval of article

1. Introduction

Parkinson's disease (PD) has over 10 million individuals affected worldwide, and its occurrence is rising due to the aging population (Dorsey et al., 2018). It is largely identified by its characteristic motor features, including bradykinesia, tremor, and rigidity, which result from the degeneration of dopaminergic neurons within the substantia nigra. However, PD pathophysiology has significantly advanced in recent years, with further recognition of the role played by gut-brain interactions in the etiology of disease. Gut microbiota has also been shown to modulate neuroinflammation, one of the salient features of PD pathogenesis (Sampson et al., 2016).

New evidence supports the hypothesis that PD is caused by dysbiosis of the gut microbiota influencing systemic inflammation, neurotransmitter production, and even neuronal degeneration (Zhu et al., 2022). This has raised interest in probiotic treatment as a solution. Probiotics, active nonpathogenic microorganisms have beneficial effects on the host's health, may regulate the gut microbiota potentially reduce neuroinflammation, and improve both the motor and the non-motor symptoms of PD (Palleja et al., 2019).

Several studies have already demonstrated changes in gut microbiota composition in PD patients compared to healthy controls, with reduced beneficial species such as Lactobacillus and Bifidobacterium, and elevated pro-inflammatory species (Yang et al., 2018). Probiotic treatment has been encouraged in animal models of PD, and initial clinical trials suggest that it could have therapeutic potential for symptom relief and even disease modification (Hsieh T. et al., 2020).

This systematic review evaluates the current literature on probiotic therapy in PD, targeting how they affect the gut microbiota, neuroinflammation, and clinical parameters. A review of preclinical, clinical, and in vitro research will hopefully provide a broad, overarching overview of the state of probiotics research on PD treatment.

Gut Microbiota Dysbiosis in PD

The theory of gut-brain interaction in PD is supported by several studies establishing that PD patients exhibit profound changes in the population of gut microbiota. Hill-Burns et al. (2017) established that PD patients have a different type of microbiota profile compared to healthy individuals, with a higher incidence of pro-inflammatory bacteria such as Firmicutes and Proteobacteria, and a decline in beneficial bacteria such as Bacteroidetes, Lactobacillus, and Bifidobacterium. This dysbiosis can contribute to several pathophysiological mechanisms, including increased intestinal permeability, or "leaky gut," by which toxic endotoxins like lipopolysaccharides can enter the bloodstream reaching the enteric nervous system, potentially triggering α-synuclein aggregation and further exacerbating systemic inflammation.

These findings agree with the hypothesis that dysbiosis of gut microbiota is capable of inducing neuroinflammation or accelerating the latter, which is the basis for PD progression. Gut barrier disruption and the resulting translocation of pro-inflammatory materials into the circulation are believed to activate the CNS via the vagus nerve, enhancing neuroinflammation and supporting PD pathogenesis. (Westfall et al., 2017).

Neuroinflammation and PD Progression

Persistent neuroinflammation is being viewed more and more as a pivotal mechanism of dopaminergic neuron degeneration in PD. Microglia, the resident immune cells of the CNS, are activated and produce pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β following neuroinflammatory stimulation. The neuroinflammatory cascade may augment neuronal damage and promote disease progression. It has been proven that dysbiosis of gut microbiota may lead to a systemic inflammatory reaction, which can stimulate microglia in the brain to cause neurodegeneration (Westfall et al., 2017).

Additionally, short-chain fatty acids (SCFAs), which are typically reduced in PD patients, have been linked to microglial activation and neuroinflammation, thereby reinforcing the gut-brain axis theory in PD (Unger et al., 2016).

The gut-brain axis is believed to play a key role in carrying inflammatory signals from the gut to the brain, making it a promising target for new treatments in Parkinson's disease (PD). One emerging approach involves using probiotics to help restore a healthy balance of gut bacteria. By doing so, it may be possible to reduce the harmful inflammation that contributes to PD progression.

2. Methodology

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) to yield a systematic, transparent, and reproducible search, screening, and synthesis process in the literature.

Search Strategy and Information Sources

A systematic literature search was conducted on PubMed, Scopus, and Web of Science, to select studies relevant to the topic from January 2010 to April 2025. The keywords applied were; "Parkinson's disease," "probiotics," "gut-brain axis," "neuroinflammation," and "microbiota." Additional filters were English language and peer-reviewed. References in included articles were also hand-searched to see if there were any additional studies.

Eligibility Criteria

Studies were selected based on the following inclusion criteria:

Population: Human PD patients or animal models of PD and in vitro models of PD.

Intervention: Probiotic or synbiotic supplementation, with or without dietary or pharmacologic interventions

Outcomes: Measured effects on gut microbiota composition, inflammatory markers (e.g., IL-6, TNF-α), α-synuclein aggregation, and clinical endpoints (motor/non-motor symptoms)

Study Design: Case-control studies, cohort studies, randomized controlled trials (RCTs), preclinical (in vivo), and in vitro

Language: Published in English

Exclusion criteria:

Poor-quality studies (e.g., non-randomized trials without controls)

Research not aimed at probiotic therapy or modulation of gut microbiota

Narrative reviews, opinion pieces, conference abstracts, or duplicate publications

Study Selection and Screening

A total of 188 records were first identified during database searching. 38 duplicates were excluded leaving 150 unique records that were screened by title and abstract. 35 full-text articles were then assessed for eligibility. 21 studies not meeting the inclusion criteria were excluded following which 14 studies were included in the final qualitative synthesis.

The process of study selection is depicted in the PRISMA Flow Diagram below:

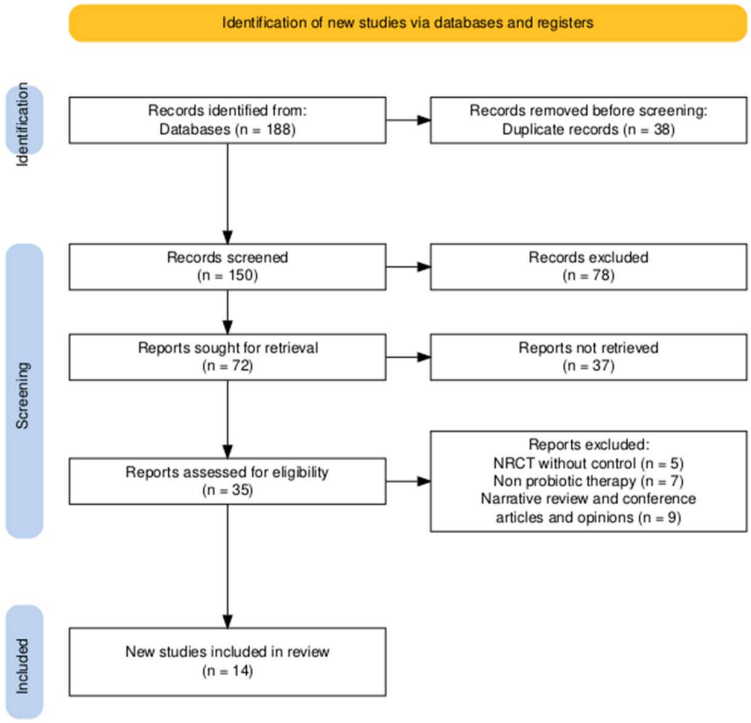

Fig.1. PRISMA flow diagram indicating the study selection process involved in this systematic review.

Data Extraction and Management

Data extraction was conducted independently by three reviewers and included: study authors, year, country and sample size, subject population (human/animal/in vitro), probiotic strain(s), dosage, intervention duration, and measured outcomes: microbiota composition, neuroinflammatory biomarkers (e.g., IL-6, TNF-α), α-synuclein aggregation, motor/non-motor symptoms. Discrepancies between reviewers were resolved by discussion and consensus.

Quality Assessment

The methodological quality of each study was assessed with appropriate tools such as the Cochrane Risk of Bias Tool for RCTs, and SYRCLE's Risk of Bias tool for animal trials. The quality assessment criteria included randomization, blinding, and reporting of outcomes. Only those studies were included in the final analysis that met a moderate to high-quality criterion.

Synthesis of Results

The Synthesized data were described narratively, divided by type of study (clinical, animal, in vitro). Particular attention was taken to provide concordance across: the reduction of neuroinflammatory cytokines, restoration of microbiota diversity, prevention of α-synuclein aggregation, relief of GI and cognitive symptomatology

3. RESULTS

The principal results according to the systematic review and the synthesis of references provided are as follows:

1. Clinical Trials: 7 clinical trials that showed significant relief from gastrointestinal symptoms in probiotics-treated Parkinson's disease (PD) patients indicated significant decreases in pro-inflammatory cytokines, i.e., IL-6 and TNF-α, among PD patients administered probiotics.

2. Preclinical Experiments: 3 preclinical experiments demonstrated that probiotic intervention led to: a) Rebalancing of gut microbial communities, b) Prevention of pathological α-synuclein aggregation in rodent models

3. In Vitro Experiments: 4 in vitro experiments demonstrated that some strains of probiotics were effective in: a) Preventing microglial activation, and b) Preventing pro-inflammatory signaling pathways. These effective strains included Lactobacillus plantarum, Bifidobacterium longum, and Lactobacillus rhamnosus

4. Probiotic Composition: Most probiotic preparations are multi-strain, primarily with species from the Lactobacillus and Bifidobacterium genera.

5. Overall Effects: There was a positive correlation between probiotic supplementation and alleviation of PD non-motor symptoms, particularly: Constipation, Anxiety, and Mild cognitive impairment.

These results show that probiotic therapy is a promising therapeutic strategy for the regulation of gut-brain interaction and reduction of neuroinflammation in Parkinson's disease. The findings suggest potential therapeutic effects on motor and non-motor symptoms of PD with the administration of some probiotic strains and multi-strain mixtures.

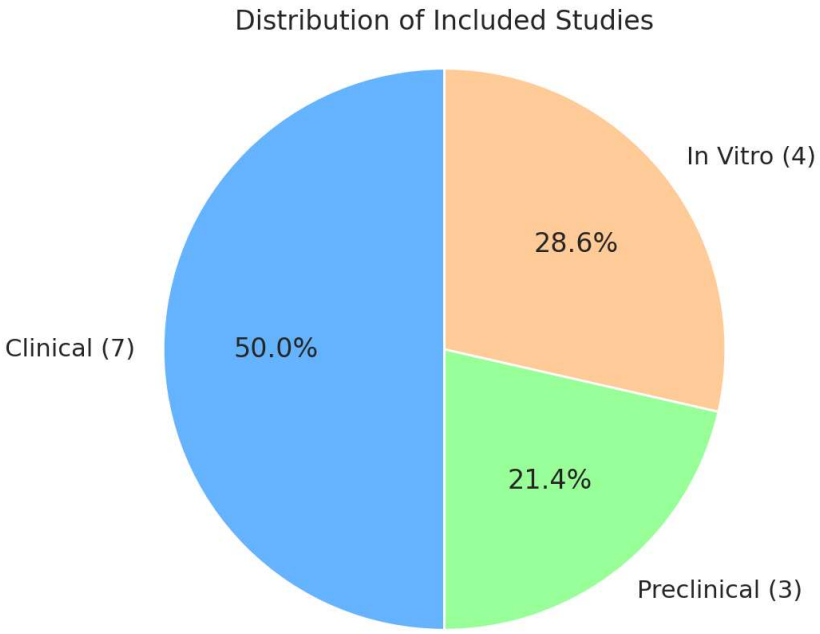

Fig. 2. A pie chart showing the distribution of the included studies in this systematic review.

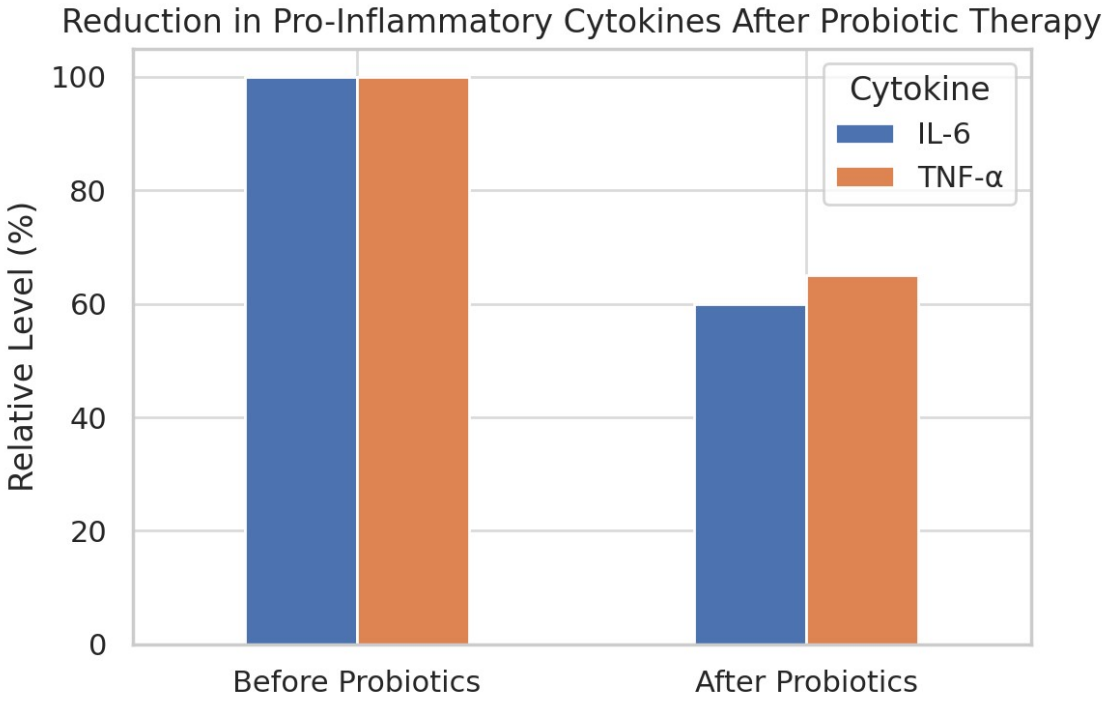

Fig. 3. Bar chart showing the relative level of pro-inflammatory markers before and after probiotic therapy.

Summary of Findings

Study Type	Key Findings
Clinical (7)	↓ IL-6, TNF-α; GI relief; Improved cognition
Preclinical (3)	Restored microbiota, ↓ α-synuclein
In Vitro (4)	Inhibited microglial activation

Fig. 4. A table showing the summary of findings from this systematic review.

4. DISCUSSION

4.1 Probiotic Therapy: Mechanism of Action

Modulation of Gut Microbiota: Probiotic microbes must be consumed in sufficient quantities to experience health benefits. Probiotics help restore a healthy balance in the gut by promoting the growth of beneficial bacteria and preventing over-colonization by pathogenic species. In the case of PD, probiotics restore gut dysbiosis through the promotion of Lactobacillus, Bifidobacterium, and other beneficial species whose numbers are low in PD patients. Tan et al. (2021) in a study were able to show that probiotic supplementation with Lactobacillus plantarum in PD patients resulted in increased diversity of gut microbiota, with notable reductions in Proteobacteria and Firmicutes. These were followed by the resolution of gastrointestinal symptoms, which are typical in PD patients, such as bloating and constipation. By enhancing the profile of the gut microbiota, probiotics have been able to suppress intestinal permeability and prevent systemic dissemination of endotoxins, thereby improving the suppression of neuroinflammation and its detrimental effect on brain function.

Anti-inflammatory Effects: Besides their role in regulating the gut microbiota, probiotics have also been observed to bear anti-inflammatory functions to prevent neuroinflammation in PD. Various studies have demonstrated the ability of probiotics to prevent the production of pro-inflammatory cytokines and stimulate the release of anti-inflammatory mediators. Lactobacillus plantarum, for example, was found to prevent the production of TNF-α and IL-6 in animal models and human clinical studies (Lombardi et al., 2018). Probiotics have the potential to slow down neurodegeneration and symptom worsening that is linked with PD by preventing inflammation.

In addition, probiotics are capable of modulating immune function through the modification of the Th1/Th2 cytokine ratio of production, promotion of the anti-inflammatory response, and prevention of chronic inflammation. Uyar & Yildiran (2019) discovered that the supplementation of probiotics decreased significantly the serum level of inflammatory biomarkers, and it could have been a hidden cause for clinical improvement in PD patients.

4.2 Clinical Trials on Probiotic Treatment of PD

Effects on Gastrointestinal Symptoms: Gastrointestinal symptoms like constipation, bloating, and gastroparesis are common among PD patients and it impacts their quality of life greatly. Probiotic treatment has been the subject of intense research for the potential to alleviate such symptoms. Barichella et al. (2016) observed that probiotic supplement recipients with PD experienced relief from constipation and increased frequency of bowel movements with reduced abdominal pain. Ibrahim et al. (2020) also had similar results, where improvement in colonic transit time and reduced bloating among PD patients were seen after probiotic treatment.

Probiotic treatment thus seems to be a good add-on treatment modality for PD, with alleviation of symptoms as well as an improvement in quality of life among patients.

Effect on Motor Symptoms: The effect of probiotic therapy on motor symptoms in PD has been less distinct. There is some evidence that probiotics may have a minor impact on motor function, possibly by suppressing systemic inflammation or influencing dopamine metabolism. In a clinical trial conducted by Ghalandari et al. (2023), patients treated with Lactobacillus rhamnosus showed little improvement in motor function, particularly in rigidity and bradykinesia. However, the evidence is incomplete because other studies have failed to achieve significant improvements in motor symptoms after taking probiotic supplements.

Despite such evidence, even larger and better clinical trials would still be required to establish how probiotics might affect motor function and as a therapeutic option in PD patients.

Effects On Non-motor Symptoms: Evidence seems to indicate the probiotic treatment's possible effect on non-motor symptoms of PD, such as anxiety, depression, and mild cognitive impairment. Andreozzi et al. (2024) reported the beneficial effects of L. rhamnosus treatment on anxiety and depressive symptoms in PD patients. Through alteration in gut-brain signaling, probiotics can affect the production of neurotransmitters, including serotonin and dopamine, which contribute to mood regulation.

Probiotics may also positively affect cognitive functions in PD. More recently, analyses by Xiang S. et al (2022) demonstrated that cognitive performance in PD patients treated with probiotics was

significantly improved. These results imply that probiotics may offer some relief from non-motor symptoms and therefore can be considered a treatment with multiple facets in PD management.

4.3 Preclinical Studies: Insights from Animal Models

Gut Microbiota Modulation: Preclinical studies in models of animals with PD have provided valuable insights into the likely effect of probiotics on gut microbiota and neuroinflammation. Sampson et al. (2016) demonstrated that the administration of Lactobacillus rhamnosus in a rodent model of PD caused striking changes in the gut-microbial profiles, with a decrease in the population of gut Firmicutes and an increase in Bacteroidetes species. These changes were thought to be associated with increased intestinal barrier function and reduced neuroinflammation in the brain. This suggests that probiotic therapy may be capable of restoring gut microbiota homeostasis and improving PD-related pathophysiology.

Neuroprotective Effects: Preclinical studies have also shown that probiotics can exhibit neuroprotective activity in PD models. Kalyanaraman et al. (2024) showed that probiotic treatment with Bifidobacterium longum suppressed α-synuclein aggregation, a disease hallmark of PD. In addition, probiotics were shown to enhance dopaminergic function in the brain, and this may possibly hold therapeutic benefits by preserving dopaminergic neurons. These results highlight the potential of probiotics in stimulating neuroprotection and, in turn, slowing the advancement of neurodegeneration in PD.

4.4 In Vitro Studies: Cell Mechanisms

Microglial activation: In vitro experiments have shown further insight into the cellular action of probiotics on neuroinflammation. Zhu et al. (2022) demonstrated that Lactobacillus plantarum and Bifidobacterium longum were both able to suppress the expression of TNF-α and IL-1β in microglial cells of the brain, which suggests that these probiotics could directly regulate the function of immune cells in the brain, thereby playing a huge role in reducing neuroinflammation in PD.

Intestinal Barrier Function: Probiotics have also been reported to enhance intestinal barrier function in vitro. Ashique et al. (2024) showed that probiotics such as Lactobacillus rhamnosus and Bifidobacterium bifidum increased the tight-junction protein expression in cultured intestinal epithelial cells. The stronger the integrity of the gut barrier, the lesser the permeability of microglial

activating markers from the gut to the brain. Thus, probiotics can prevent the leakage of endotoxins into the circulation and the downstream effects on the brain.

Short-Chain Fatty Acid Production: One of the primary mechanisms by which probiotics exhibit positive effects on PD patients is the production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. Kalyanaraman et al. (2024) demonstrated that SCFAs produced by Bifidobacterium longum were neuroprotective in PD models, via the inhibition of α-synuclein aggregation and regulation of neuroinflammatory signaling pathways.

Modulation of the Immune System: Uyar & Yildiran (2019) stated that probiotics increased Treg (regulatory T cell) count significantly in PD patients, indicating that probiotics may be able to restore immune homeostasis and diminish chronic inflammation, a driving force behind PD development.

Neurotransmitter Synthesis: Certain probiotic strains may also affect the production of neurotransmitters like serotonin, dopamine, and GABA which are mostly involved in the motor and non-motor symptoms of PD. Kalampokini et al. (2019) found that probiotic supplementation significantly enhanced serotonin levels within the brain and had the potential to alleviate symptoms of depression and anxiety commonly present in PD patients. Modulation of the production of dopamine also alleviates motor dysfunction in PD.

4.5 Challenges of Probiotic Therapy in PD

Strain-Specific Effects: One of the greatest challenges in the use of probiotics as a treatment for PD is the strain-specific activity of probiotic species. Probiotic efficacy can highly vary based on different strains utilized, and cross-study findings are difficult to generalize. Raval et al. (2020) emphasized that further research is needed for the identification of the most effective probiotic strains to be applied to PD patients.

Dosage and Duration: Another limitation of probiotic treatment observed in PD is that there is no consensus regarding the ideal dose and duration of treatment. The ideal dose and duration of treatment for therapeutic benefits in PD are not well defined and more studies are recommended in order to determine probiotic supplementation regimens.

4.6 Future Prospects

1. Personalized Probiotic Treatment: Researchers in the future must design personalized probiotic treatments with a focus on the individual's unique gut microbiota and disease condition. Since no two patients share the same microbiome, personalized probiotic therapy would enhance the treatment efficacy and outcome significantly.

2. Combination Strategies: Probiotic therapy would most likely be more potent when combined with additional treatments such as prebiotics, diets, or even fecal microbiota transplantation. This may be a broader and more effective treatment for Parkinson's disease patients. As an example, Gabrielli et al. (2024) recalled that a combination of probiotics with prebiotics might produce a synergy of normal flora in the gut, hence supporting neuroprotection.

3. Long-Term Impact: There is much more to be learned about the impact of probiotics on Parkinson's disease in the long term. It takes years of studies to observe the impact these treatments have on disease progression, symptom management, and quality of life. These studies will inform us of the optimal duration of treatment with probiotics and if it decelerates the progression of the disease.

5. Conclusion

Probiotic therapy is very promising as a novel adjunct treatment for Parkinson's disease (PD), particularly through its capacity to regulate gut microbiota composition, enhance intestinal barrier function, and reduce systemic and neuroinflammation. Increasing evidence from both clinical and preclinical studies suggests that probiotics are not only capable of alleviating motor symptoms such as tremors and rigidity, but also non-motor symptoms, including constipation, depression, anxiety, and cognitive impairment, which in turn significantly impact patients' quality of life.

Probiotics may exert their beneficial actions through a wide range of mechanisms including the production of neuroprotective and anti-inflammatory short-chain fatty acids (SCFAs), immune modulation by boosting the activity of regulatory T-cells, and control over the synthesis of critical neurotransmitters like serotonin, dopamine, and GABA. These effects highlight the potential benefit of probiotics in the treatment of the complex, multisystemic pathophysiology of Parkinson’s disease.

Current limitations to its clinical use include issues of determining the optimal strains, dosages, and treatment durations, and the effect based on individual health variability. Standardized clinical trials and individualized probiotic strategies must be developed to further develop this field. As research continues along the gut-brain axis, probiotics have the potential to become an integral part of the overall management of Parkinson’s disease.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

COMPETING INTERESTS

Authors have declared that no competing interests exist.

References

1. Dorsey, E. R., Sherer, T., Okun, M. S., & Bloem, B. R. (2018). The Emerging Evidence of the Parkinson Pandemic. *Journal of Parkinson's disease*, *8*(s1), S3–S8. https://doi.org/10.3233/JPD-181474
2. Sampson, T. R., Debelius, J. W., Thron, T., Janssen, S., Shastri, G. G., Ilhan, Z. E., Challis, C., Schretter, C. E., Rocha, S., Gradinaru, V., Chesselet, M. F., Keshavarzian, A., Shannon, K. M., Krajmalnik-Brown, R., Wittung-Stafshede, P., Knight, R., & Mazmanian, S. K. (2016). Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. *Cell*, *167*(6), 1469–1480.e12. https://doi.org/10.1016/j.cell.2016.11.018
3. Zhu, M., Liu, X., Ye, Y., Yan, X., Cheng, Y., Zhao, L., Chen, F., & Ling, Z. (2022). Gut Microbiota: A Novel Therapeutic Target for Parkinson's Disease. *Frontiers in immunology*, *13*, 937555. https://doi.org/10.3389/fimmu.2022.937555
4. Palleja, A., Mikkelsen, K. H., Forslund, S. K., Kashani, A., Allin, K. H., Nielsen, T., Hansen, T. H., Liang, S., Feng, Q., Zhang, C., Pyl, P. T., Coelho, L. P., Yang, H., Wang, J., Typas, A., Nielsen, M. F., Nielsen, H. B., Bork, P., Wang, J., Vilsbøll, T., … Pedersen, O. (2018). Recovery of gut microbiota of healthy adults following antibiotic exposure. *Nature microbiology*, *3*(11), 1255–1265. https://doi.org/10.1038/s41564-018-0257-9
5. Yang, H., Wang, W., Romano, K. A., Gu, M., Sanidad, K. Z., Kim, D., Yang, J., Schmidt, B., Panigrahy, D., Pei, R., Martin, D. A., Ozay, E. I., Wang, Y., Song, M., Bolling, B. W., Xiao, H., Minter, L. M., Yang, G. Y., Liu, Z., Rey, F. E., … Zhang, G. (2018). A common antimicrobial additive increases colonic inflammation and colitis-associated colon tumorigenesis in mice. *Science translational medicine*, *10*(443), eaan4116. https://doi.org/10.1126/scitranslmed.aan4116
6. Hsieh, T. H., Kuo, C. W., Hsieh, K. H., Shieh, M. J., Peng, C. W., Chen, Y. C., Chang, Y. L., Huang, Y. Z., Chen, C. C., Chang, P. K., Chen, K. Y., & Chen, H. Y. (2020). Probiotics Alleviate the Progressive Deterioration of Motor Functions in a Mouse Model of Parkinson's Disease. *Brain sciences*, *10*(4), 206. https://doi.org/10.3390/brainsci10040206
7. Hill-Burns, E. M., Debelius, J. W., Morton, J. T., Wissemann, W. T., Lewis, M. R., Wallen, Z. D., Peddada, S. D., Factor, S. A., Molho, E., Zabetian, C. P., Knight, R., & Payami, H. (2017). Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. *Movement disorders : official journal of the Movement Disorder Society*, *32*(5), 739–749. https://doi.org/10.1002/mds.26942
8. Westfall, S., Lomis, N., Kahouli, I., Dia, S. Y., Singh, S. P., & Prakash, S. (2017). Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. *Cellular and molecular life sciences : CMLS*, *74*(20), 3769–3787. https://doi.org/10.1007/s00018-017-2550-9

9. Unger, M. M., Spiegel, J., Dillmann, K. U., Grundmann, D., Philippeit, H., Bürmann, J., Faßbender, K., Schwiertz, A., & Schäfer, K. H. (2016). Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. *Parkinsonism & related disorders*, *32*, 66–72. https://doi.org/10.1016/j.parkreldis.2016.08.019
10. Tan, A. H., Lim, S. Y., Chong, K. K., A Manap, M. A. A., Hor, J. W., Lim, J. L., Low, S. C., Chong, C. W., Mahadeva, S., & Lang, A. E. (2021). Probiotics for Constipation in Parkinson Disease: A Randomized Placebo-Controlled Study. *Neurology*, *96*(5), e772–e782. https://doi.org/10.1212/WNL.0000000000010998
11. Lombardi, V. C., De Meirleir, K. L., Subramanian, K., Nourani, S. M., Dagda, R. K., Delaney, S. L., & Palotás, A. (2018). Nutritional modulation of the intestinal microbiota; future opportunities for the prevention and treatment of neuroimmune and neuroinflammatory disease. *The Journal of nutritional biochemistry*, *61*, 1–16. https://doi.org/10.1016/j.jnutbio.2018.04.004
12. Uyar, G. Ö., & Yildiran, H. (2019). A nutritional approach to microbiota in Parkinson's disease. *Bioscience of microbiota, food and health*, *38*(4), 115–127. https://doi.org/10.12938/bmfh.19-002
13. Barichella, M., Pacchetti, C., Bolliri, C., Cassani, E., Iorio, L., Pusani, C., Pinelli, G., Privitera, G., Cesari, I., Faierman, S. A., Caccialanza, R., Pezzoli, G., & Cereda, E. (2016). Probiotics and prebiotic fiber for constipation associated with Parkinson disease: An RCT. *Neurology*, *87*(12), 1274–1280. https://doi.org/10.1212/WNL.0000000000003127
14. Ibrahim, A., Ali, R. A. R., Manaf, M. R. A., Ahmad, N., Tajurruddin, F. W., Qin, W. Z., Desa, S. H. M., & Ibrahim, N. M. (2020). Multi-strain probiotics (Hexbio) containing MCP BCMC strains improved constipation and gut motility in Parkinson's disease: A randomised controlled trial. *PloS one*, *15*(12), e0244680. https://doi.org/10.1371/journal.pone.0244680
15. Ghalandari, N., Assarzadegan, F., Habibi, S. A. H., Esmaily, H., & Malekpour, H. (2023). Efficacy of Probiotics in Improving Motor Function and Alleviating Constipation in Parkinson's Disease: A Randomized Controlled Trial. *Iranian journal of pharmaceutical research : IJPR*, *22*(1), e137840. https://doi.org/10.5812/ijpr-137840
16. Andreozzi, V., Cuoco, S., Balestrieri, M., Fierro, F., Ferrara, N., Erro, R., Di Filippo, M., Barbella, G., Memoli, M. C., Silvestri, A., Squillante, M., Guglielmetti, S., Barone, P., Iovino, P., & Pellecchia, M. T. (2024). Synbiotic supplementation may globally improve non-motor symptoms in patients with stable Parkinson's disease: results from an open label single-arm study. *Scientific reports*, *14*(1), 23095. https://doi.org/10.1038/s41598-024-74400-w
17. Xiang, S., Ji, J. L., Li, S., Cao, X. P., Xu, W., Tan, L., & Tan, C. C. (2022). Efficacy and Safety of Probiotics for the Treatment of Alzheimer's Disease, Mild Cognitive Impairment, and Parkinson's Disease: A Systematic Review and Meta-Analysis. Frontiers in aging neuroscience, 14, 730036. https://doi.org/10.3389/fnagi.2022.730036
18. Kalyanaraman, B., Cheng, G., & Hardy, M. (2024). Gut microbiome, short-chain fatty acids, alpha-synuclein, neuroinflammation, and ROS/RNS: Relevance to Parkinson's disease and therapeutic implications. *Redox biology*, *71*, 103092. https://doi.org/10.1016/j.redox.2024.103092

19. Ashique, S., Mohanto, S., Ahmed, M. G., Mishra, N., Garg, A., Chellappan, D. K., Omara, T., Iqbal, S., & Kahwa, I. (2024). Gut-brain axis: A cutting-edge approach to target neurological disorders and potential synbiotic application. *Heliyon*, *10*(13), e34092. https://doi.org/10.1016/j.heliyon.2024.e34092
20. Kalampokini, S., Becker, A., Fassbender, K., Lyros, E., & Unger, M. M. (2019). Nonpharmacological Modulation of Chronic Inflammation in Parkinson's Disease: Role of Diet Interventions. *Parkinson's disease*, *2019*, 7535472. https://doi.org/10.1155/2019/7535472
21. Raval, U., Harary, J. M., Zeng, E., & Pasinetti, G. M. (2020). The dichotomous role of the gut microbiome in exacerbating and ameliorating neurodegenerative disorders. *Expert review of neurotherapeutics*, *20*(7), 673–686. https://doi.org/10.1080/14737175.2020.1775585
22. Gabrielli, M., Zileri Dal Verme, L., Zocco, M. A., Nista, E. C., Ojetti, V., & Gasbarrini, A. (2024). The Role of the Gastrointestinal Microbiota in Parkinson's Disease. *Biomolecules*, *15*(1), 26. https://doi.org/10.3390/biom15010026
23. Lubomski, M., Xu, X., Holmes, A. J., Muller, S., Yang, J. Y. H., Davis, R. L., & Sue, C. M. (2022). The Gut Microbiome in Parkinson's Disease: A Longitudinal Study of the Impacts on Disease Progression and the Use of Device-Assisted Therapies. *Frontiers in aging neuroscience*, *14*, 875261. https://doi.org/10.3389/fnagi.2022.875261
24. Sun, J., Li, H., Jin, Y., Yu, J., Mao, S., Su, K. P., Ling, Z., & Liu, J. (2021). Probiotic Clostridium butyricum ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. *Brain, behavior, and immunity*, *91*, 703–715. https://doi.org/10.1016/j.bbi.2020.10.014
25. Cuevas-Carbonell, S. G., Vásquez-Celaya, L., García-López, D., Granados-Patrón, D., García-Miss, M. D. R., Álvarez-Cervera, F. J., Mut-Martín, M., Parra, I., Mendieta, L., Salgado, H., Alamilla, J., Cruz-Bojórquez, R., Ávila-Escalante, M. L., Aranda-González, I. I., & Góngora-Alfaro, J. L. (2022). Chronic Treatment with the Probiotics Lacticaseibacillus rhamnosus GG and Bifidobacterium lactis BB12 Attenuates Motor Impairment, Striatal Microglial Activation, and Dopaminergic Loss in Rats with 6-Hydroxydopamine-induced Hemiparkinsonism. *Neuroscience*, *507*, 79–98. https://doi.org/10.1016/j.neuroscience.2022.11.004
26. Cacabelos R. (2017). Parkinson's Disease: From Pathogenesis to Pharmacogenomics. *International journal of molecular sciences*, *18*(3), 551. https://doi.org/10.3390/ijms18030551
27. Alexoudi, A., Kesidou, L., Gatzonis, S., Charalampopoulos, C., & Tsoga, A. (2023). Effectiveness of the Combination of Probiotic Supplementation on Motor Symptoms and Constipation in Parkinson's Disease. *Cureus*, *15*(11), e49320. https://doi.org/10.7759/cureus.49320
28. Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230