Exploration of Neuroprotective Therapy

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Therapeutic role of probiotics in motor and non-motor symptoms of Parkinson's disease

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Academic Editor: Ming Xiao, Nanjing Medical University, China
Received: August 18, 2025 **Accepted:** November 28, 2025 **Published:** December 15, 2025

Cite this article: Páez-García S, Hernández-Triana D, Esparza-Salazar F, Barreto GE, Rodriguez-Oroz MC, Borda MG. Therapeutic role of probiotics in motor and non-motor symptoms of Parkinson's disease. Explor Neuroprot Ther. 2025;5:1004129. https://doi.org/10.37349/ent.2025.1004129

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms, in which gut microbiota alterations have emerged as a potential pathogenic factor, causing disruption of the brain-gut-microbiota (BGM) axis. Recent evidence supports the role of BGM axis disruption in enhancing neuroinflammation, alpha-synuclein (α-syn) aggregation, and dopaminergic neurodegeneration. Emerging therapeutic strategies targeting dysbiosis, such as probiotics and fecal microbiota transplantation (FMT), have become a new focus of investigation for PD treatment. Proposed mechanisms include modulation of immune responses, enhancement of intestinal barrier integrity, production of neuroactive metabolites such as short-chain fatty acids, and reduction of oxidative stress. This narrative review summarizes current evidence on probiotics as a therapeutic strategy in PD. By analyzing data from randomized controlled trials and preclinical studies, we highlight the beneficial effects of probiotics in improving motor and non-motor symptoms of PD, including constipation, depression, and anxiety. Strains such as *Lactobacillus plantarum* PS128 and *Bifidobacterium animalis* Probio-M8 show particular promise. Although probiotics have demonstrated a favorable safety profile and potential as an adjunctive therapy for PD, future research should focus on standardized protocols, biomarker identification, and exploration of combined microbiota-targeted strategies.

Keywords

Parkinson's disease, gut-brain axis, microbiota, probiotics, neuroinflammation, non-motor symptoms, motor symptoms

Introduction

Parkinson's disease (PD) is a complex and progressive neurodegenerative disorder recognized as the second most prevalent worldwide, with an estimated prevalence of approximately 1.5 cases per 1,000 individuals [1, 2]. Its classic pathology centers in the loss of dopaminergic neurons in the substantia nigra of the midbrain, leading to dopamine deficiency in the striatum and the manifestation of cardinal motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability. At the molecular level, the disease is characterized by the abnormal misfolding and aggregation of the alpha-synuclein (α-syn) protein into intracellular inclusions known as Lewy bodies and Lewy neurites [3, 4]. The cause of most PD cases remains uncertain, considered to be the result of a complex interaction between genetic susceptibility and environmental factors [5]. Current therapies, primarily based on dopamine replacement, offer symptomatic relief for motor disorders but do not halt disease progression, and they often fail to address the broad spectrum of non-motor symptoms, such as autonomic dysfunction, sleep disorders, cognitive impairment, and neuropsychiatric symptoms, which impose a significant burden on patients' quality of life [6].

Interestingly, PD patients experience gastrointestinal (GI) symptoms years before their motor signs appear [7]. Chronic constipation, dysphagia, and other gut disturbances are frequently reported in early prodromal stages of PD [6, 7]. These observations align with Braak's "gut-origin" hypothesis, where misfolded α-syn may first arise in the enteric nervous system and then subsequently reach the brain via the vagus nerve [8]. In this context, the brain-gut-microbiota (BGM) axis has emerged as a key pathogenic mechanism. Gut microbes synthesize a wide array of bioactive molecules such as short-chain fatty acids (SCFAs), neurotransmitters [e.g., serotonin, gamma-aminobutyric acid (GABA)], and other metabolites that can either enter the circulation or signal through the vagus nerve to influence the central nervous system (CNS) [9]. The gut microbiota also shapes immune status. Experimental work has shown that microbiota-derived SCFAs regulate microglial maturation and function, while microbiota perturbations can alter the blood-brain barrier integrity, mechanisms that are highly relevant to neuroinflammation in PD [10], highlighting the bidirectional communication between the gut and the brain. To support this, recent studies have found that the gut microbiota of PD patients differ markedly from healthy controls, and may contribute to disease progression by facilitating α-syn aggregation, disruption of SCFA metabolism, and enhancing microglial activation [6].

Given these connections, multiple strategies that modulate the gut microbiome are under active investigation as potential therapeutic options in PD. Current approaches include dietary modulation, administration of prebiotics and certain probiotic strains, fecal microbiota transplantation (FMT), and targeted microbial-based therapies [11, 12], all seeking to restore microbial balance and attenuate gut-brain axis-driven neurodegeneration. Regarding probiotic supplementation, several human and in vivo studies have shown it to improve motor function and non-motor symptoms (e.g., constipation, depression, anxiety, sleep disturbances) in PD patients [13–15]. Fecal microbiota transplants have also been reported to have beneficial effects [7]. In general, dietary approaches, probiotics, and FMT are able to transform the gut microbiota and have been observed to attenuate neuroinflammation and improve neurological function in neurodegenerative models [10]. In vitro studies show that probiotics can enhance neuroprotection and gut health in PD models by activating neurotrophic pathways, including the upregulation of brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [16]; reducing oxidative stress, particularly by decreasing reactive oxygen species (ROS) [17]; strengthening intestinal barrier integrity and modulating inflammatory responses [18–20].

Although probiotics have been recognized as a potential therapeutic strategy in PD patients by showing a beneficial effect in both PD motor and non-motor symptoms, the precise mechanisms underlying these effects, the strain-specific actions of probiotics, optimal dosing strategies, and the long-term clinical efficacy of microbiome-targeted interventions remain largely undefined. Moreover, few studies have comprehensively integrated molecular insights with clinical outcomes across both motor and non-motor domains [16, 21].

Therefore, in this narrative review, we synthesize mechanistic and translational evidence from animal and human studies to explore the potential therapeutic impact of probiotics and other microbiome-modulating strategies in PD, highlighting current advances, knowledge gaps, and future research directions.

Methods

A comprehensive literature search was conducted using PubMed, EMBASE, Scopus, Web of Science, and Google Scholar databases. The search strategy employed a combination of Medical Subject Headings (MeSH), Emtree terms, and free-text keywords, including "Parkinson's Disease," "Microbiota," "Gut-Brain Axis," "Brain-Gut-Microbiota Axis," "Probiotics," "Prebiotics," "Synbiotics," "Psychobiotics," "Postbiotics," "Fecal Microbiota Transplantation," "Diet, Microbiota-Directed," "Dietary Supplements," "Dysbiosis," "Antibiotics," "Short-Chain Fatty Acids," "Lipopolysaccharides," "Neuroinflammation," "Enteric Nervous System," "Intestinal Permeability".

The initial database searches allowed for a preliminary selection of relevant articles, which served as the foundation for further identification of studies through the snowball method. This technique involved reviewing the reference lists of the selected articles and tracking citations of key sources to identify additional literature relevant to the topic.

This review included all types of scientific articles, as determined by the authors' criteria, addressing the relationship between PD, gut microbiota, and/or probiotics, including randomized controlled trials (RCTs), observational studies, systematic reviews, meta-analyses, experimental animal studies, narrative reviews, and book chapters. There was no language restriction. Although no publication year restrictions were applied, studies published from 2020 onward were prioritized to ensure the inclusion of recent evidence.

Studies that did not assess the effect of probiotics on the specific PD symptoms considered in this review, as well as those for which full-text access was unavailable or that were available only in abstract form, were excluded.

Articles were screened based on title, abstract, and full text. Those deemed relevant to the pathophysiological mechanisms linking microbiota to PD or addressing the therapeutic implications of probiotics were selected for qualitative synthesis. A total of 105 articles were ultimately included in this review.

BGM axis disruption in PD

Introduction to the BGM axis

To understand the therapeutic potential of probiotics in PD, it is first essential to explore the BGM axis and its pathogenic role in the disease. The BGM axis is a complex, bidirectional communication network between the GI tract (GIT) and the nervous system [22], tightly regulated by the local microbial community, collectively known as the gut microbiota [11]. These microorganisms (mainly composed of *Lactobacillus* spp., *Bifidobacterium* spp., *Faecalibacterium prausnitzii*, and *Prevotella* spp., among others [11, 16]) influence multiple physiological processes, including neurotransmission and neural development [23]. The main components of the BGM axis include: (1) the GIT, from the epithelial barrier to the associated immune system; (2) the gut microbiota, encompassing bacteria, fungi, viruses, and other resident microorganisms; and (3) the nervous system, particularly the enteric, autonomic, and central branches [23, 24], as well as the blood-brain barrier [25, 26]. Communication within this axis occurs through various mechanisms, including direct neural pathways (e.g., the vagus nerve) [22], immune signaling, and microbial metabolites such as SCFAs (particularly acetate, propionate and butyrate) [27, 28], neurotransmitters (such as dopamine, serotonin, GABA and acetylcholine) [29, 30], lipopolysaccharides (LPS) [31], and bile acids [32].

Role in immune regulation

The gut microbiota plays a central role in shaping immune responses [33, 34]. Alterations in its composition, commonly referred to as dysbiosis, can disrupt gut barrier integrity (mainly by the decrease of

SCFAs production, which are essential for maintaining tight junction protein expression and epithelial barrier function), leading to increased intestinal permeability, or so-called "leaky gut" [35]. These alterations facilitate the translocation of bacterial products and inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and interferon-gamma (IFN-γ), from the gut lumen into the systemic circulation, leading to the activation of Toll-like receptors (TLR), consequently triggering the release of systemic proinflammatory cytokines, endotoxins, and oxidative stress markers [36–38]. Systemic inflammation is linked to the pathogenesis of PD, as circulating inflammatory mediators can cross the blood-brain barrier, promoting neuroinflammation (by activating microglia and astrocytes), α-syn aggregation, and degeneration of dopaminergic neurons [34, 39].

Other functions of the gut microbiota

Beyond immune modulation, the microbiota also contributes to neural development and brain function [23]. Animal studies have shown that germ-free models lacking a microbiota exhibit abnormal brain morphology and altered behavior [40, 41]. External factors such as chronic stress and diet, known to impact microbiota composition, may also indirectly influence the BGM axis and are associated with neuropsychiatric symptoms like anxiety and depression [30, 42].

Dysbiosis in PD

Disruption of the BGM axis in PD is strongly associated with dysbiosis. Multiple studies have reported a reduction in bacterial diversity, particularly a decreased abundance of taxa such as Prevotellaceae, *Faecalibacterium*, Lachnospiraceae, and *Roseburia*, organisms generally considered beneficial due to their anti-inflammatory properties (as they have the ability to produce SCFAs) and role in maintaining gut barrier integrity [22, 43, 44]. Conversely, increased levels of certain pro-inflammatory taxa associated with LPS production have been reported in PD patients. These include *Akkermansia muciniphila* (implicated in mucosal barrier degradation and pro-inflammatory responses), *Lactobacillus*, Bifidobacteriaceae (though some studies have also linked its reduction with disease progression), Ruminococcaceae, Christensenellaceae, Enterobacteriaceae, and *Megasphaera*, among others [22, 43, 44].

This microbial imbalance may contribute to PD pathophysiology through multiple, interconnected mechanisms that lead to the creation of a pro-inflammatory microenvironment [22, 45]. A central process involves the modulation of α-syn aggregation and propagation, considered key pathological features of PD [24]. Bacterial components such as functional amyloids and LPS have been shown to promote α-syn misfolding by inducing its production and neuroinflammation by activating the microglia [46]. According to Braak's hypothesis, α-syn has been detected in enteric neurons and GI tissues long before the onset of motor symptoms, contributing to GI symptoms [8, 22]. This model proposes a prion-like propagation of misfolded α-syn from the gut to the CNS, potentially via the vagus nerve [22, 47]. Other theories suggest bidirectional transmission between the gut and the brain, possibly involving systemic circulation or alternative neural routes [22, 47].

Together, these findings highlight the central role of the BGM axis and its dysregulation in PD pathogenesis, positioning the gut microbiota as both a potential biomarker and a promising therapeutic target. This provides strong support for exploring probiotics as a potential disease-modifying approach.

Probiotics as a therapeutic option and other microbiome-targeted strategies

The World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) define probiotics as live microorganisms that, when administered in adequate amounts, confer health benefits to the host by supporting the intestinal microbiota and, consequently, the gut-brain axis [48]. They are commonly classified as dietary supplements and are available in various formulations, including tablets, powders, and capsules [34, 39].

Recent evidence suggests that probiotics may exert neuroprotective effects in PD by modulating inflammation and restoring gut-brain homeostasis [13]. By reshaping gut microbiota, increasing SCFA production, and strengthening the intestinal barrier, probiotics reduce inflammation and oxidative stress that favor α-syn misfolding [21, 27]. Preclinical studies also show that probiotic supplementation can attenuate microglial activation and limit α-syn propagation via the vagus nerve, highlighting a bidirectional interaction between gut dysbiosis and α-syn pathology [49]. Below are several representative examples of probiotic strains that have shown promise in both preclinical and clinical studies of PD.

Firstly, *Lactobacillus plantarum* PS128 has demonstrated a reduction in nigral dopaminergic neuronal death and improvement in motor deficits in mouse models with PD. This probiotic strain was shown to reduce inflammation (by decreasing the abundance of proinflammatory bacteria such as Enterobacteriaceae and reducing LPS levels) and to increase the expression of brain neurotrophic factors (BDNF and GDNF) [50, 51]. In a study conducted by Lee et al. (2023) [51], PS128 in male mice was administered for 6 weeks and compared to a control group, resulting in improved coordination and balance. Another study conducted by Liao et al. (2020) [52] evaluated the neuroprotective properties of PS128 in a PD mice model, reporting that the intervention improved walking time according to the narrow-beam scale test ($p = 0.001$) and increased dopaminergic neuronal survival [restoring striatal tyrosine hydroxylase (TH) expression from ~30 to ~75% of control levels; $p < 0.001$], compared to the control group. Finally, Lu et al. (2021) [53] evaluated a 12-week intervention with PS128 in PD patients, showing an improvement in Unified Parkinson's Disease Rating Scale (UPDRS) scores ($p = 0.004$), demonstrating its potential effects on motor symptoms in patients with PD.

Secondly, *Bifidobacterium infantis* and *Bifidobacterium breve*. A systematic review conducted by Reiriz et al. (2025) [54] demonstrated that the use of these probiotic strains in PD animal models, alone or in combination, enhanced neuroprotective effects and delayed the progression of the disease by preventing the decrease in spinal column density and by improving motor deficits ($p < 0.0001$). Additionally, a study conducted by Georgescu et al. (2016) [55] demonstrated that a 3-month intervention with this probiotic strain improved abdominal pain and the severity of Non-Motor Symptoms Scale-Movement Disorder Society (NMS-MDS) score compared to the control group ($p = 0.0001$).

Another promising strain is *Clostridium butyricum*, demonstrated to improve motor function and decrease neuroinflammation in vivo models. A study conducted by Sun et al. (2021) [56] evaluated a 4-week intervention of this probiotic strain in mice with PD, showing an improvement in dopaminergic neuron preservation, a reduction in microglial activation, and an enhancement in motor function. Similarly, Liao et al. (2025) [57] showed a reduction in oxidative stress after an intervention with *Clostridium butyricum* in PD mice, protecting dopaminergic neurons, decreasing neuroinflammation, and improving motor deficits. Finally, Wang et al. (2023) [58] conducted an experimental in vivo study with mice with PD showing that this intervention significantly improved motor function, as evidenced by better performance in the pole and hanging wire tests, and increased mobility and exploratory behavior in the open field test.

A combination of *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum* strains has also been shown to improve cognitive function, reduce neuronal damage, and exhibit neuroprotective and immunomodulatory functions through GABA elevation in vivo models [59]. Nosrani et al. (2021) [59] demonstrated that a 14-day intervention with these probiotic strains in Wistar rats with PD improved cognitive function (spatial learning and memory), as the performance in the Morris maze improved ($p < 0.0001$), and also showed a reduction in the number of injured neurons. Moreover, Dong et al. (2025) [60] demonstrated that *Lactobacillus reuteri*-derived GABA improved motor performance and reduced nigrostriatal neuron loss in MPTP-induced PD mice ($p < 0.05$), accompanied by lower markers of oxidative damage and iron overload ($p < 0.01$).

SLAB51, another probiotic strain, has been demonstrated to improve motor impairment and cognitive performance in animal models with PD [61]. Castelli et al. (2020) [18] performed a controlled in vitro and in vivo laboratory experimental study demonstrating that SLAB51 exerted neuroprotective effects in rats with induced PD, enhancing BDNF/TrkB signaling, reducing oxidative stress and neuroinflammation, preserving dopaminergic markers, and improving motor performance.

Finally, Visñuk et al. (2020) [62] conducted an in vivo study that demonstrated that a 6-week intervention with a combination of *Lactobacillus plantarum* CRL 2130, *Streptococcus thermophilus* CRL 807, and *Streptococcus thermophilus* CRL 808 improved motor function by reducing α-syn accumulation and decreasing inflammatory cytokines using the polo test.

In addition to the probiotic strains described above, several other microorganisms have demonstrated potential benefits in PD through mechanisms such as modulation of neuroinflammation and preservation of dopaminergic neurons, therefore improving both motor and non-motor symptoms. Furthermore, other microbiome-targeted strategies, including specific dietary interventions, prebiotics, FMT, and targeted microbial-based therapies, are at various stages of translational and clinical development and have also shown therapeutic promise. The mechanisms underlying their therapeutic effects are summarized in Table 1 [27, 42, 63–72].

Effects on non-motor symptoms of PD

Effects on GI symptoms of PD

GI dysfunction, especially constipation, is a prevalent non-motor symptom in PD, affecting up to 90% of patients and often appearing years before motor symptoms [73–75]. Consequently, this domain has been widely explored as a target for probiotic interventions in PD.

The body of evidence includes numerous double-blind, RCTs with intervention periods typically ranging from 4 to 12 weeks. Meta-analyses of these trials, which have collectively enrolled hundreds of patients, show remarkably consistent and positive results [14, 72, 76]. Probiotic supplementation leads to a clinically meaningful increase in bowel movement frequency, with pooled data indicating an average increase of approximately one additional spontaneous bowel movement (SBM) per week [14, 72, 76].

Beyond frequency, probiotics have also been shown to improve stool consistency, as measured by the Bristol Stool Scale (BSS), leading to softer, more normalized stools. These physiological improvements are accompanied by significant enhancements in patient-reported outcomes such as stool frequency and stool consistency [14]. Studies consistently show that probiotics improve constipation-related quality of life, measured by the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire, and reduce the need for rescue laxative use [13, 14].

In the current body of literature, probiotic interventions in humans have predominantly been evaluated over treatment periods of 4, 8, or 12 weeks, with the following outcomes.

4-week interventions

A study by Barichella et al. (2016) [77] provided fermented milk containing multiple strains and reported a significant increase in the number of complete bowel movements compared to placebo. A landmark class I evidence trial by Tan et al. (2021) [78] used a capsule with eight strains (*Lactobacillus* and *Bifidobacterium* species) and found it increased SBMs by 1.3 per week and significantly improved stool consistency and quality of life compared to placebo ($p < 0.01$ for all).

8-week interventions

A trial by Ibrahim et al. (2020) [79] using an 8-week course of a multi-strain probiotic sachet with prebiotics found significant improvements in both bowel movement frequency and overall gut transit time. More recently, Ghalandari et al. (2023) [80] conducted an 8-week trial using a high-dose, multi-strain probiotic containing eight strains of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus thermophilus*. This intervention doubled the median bowel movement frequency from two to four per week compared to placebo and significantly improved stool consistency.

12-week interventions

A study by Du et al. (2022) [81] reported that a multi-strain supplement containing *Bacillus*, *Lactobacillus*, *Bifidobacterium*, and *Enterococcus* species led to an increase of 1.09 complete bowel movements per week

Table 1. Mechanistic pathways and therapeutic effects of microbiome-targeted interventions in PD.

Microbiota-targeted strategy	Mechanistic pathways	Examples	References
Dietary interventions	• ↑ SCFAs improve blood-brain and intestinal barrier integrity. • ↓ Intestinal dysbiosis and ↑ butyrate-producing bacteria, reducing neuroinflammation. • Induce immune modulation and ↓ oxidative stress.	High-fiber diet and Mediterranean diet.	[27, 42, 63, 64]
Prebiotics	• Stimulate growth of *Bifidobacterium* and *Lactobacillus*, ↑ butyrate, supporting dopaminergic neuron survival. • ↓ Intestinal permeability and endotoxin translocation, reducing microglial activation. • ↓ Neuroinflammation through inhibition of the TLR4/NF-κB pathway, improving motor and non-motor symptoms.	Resistant fermentable fiber blend (starch and inulin).	[64–67]
Fecal microbiota transplantation (FMT)	• Restores microbial diversity and gut barrier integrity via gut-brain axis modulation. • ↑ SCFAs and ↓ α-syn aggregates, protecting dopaminergic neurons.	Randomized placebo-controlled trial of FMT improves autonomic symptoms in PD.	[68, 69]
Specific microbial therapies	• Activate neurotrophic pathways (BDNF, PI3K) and inhibit pro-inflammatory cascades. • Promote dopaminergic neuron survival and neuroprotection.	Targeted or engineered strains (e.g., next-generation probiotics, bacteriophages, SCFA-producing bacteria).	[64, 70, 71]
Probiotics	• Live microorganisms that rebalance gut microbiota and enhance intestinal barrier integrity. • ↑ SCFAs modulate microglial activity, ↓ oxidative stress, and support dopaminergic neuron survival. • Indirectly act on the gut-brain axis by producing neuroactive metabolites and ↓ pro-inflammatory cytokines.	*Lactobacillus* + *Bifidobacterium* regimens.	[27, 72]

α-syn: alpha-synuclein; SCFAs: short-chain fatty acids; PD: Parkinson's disease.

and improved scores on constipation symptom and quality of life scales. In another 12-week study, Sun et al. (2022) [82] focused on a single-strain intervention with *Bifidobacterium animalis* subsp. *lactis* Probio-M8, demonstrating significant improvements in stool consistency and constipation-related quality of life ($p < 0.001$).

In vivo studies

The beneficial effects observed in human trials are strongly supported by preclinical research in animal models of PD, which allows for a deeper investigation into the foundational processes. These studies show that probiotics can directly counteract the GI pathology associated with the disease.

For instance, Chu et al. (2023) [83] demonstrated the protective effects of *Lactobacillus plantarum* CCFM405. The administration of this probiotic led to an increase in colon length, restored the integrity of the gut microbiota by upregulating the expression of tight junction proteins like occludin and ZO-1, and increased the number of fecal pellets in PD mice.

A study by Dong et al. (2024) [84] in a mouse model of PD evaluated the effects of *Bifidobacterium animalis* subsp. *lactis* NJ241. This probiotic not only mitigated weight loss but also significantly improved GI motility, as measured by an increased travel distance of Evans blue dye in the small intestine compared to untreated PD mice ($p = 0.024$). Critically, the study linked this gut-level improvement to neuroprotection, as NJ241 treatment protected dopaminergic neurons, inhibited the activation of inflammatory glial cells in the substantia nigra, and increased the levels of beneficial SCFAs. The researchers also found that these effects were connected to an increase in the gut hormone glucagon-like peptide-1 (GLP-1) and the activation of the protective GLP-1 receptor (GLP-1R)/PGC-1α signaling pathway in the brain.

Taken together, these high-quality trials indicate that multi-strain probiotic supplementation confers measurable benefits in alleviating PD-related constipation and enhancing quality of life, as outlined in Table 2 [77–84].

Effects on neuropsychiatric symptoms of PD

Neuropsychiatric symptoms are highly prevalent in PD [85]. Depression and anxiety are the most common neuropsychiatric manifestations of PD, affecting up to 40% and over 50% of patients, respectively, and are considered intrinsic to its pathophysiology [86, 87]. The gut-brain axis has emerged as a key pathophysiological link in several neuropsychiatric disorders, and growing evidence supports the role of probiotics as potential modulators of this bidirectional communication. Based on current evidence, ongoing research is exploring probiotics as potential interventions for neuropsychiatric symptoms in PD. Recent studies indicate that the use of certain probiotic strains has a positive impact on anxiety and depression in PD patients [13, 88, 89].

Anxiety

Anxiety is a common non-motor symptom in PD, with prevalence ranging from 25–40% in different cohorts and clinical stages [90]. Recent evidence suggests that probiotic supplementation may have a clinically relevant effect on these symptoms. Disease-specific evidence comes from a key RCT by Sun et al. (2022) [82], which evaluated a *Bifidobacterium*, *Lactobacillus*, and *Enterococcus* probiotic combination in PD patients over 12 weeks. The probiotic intervention significantly reduced anxiety scores on the Hamilton Anxiety Rating Scale (HAMA). Similarly, Kim et al. (2019) [91] demonstrated that the use of *Bifidobacterium bifidum* probiotic strain reduced stress levels and enhanced cognitive flexibility, supporting its mental health, and Yang et al. (2023) [92] demonstrated a reduction in HAMA score following an intervention with *Lacticaseibacillus paracasei*. Finally, Zeng et al. (2024) [93] showed a decrease in the Self-Rating Anxiety Scale (SAS) compared to the placebo group, using a 12-week course of *Bacteroides fragilis* BF839 combined with earthworm protein, showing an improvement of anxiety symptoms.

Corroborating these findings, two meta-analyses by Park et al. (2023) [89] and Nisa et al. (2024) [88] reported a significant reduction in anxiety associated with probiotic use, aligning with other comprehensive reviews, which consistently note that effects are modest in the general population but become more pronounced in PD patients [94].

There was only one in vivo study that evaluated this outcome. It was conducted by Xie et al. (2020) [95], showing no effects in anxiety-like behavior after 6 weeks of treatment with *Lacticaseibacillus rhamnosus* HA-114 probiotic strain, in mouse models with PD (measured by the elevated plus maze test, $p = 0.973$).

Depression

Depression is another prevalent non-motor symptom in PD, affecting approximately 30–50% of patients and frequently preceding the onset of motor manifestations [90]. Sun et al. (2022) [82] and Yang et al. (2023) [92] demonstrated significant improvements in Hamilton Depression Rating Scale 17 (HAMD-17) scores in the probiotic-treated group (*Bifidobacterium*, *Lactobacillus*, and *Enterococcus* probiotic combination and *Lacticaseibacillus paracasei*, respectively) compared to placebo [82, 92]. In contrast, Lu et al. (2021) [53] evaluated this outcome with the Beck Depression Inventory-II (BDI-II), showing no

Table 2. Experimental studies showing gastrointestinal symptoms improvement induced by probiotic interventions in PD.

Study (year)	Probiotic(s)	Duration	Dose/Presentation	Outcome
Human studies				
Barichella et al. (2016) [77]	Fermented milk with strains of (*Streptococcus*, *Enterococcus*, *Lactobacillus*, *Bifidobacterium*) and prebiotic fiber	4 weeks	125 g of fermented milk containing 250 × 10^9 CFU, once daily	Superior to placebo in improving the number of complete bowel movements ($p = 0.002$).
Ibrahim et al. (2020) [79]	Multi-strain probiotic (Hexbio) (*Lactobacillus* spp., *Bifidobacterium* spp.) with fructo-oligosaccharides (FOS)	8 weeks	Hexbio sachet with 30 × 10^9 CFU, 2% FOS, and lactose, twice daily	Improved bowel movement frequency ($p < 0.001$) and total gut transit time ($p = 0.028$).
Tan et al. (2021) [78]	Multistrain (*Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus gasseri*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Enterococcus faecalis*, *Enterococcus faecium*)	4 weeks	10 × 10^9 CFU capsule, once daily	Increased spontaneous bowel movements by 1.3/week ($p < 0.001$); improved stool consistency ($p = 0.009$) and quality of life ($p = 0.001$).
Sun et al. (2022) [82]	Probio-M8 (*Bifidobacterium animalis* subsp. *lactis*)	3 months	2 g of Probio-M8 powder (3 × 10^{10} CFU/day; maltodextrin as excipient) daily	Significant improvement in gastrointestinal symptoms, including Bristol scores ($p < 0.001$) and Patient Assessment of Constipation Quality of Life Questionnaire ($p < 0.001$).
Du et al. (2022) [81]	*Bacillus licheniformis*, *Lactobacillus acidophilus*, *Bifidobacterium longum*; *Enterococcus faecalis*	12 weeks	2.5 × 10^9 CFU two capsules, three times daily	Increased complete bowel movements by 1.09/week ($p < 0.001$); improved Bristol Stool Scale, Patient Assessment of Constipation Symptoms Questionnaire, and Patient Assessment of Constipation Quality of Life Questionnaire scores ($p < 0.05$ for all).
Ghalandari et al. (2023) [80]	Comflor® (*Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium breve*, and *Streptococcus thermophilus*)	8 weeks	4.5 × 10^{11} CFU capsule, once daily	Doubled bowel movement frequency ($p = 0.02$) and improved stool consistency ($p = 0.04$).
In vivo studies of animals				
Chu et al. (2023) [83]	*Lactobacillus plantarum* CCFM405	8 weeks	1 × 10^9 CFU/0–2 mL in saline by oral gavage, once daily	Alleviated motor deficits ($p < 0.05$) and constipation symptoms ($p < 0.05$). Reduced dopaminergic neuron loss ($p < 0.05$), intestinal inflammation, and neuroinflammation ($p < 0.05$). Increased number of fecal pellets in PD mice ($p < 0.05$) and fecal/serum branched-chain amino acids.
Dong et al. (2024) [84]	*Bifidobacterium animalis* subsp. *lactis* NJ241	28 days	1 × 10^9 CFU/0.2 mL in saline by oral gavage, once daily	Mitigated gastrointestinal dysfunction ($p = 0.024$) and motor deficits ($p < 0.05$). Protected dopaminergic neurons ($p < 0.05$). Reduced neuroinflammation ($p < 0.05$). Increased SCFAs and colonic GLP-1 ($p < 0.05$).

PD: Parkinson's disease; SCFAs: short-chain fatty acids; GLP-1: glucagon-like peptide-1.

significant results with probiotic intervention. On the other hand, Zeng et al. (2024) [93] conducted a clinical trial using an intervention with *Bacteroides fragilis* BF839 combined with earthworm protein for 12 weeks in PD patients, showing a decrease in the scores of an extended version of the HAMD-24, compared to the placebo group. Meta-analyses such as Park et al. (2023) [89], Chu et al. (2023) [83], and Nisa et al. (2024) [88] reported a significant reduction in depressive symptoms following probiotic supplementation. There is limited direct animal research evaluating the effect of probiotics on depression in PD models.

Evidence regarding the effect of probiotics on neuropsychiatric symptoms in PD is scarce, with only a small number of human studies and a single in vivo study evaluating this outcome. Although most of these studies have shown beneficial effects and the pooled effect from meta-analyses was positive, further research should focus on this area. Table 3 summarizes the studies reporting a beneficial effect on anxiety and depression symptoms [82, 92, 93].

Table 3. Experimental studies showing depression and anxiety symptoms improvement induced by probiotic interventions in PD.

Study (year)	Probiotic(s)	Duration	Dose/Presentation	Outcome
Human studies				
Sun et al. (2022) [82]	Probio-M8 (*Bifidobacterium animalis* subsp. *lactis*)	3 months	2 g of Probio-M8 powder (3×10^{10} CFU/day; maltodextrin as excipient) daily	Depression (HAMD-17): significant improvement vs. control ($p < 0.001$). Anxiety (HAMA): significant improvement vs. control ($p < 0.001$).
Yang et al. (2023) [92]	*Lacticaseibacillus paracasei* strain Shirota (LcS)	12 weeks	Fermented milk drink containing 1×10^{11} CFU of LcS, once daily	Depression (HAMD-17): significant improvement vs. control ($p = 0.010$). Anxiety (HAMA): significant improvement vs. control ($p = 0.005$).
Zeng et al. (2024) [93]	*Bacteroides fragilis* BF839 + earthworm protein	12 weeks	10 g supplement dissolved in 200 mL water, twice daily (each 10 g containing 10^6 BF839 and 0.3 g earthworm protein)	Depression: significant reduction in HAMD-24 score (−3.91 ± 3.99 vs. +1.15 ± 3.42, $p < 0.001$). Anxiety: significant reduction in SAS score (−7.04 ± 5.71 vs. −1.23 ± 2.34, $p < 0.001$). Both improvements sustained through 12 weeks compared to placebo.

PD: Parkinson's disease; HAMD-17: Hamilton Depression Rating Scale 17; HAMA: Hamilton Anxiety Rating Scale; SAS: Self-Rating Anxiety Scale.

Effects of PD-related sleep disorders

Sleep disturbances, including insomnia and rapid eye movement (REM) sleep behavior disorder (RBD), affect up to 80% of PD patients [96]. Recent studies highlight the potential of probiotics to alleviate these issues, such as an RCT by Sun et al. (2022) [82], which found that *Bifidobacterium animalis* Probio-M8 significantly improved sleep quality on the Parkinson's Disease Sleep Scale (PDSS). Additionally, a 2025 pilot RCT by Du et al. (2025) [97] found that 8-week probiotic therapy improved scores on the Pittsburgh Sleep Quality Index (PSQI) in PD patients with probable RBD. Probiotics showing benefits of PD-related sleep disorders are shown in Table 4 [82, 97].

Table 4. Experimental studies showing sleep parameters improvement induced by probiotic interventions in PD.

Study (year)	Probiotic(s)	Duration	Dose/Presentation	Sleep outcome
Human studies				
Sun et al. (2022) [82]	Probio-M8 (*Bifidobacterium animalis* subsp. *lactis*)	3 months	2 g of Probio-M8 powder (3×10^{10} CFU/day; maltodextrin as excipient) daily	Improved sleep quality on the Parkinson's Disease Sleep Scale (PDSS) ($p = 0.05$).
Du et al. (2025) [97]	*Bacillus licheniformis*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis*	12 weeks	*Bacillus licheniformis* (2.5×10^9 CFU/capsule once daily); *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis* (each 1.0×10^7 CFU/capsule once daily)	UPDRS scores decreased significantly in the probiotic group, $p = 0.048$.

PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale.

Effects of PD-related cognitive dysfunction

In contrast to the positive findings for mood and sleep, the evidence supporting the benefit of probiotics for cognitive impairment in PD patients is currently understudied or inconclusive [30, 88, 98, 99]. Numerous studies in rodent models of PD show that probiotics can improve cognitive performance and offer neuroprotection (Table 4) [59, 95, 100]. Two RCTs conducted in patients with PD evaluated the effects of

specific probiotic strains on cognitive function. Sun et al. (2022) [82] was the only study to report a significant improvement in Mini-Mental State Examination (MMSE) scores in the intervention group, whereas Yang et al. (2023) [92] found no difference in MMSE scores between the intervention and control groups after 12 weeks of treatment. Meta-analyses assessing cognition have either focused on other conditions like Alzheimer's disease or have not reported specific cognitive outcomes for their PD cohorts [30, 88, 98, 99]. Although in vivo studies have demonstrated a beneficial effect of probiotics on cognitive function, robust clinical evidence in human populations is still lacking and should be a focus for future research [76]. The duration of the interventions that measured this outcome varied from 2 to 12 weeks. Future research should focus on longer treatment durations, as cognitive effects may require extended periods to manifest and be sustained. Studies showing a beneficial effect of probiotic treatment on the cognitive function of PD patients are described in Table 5 [59, 82, 95, 100].

Table 5. Experimental studies showing cognitive symptoms improvement induced by probiotic interventions in PD.

Study (year)	Probiotic(s)	Duration	Dose/Presentation	Cognitive outcome
Human studies				
Sun et al. (2022) [82]	*Bifidobacterium animalis* subsp. *lactis* Probio-M8 (Probio-M8), Benserazide	3 months	3×10^{10} CFU/daily	MMSE scores were greater in the Probio-M8 group than in the placebo group at baseline ($p < 0.001$), 1 month ($p < 0.001$), and 3 months ($p = 0.042$).
In vivo studies of animals				
Valvaikar et al. (2024) [100]	*Bifidobacterium breve* Bif11	21 days	1×10^{10} CFU daily	It was reported that PD rats had lower cognitive performance in the maze test, and when treated with Bif11, their working memory improved significantly ($p = 0.001$).
Nosrani et al. (2021) [59]	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, *Lactobacillus fermentum*	14 days	2×10^{9} CFU of each strain/day, oral administration	In 6-OHDA PD rats, decreased escape latency in the Morris water maze ($p < 0.0001$) and increased time in the target quadrant during probe trial ($p < 0.0001$), indicating improved spatial learning and memory.
Xie et al. (2020) [95]	*Lacticaseibacillus rhamnosus* HA-114	6 weeks	Rehydrated with distilled water; initial concentration 1×10^{9} CFU/mL, reduced to 1×10^{8} CFU/mL from day 5; provided in drinking water, changed every 2 days	Novel Object Recognition (hippocampal-independent, 5 min retention): all groups showed good memory retention (sham + probiotics: $p = 0.001$; PD + placebo: $p = 0.031$; PD + probiotics: $p < 0.001$). Novel Place Recognition (hippocampal-dependent, 5 min retention): PD + placebo group impaired: $p = 0.62$; PD + probiotics group restored memory retention: $p = 0.032$.

PD: Parkinson's disease; MMSE: Mini-Mental State Examination; 6-OHDA: 6-hydroxydopamine.

Effects on motor symptoms of PD

As previously mentioned, gut dysbiosis has been increasingly recognized as a contributor to the pro-inflammatory state that may worsen the clinical course of PD. Rebalancing the gut microbiota through probiotic supplementation has emerged as a potential strategy to reduce neuroinflammation and microglial activation, which in turn could help protect dopaminergic neurons and improve motor symptoms [101]. Since tremor, rigidity, bradykinesia, and gait disturbances are key features of PD and significantly affect patients' quality of life, therapeutic approaches aimed at alleviating these symptoms are of particular clinical interest.

Several RCTs have assessed the impact of probiotic interventions on motor outcomes in patients with PD. Motor function has been primarily evaluated using validated tools such as the UPDRS and its MDS revision, with parts III (motor examination) and IV (motor complications) being the most relevant for motor assessment [102].

Probiotic interventions have typically been administered over 8-week to 12-week periods, with MDS-UPDRS (particularly parts III and IV) frequently used to assess motor outcomes.

8-week interventions

Ibrahim et al. (2020) [79] conducted an 8-week trial using a multi-strain probiotic with *Lactobacillus* and *Bifidobacterium* species (30×10^9 CFU) plus fructo-oligosaccharides, showing no significant differences in MDS-UPDRS scores compared to placebo. Similarly, Ghalandari et al. (2023) [80] administered Comflor® capsules for 8 weeks (total 4.5×10^{11} CFU of *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium breve*, and *Streptococcus thermophilus*), reporting no significant differences in motor outcomes.

12-week interventions

Yang et al. (2023) [92] evaluated a 12-week intervention using *Lacticaseibacillus paracasei* fermented milk (1×10^{10} CFU) and found no significant changes in MDS-UPDRS motor scores, though there was a notable reduction in non-motor symptoms (MDS-UPDRS I: mean difference −0.99; 95% CI: −1.62 to −0.37; p = 0.002). Zeng et al. (2024) [93] combined *Bacteroides fragilis* 839 with an earthworm protein supplement for 12 weeks, reporting reductions in all UPDRS sub-scores. Andreozzi et al. (2024) [103] tested Enterolactis Duo (*Lacticaseibacillus paracasei* DG + inulin) for 12 weeks but found no significant improvements in UPDRS-III scores. Zali et al. (2024) [104] administered a probiotic and vitamin D supplement (BioZen D, containing 2×10^9 CFU of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus paracasei*, *Bifidobacterium longum*, and *Bacillus coagulans*, plus 400 IU of vitamin D), showing significant improvements in all UPDRS domains except part II (activities of daily living).

Sun et al. (2022) [82] assessed the effects of Probio-M8 (*Bifidobacterium animalis* subsp. *lactis*) over a 3-month period, observing a significant reduction in UPDRS-III scores at both 1 and 3 months (p = 0.037 and p = 0.016, respectively).

Notably, Lu et al. (2021) [53] used *Lactobacillus plantarum* PS128 over 12 weeks and incorporated symptom diaries to better capture ON/OFF fluctuations. Their findings showed significant improvements in UPDRS motor scores in both OFF and ON states (p = 0.004 and p = 0.007, respectively), along with a reduction in fluctuation duration.

In vivo studies

Several in vivo studies support the neuroprotective and motor benefits of probiotics in PD models. Hsieh et al. (2020) [105] reported that 16 weeks of a six-strain probiotic mix improved balance, coordination, and gait, while preserving dopaminergic neurons in transgenic mice ($p < 0.05$). Similarly, Sun et al. (2021) [56] showed that a 4-week course of *Clostridium butyricum* enhanced motor performance ($p < 0.01$), reduced microglial activation, and preserved nigral neurons.

Parra et al. (2023) [106] found that Microbiot® (*Lactobacillus rhamnosus GG* and *Bifidobacterium animalis* ssp. *lactis Bb12*) partially improved motor performance and reduced neuroinflammation in LPS-induced PD rats. Likewise, Castelli et al. (2020) [18] demonstrated that SLAB51 supplementation improved motor tests and preserved dopaminergic neurons while reducing microgliosis and oxidative stress. Finally, Wang et al. (2023) [58] showed that an engineered *Clostridium butyricum*-GLP-1 strain enhanced motor outcomes, preserved dopaminergic neurons [↑ TH and dopamine transporter (DAT) expression, ↓ α-syn accumulation], promoted mitophagy, attenuated oxidative stress, restored gut microbiota balance, and improved intestinal barrier integrity.

Taken together, these preclinical studies complement human findings by demonstrating that probiotics not only modulate neuroinflammatory and neuroprotective pathways but also translate into measurable motor benefits in animal models of PD. Future human research should aim to replicate the probiotic strains and treatment durations that demonstrated efficacy in animal models, in order to confirm their translational potential in motor symptoms of PD.

Although the exact mechanisms linking gut dysbiosis to motor symptom progression in PD remain not fully understood, current findings support the hypothesis that microbial modulation, especially through

targeted probiotic interventions, may have beneficial effects on motor outcomes and serve as a potential complementary intervention for PD patients (shown in Table 6). Despite a few studies showing inconsistent results, pooled data suggest a general trend toward improved motor function despite the duration of the interventions (that varied from 8 to 12 weeks), particularly reflected in reduced UPDRS-III scores following probiotic supplementation [14, 89, 107, 108]. Two meta-analyses, by Xie et al. (2023) [14] and Park et al. (2023) [89], aligned with the results of human-based RCTs available in current literature, demonstrated significant associations between probiotic use and reductions in UPDRS-III scores [weighted mean difference (WMD) = −6.58; 95% CI: −12.02 to −1.14 and standardized MD (SMD) = −0.65; 95% CI: −1.11 to −0.19, respectively]. These effects are thought to result from reduced neuroinflammation, increased production of SCFAs, and improved gut-brain axis signaling.

Other microbiota-directed interventions

Other strategies, such as FMT, have also been explored. FMT involves transplanting processed stool from a thoroughly screened healthy donor into a recipient's GIT to restore microbial diversity, improve SCFA production, reduce pro-inflammatory taxa, and enhance intestinal barrier integrity and motility [109, 110]. Bruggeman et al. (2024) [111] reported a significant improvement in MDS-UPDRS motor scores 12 months post-FMT in an OFF-medication state (−5.8 points; 95% CI: −11.4 to −0.2; $p = 0.0235$). DuPont et al. (2023) [68] used an orally administered, lyophilized FMT product twice weekly for 12 weeks in PD patients with constipation, showing improvements in motor scores at 1, 4, and 9 months, though full comparison with placebo across all time points was not reported. In contrast, Scheperjans et al. (2024) [112] used a single-dose FMT via colonoscopy without antibiotic pre-treatment and observed no significant differences in motor scores compared to placebo at 6- and 12-month follow-up. Regarding safety, FMT is generally well tolerated, with most adverse events being mild and transient GI symptoms such as diarrhea, abdominal discomfort, or bloating [113]. Serious adverse events are rare, and direct safety comparisons with probiotic interventions have not yet been conducted [7].

Discussion

The findings summarized in this review suggest that targeting the BGM axis may offer a promising therapeutic pathway in PD. Across RCT and systematic reviews, probiotics have shown consistent benefits for motor and non-motor symptoms. Preclinical studies further strengthen this concept, showing that various probiotic strains and related microbiome-based approaches such as prebiotics, dietary modulation, FMT, and engineered microbial therapies can reduce neuroinflammation, protect dopaminergic neurons, and restore gut-brain homeostasis, supporting the biological rationale for these clinical outcomes.

Despite the growing number and diversity of studies exploring the therapeutic role of probiotics in PD, several key challenges remain. Many clinical trials are limited by small sample sizes, short intervention periods, and inconsistent outcome measures, particularly the lack of comprehensive tools to assess non-motor symptoms [14, 15]. In addition, there is significant heterogeneity across studies in terms of probiotic strains, dosages, treatment durations, and administration methods [14, 15]. This variability makes direct comparison between trials difficult and limits reproducibility, as differences in bacterial composition, CFU concentration, and delivery formats may lead to divergent outcomes even when assessing similar endpoints. In addition, most clinical trials have been limited to short durations (4–12 weeks), leaving the long-term efficacy and sustainability of probiotic benefits in PD largely unknown. These factors not only complicate comparisons between studies but also increase the risk of bias and limit the generalizability of the findings.

Moreover, most of the data supporting the therapeutic effects of probiotics and other microbiome-targeted interventions in PD come from preclinical studies. Although these models have been valuable for advancing our understanding of gut-brain interactions and clarifying mechanisms of neuroprotection, they only reproduce selected aspects of PD, such as dopaminergic neuronal loss or α-syn aggregation, and fail to capture its complex, progressive, and multifactorial nature [13, 21, 27]. Furthermore, interspecies differences in microbiota composition, immune responses, and environmental factors limit the direct

Table 6. Experimental studies showing motor symptom improvement induced by probiotic interventions in PD.

Study (year)	Probiotic(s)	Duration	Dose/Presentation	Motor outcome
Human studies				
Lu et al. (2021) [53]	*Lactobacillus plantarum* PS128	12 weeks	Two capsules containing PS128 (30 billion colony-forming units per capsule) daily, oral	Improvement in UPDRS motor scores in both ON and OFF states (p = 0.004 and 0.007, respectively). Decreased akinesia subscores in the OFF state (p = 0.012). Reduced duration of OFF periods (p = 0.04) and increased ON periods (p = 0.031).
Sun et al. (2022) [82]	Probio-M8 (*Bifidobacterium animalis* subsp. *lactis*)	3 months	2 g of Probio-M8 powder (3×10^{10} CFU/day; maltodextrin as excipient) daily	Significant reduction in UPDRS part III at 1 and 3 months (p = 0.037, 0.016, respectively).
Zali et al. (2024) [104]	BioZen D® containing: *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus paracasei*, *Bifidobacterium longum*, *Bacillus coagulans* + vitamin D	12 weeks	2×10^9 CFU + 400 IU vitamin D per capsule, 1 oral capsule a day	Significant improvement in all MDS-UPDRS domains (parts I, III, and IV), except for part II ($p \leq 0.001$).
Zeng et al. (2024) [93]	*Bacteroides fragilis* 839 + earthworm protein supplement	12 weeks	10 g of BF839 + earthworm protein supplement solution (contains 10^6 BF839 and 0.3 g earthworm protein) dissolved in 200 mL of water, twice daily	Reduction in all UPDRS subscale scores, including part III (p varying from 0.001 to 0.026 in UPDRS parts I to IV).
In vivo studies of animals				
Hsieh et al. (2020) [105]	*Bifidobacterium bifidum*, *Bifidobacterium longum*, *Lactobacillus rhamnosis*, *Lactobacillus rhamnosus* GG, *Lactobacillus plantarum* LP28, *Lactococcus lactis* subsp. *Lactis*	16 weeks	10^{10} CFU/mouse/day, oral	Improved balance and coordination (beam walking test and reduced traversal time, $p < 0.05$ to $p < 0.001$), and gait (measured by walking speed, step length, stride length, step width, stance and swing phase times, $p < 0.05$); preserved TH + dopaminergic neurons in substantia nigra pars compacta ($p < 0.05$).
Sun et al. (2021) [56]	*Clostridium butyricum*	4 weeks	5×10^8 CFU/mouse/day, intragastric	Shorter pole descent times, reduced beam latency and foot slips, decreased immobility, and increased open field crossings (all with a $p < 0.01$).
Parra et al. (2023) [106]	Microbiot®: *Lactobacillus rhamnosus GG* + *Bifidobacterium animalis* ssp. *lactis Bb12*)	15 days	1×10^9 CFU/strain/day, oral	Partial motor benefits: reduced type 3 step errors (day 7, $p < 0.05$) and improved stand phase (day 13, $p < 0.01$).
Castelli et al. (2020) [18]	SLAB51 (*Bifidobacterium* and *Lactobacillus* strains)	5 weeks (2 pre + 3 post-lesion)	Oral gavage, daily (dose not specified in summary)	Restored contralateral forelimb use ($p < 0.005$), reduced biased swings ($p < 0.005$), and decreased apomorphine-induced rotations ($p < 0.005$).
Wang et al. (2023) [58]	*Clostridium butyricum*-pMTL007-GLP-1 (engineered strain expressing GLP-1)	7 days	1×10^8 CFU/mL, oral gavage, resuspended in saline with 0.01% gelatin	Significant motor improvement in MPTP-induced PD mice: reduced pole test descent time ($p < 0.01$), improved hanging wire test score, increased total distance traveled, and central area exploration in the open field test (both $p < 0.01$).

PD: Parkinson's disease; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; TH: tyrosine hydroxylase; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

translation of these findings to humans [114–116]. Even so, preclinical research remains essential for identifying mechanistic pathways and prioritizing promising probiotic and microbiome-based strategies for future clinical evaluation.

Another potential limitation is that mechanistic insights are still limited, as few studies have explored how probiotics affect the body at a molecular level, including changes in microbiota, gene expression, or inflammation. Although recent trials have increasingly included microbiota sequencing [82, 92, 93, 103], metabolomic profiling [82, 92, 93, 103], and inflammatory marker analyses [53, 98, 104], mechanistic evidence remains indirect and incomplete, especially in human studies [117]. Some reports have shown associations between probiotic use and changes in gut microbial composition [118, 119], SCFA production [120], and circulating cytokines [82, 104]. However, most authors also acknowledge that these analyses were limited in depth and scope. Overall, while current findings suggest possible BGM interactions involving SCFA metabolism and neuroinflammation, the causal relationships and long-term biological relevance of these effects remain unclear. Many studies did not include metabolomic or transcriptomic validation [53, 77–80], failed to confirm probiotic colonization [79, 81, 103], or combined multiple interventions (e.g., vitamin D or prebiotics) [93, 104], which makes it difficult to isolate specific mechanisms. Therefore, our current understanding of how probiotics exert their effects in PD is still preliminary and requires more focused mechanistic research in human populations.

When analyzing RCTs that assessed motor outcomes, it is essential to consider potential confounders that may affect observed improvements, such as the concurrent use of dopaminergic medications, which can influence motor symptom improvements. Most trials investigating the effects of probiotics on motor outcomes reported participants' baseline pharmacological treatments, with the majority already receiving levodopa and a smaller yet considerable proportion using dopamine agonists or other dopaminergic medications. Although these studies acknowledged medication use at baseline, they generally did not specify its influence on outcomes or report any dosage adjustments or new initiations of dopaminergic therapy during or shortly before the intervention. In the study by Lu et al. (2021) [53], motor assessments were conducted both in OFF and ON states after standardized medication withdrawal, demonstrating significant improvements in UPDRS-III scores and ON-OFF duration after PS128 supplementation, suggesting effects beyond acute dopaminergic influence. Similarly, Zeng et al. (2024) [93] observed greater UPDRS improvement in patients not receiving levodopa, underscoring the need to control for dopaminergic therapy when evaluating probiotic efficacy. To better control for this potential confounder, future studies should explicitly exclude patients who have recently initiated dopaminergic treatment or who require dosage modifications during the trial, as exemplified by Zeng et al. (2024) [93], and should standardize OFF/ON assessments as in Lu et al. (2021) [53] to better isolate the direct effects of probiotic interventions.

In terms of population variability, most trials to date have been conducted in Italy [77], Iran [80, 104], China [53, 82, 92, 93, 97], and Malaysia [78]. Across regions, there is a substantial difference in diet patterns, genetics, and baseline microbiota composition [121, 122]. Therefore, additional studies in other regions are needed to validate these findings and account for population-specific variability that may influence probiotic efficacy.

Although several studies characterize disease severity using the Hoehn and Yahr scale [53, 77, 79–81, 92, 93], none of the trials conducted to date have analyzed outcomes according to early versus advanced PD stages. This gap prevents determining whether probiotic efficacy varies across disease progression. Future trials should include prespecified subgroup analyses by Hoehn and Yahr stage to clarify potential stage-dependent responses to probiotic therapy.

Additionally, identifying reliable biomarkers and understanding each patient's unique microbial profile could help adjust treatments to those most likely to benefit. Current evidence suggests that probiotics can reduce peripheral systemic inflammation, reflected by decreased CRP, IL-1, IL-8, and TNF-α levels, while showing no effect on intestinal inflammation measured by fecal calprotectin [16, 107]. Oxidative stress markers also appear modulated, with increased glutathione (GSH) and decreased malondialdehyde (MDA) levels, indicating improved antioxidant status [13, 123]. SCFAs quantified in plasma and feces are used to assess microbial metabolic activity, although changes are not always significant [107]. However, further studies are needed to validate these biomarkers and determine their reliability in monitoring probiotic effects in PD.

Publication bias may influence the current evidence, as studies with positive probiotic results are more likely to be published. Among systematic reviews, two evaluated the potential risk of bias. First, Xie et al. (2023) [14], focusing on constipation, found symmetrical funnel plots suggesting a low risk of publication bias, whereas Park et al. (2023) [89] identified significant bias for several outcomes (e.g., GI motility and inflammatory markers) using Egger's test. Overall, these findings suggest a low to moderate risk of publication bias, highlighting the need for further analyses of bias within RCTs. Upcoming reviews should continue to assess and report publication bias to provide more balanced estimates of probiotic efficacy in PD.

Future research should prioritize larger, multicenter randomized trials with extended follow-up to better establish the long-term efficacy and safety of probiotic interventions in PD. To enhance consistency and comparability across studies, standardized protocols are needed, particularly regarding the assessment of non-motor symptoms and the analytical methods used to characterize the gut microbiota. Promising preclinical findings should be translated into rigorously designed human studies to determine their true clinical relevance. Finally, integrating probiotics with complementary strategies, such as dietary interventions or conventional pharmacologic treatments, may optimize therapeutic outcomes and support more targeted, personalized, and less invasive approaches for patients with PD.

Conclusions

PD is more than just dopaminergic neurodegeneration; it is a complex, multisystem disorder. Increasing evidence suggests that the BGM axis may play a key role, with direct implications for neuroinflammation, glial activation, and disruption of blood-brain barrier integrity. Probiotic therapy has emerged as a promising approach with the potential to influence the progression of central neurodegeneration. Several studies have reported clinical improvements in PD patients treated with various probiotic strains, underscoring both their efficacy and safety. These findings point to new therapeutic avenues that extend beyond the traditional dopaminergic framework. However, further multicenter, controlled studies with longer follow-up and standardized protocols are needed to more conclusively evaluate their therapeutic potential, clarify strain-specific effects, and validate reliable biomarkers that could serve to monitor treatment response and guide personalized interventions in PD.

Abbreviations

BDNF: brain-derived neurotrophic factor

BGM: brain-gut-microbiota

CNS: central nervous system

FMT: fecal microbiota transplantation

GABA: gamma-aminobutyric acid

GDNF: glial cell-derived neurotrophic factor

GI: gastrointestinal

GIT: gastrointestinal tract

GLP-1: glucagon-like peptide-1

HAMA: Hamilton Anxiety Rating Scale

HAMD-17: Hamilton Depression Rating Scale 17

IL-1β: interleukin-1 beta

LPS: lipopolysaccharides

MMSE: Mini-Mental State Examination

NMS-MDS: Non-Motor Symptoms Scale-Movement Disorder Society

PD: Parkinson's disease

PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha

RBD: rapid eye movement sleep behavior disorder

RCTs: randomized controlled trials

SBM: spontaneous bowel movement

SCFAs: short-chain fatty acids

TH: tyrosine hydroxylase

TNF-α: tumor necrosis factor-alpha

UPDRS: Unified Parkinson's Disease Rating Scale

α-syn: alpha-synuclein

Declarations

Author contributions

SPG: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing—original draft, Writing—review & editing. DHT: Conceptualization, Formal analysis, Investigation, Resources, Writing—original draft. FES: Conceptualization, Formal analysis, Investigation, Resources, Writing—original draft. GEB: Conceptualization, Project administration, Supervision, Writing—review & editing. MCRO: Conceptualization, Project administration, Supervision, Writing—review & editing. MGB: Conceptualization, Project administration, Supervision, Writing—review & editing, Funding acquisition. All authors read and approved the submitted version.

Conflicts of interest

All authors meet the authorship criteria as defined by the International Committee of Medical Journal Editors (ICMJE), declare that they have no conflicts of interest, and confirm that no related papers from the same study, nor any similar manuscripts, have been published elsewhere.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Miguel Germán Borda was supported by the Norwegian Health Association. In addition, this paper represents independent research supported by the Norwegian government, through hospital owner Helse Vest (Western Norway Regional Health Authority). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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References

1. Zhu J, Cui Y, Zhang J, Yan R, Su D, Zhao D, et al. Temporal trends in the prevalence of Parkinson's disease from 1980 to 2023: a systematic review and meta-analysis. Lancet Healthy Longev. 2024;5:e464–79. [DOI] [PubMed]
2. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. Lancet Neurol. 2021;20:385–97. [DOI] [PubMed] [PMC]
3. Gikoska M, Gilbert T, Wierzbicki LA, Thompson AR. Dysbiosis of the Gut Microbiota Being a Contributing Factor to Parkinson's Disease: A Literature Review. Preprints 202410.0016.v1 [Preprint]. 2024 [cited 2025 Jul 27]. Available from: https://www.preprints.org/manuscript/202410.0016
4. Kouli A, Torsney KM, Kuan W. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects. Brisbane (AU): Codon; 2018. pp. 3–26. [DOI]
5. Feng M, Zou Z, Shou P, Peng W, Liu M, Li X. Gut microbiota and Parkinson's disease: potential links and the role of fecal microbiota transplantation. Front Aging Neurosci. 2024;16:1479343. [DOI] [PubMed] [PMC]
6. Yemula N, Dietrich C, Dostal V, Hornberger M. Parkinson's Disease and the Gut: Symptoms, Nutrition, and Microbiota. J Parkinsons Dis. 2021;11:1491–505. [DOI] [PubMed] [PMC]
7. Nabil Y, Helal MM, Qutob IA, Dawoud AIA, Allam S, Haddad R, et al. Efficacy and safety of fecal microbiota transplantation in the management of parkinson's disease: a systematic review. BMC Neurol. 2025;25:291. [DOI] [PubMed] [PMC]
8. Kim S, Kwon S, Kam T, Panicker N, Karuppagounder SS, Lee S, et al. Transneuronal Propagation of Pathologic α-Synuclein from the Gut to the Brain Models Parkinson's Disease. Neuron. 2019;103:627–41.e7. [DOI] [PubMed] [PMC]
9. Holmqvist S, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Björklund T, et al. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014;128:805–20. [DOI] [PubMed]
10. Caradonna E, Nemni R, Bifone A, Gandolfo P, Costantino L, Giordano L, et al. The Brain-Gut Axis, an Important Player in Alzheimer and Parkinson Disease: A Narrative Review. J Clin Med. 2024;13:4130. [DOI] [PubMed] [PMC]
11. Yadav S, Raj RG. Parkinson's disease and the gut microbiota connection: unveiling dysbiosis and exploring therapeutic horizons. Neuroscience. 2025;581:1–15. [DOI] [PubMed]
12. Benvenuti L, Salvo CD, Bellini G, Seguella L, Rettura F, Esposito G, et al. Gut-directed therapy in Parkinson's disease. Front Pharmacol. 2024;15:1407925. [DOI] [PubMed] [PMC]
13. Chu C, Yu L, Li Y, Guo H, Zhai Q, Chen W, et al. Meta-analysis of randomized controlled trials of the effects of probiotics in Parkinson's disease. Food Funct. 2023;14:3406–22. [DOI] [PubMed]
14. Xie L, Chen D, Zhu X, Cheng C. Efficacy and safety of probiotics in Parkinson's constipation: A systematic review and meta-analysis. Front Pharmacol. 2023;13:1007654. [DOI] [PubMed] [PMC]
15. Jin X, Dong W, Chang K, Yan Y, Liu X. Efficacy of probiotic supplements on Parkinson's disease: A systematic review and meta-analysis. Complement Ther Med. 2024;82:103045. [DOI] [PubMed]
16. Leta V, Chaudhuri KR, Milner O, Chung-Faye G, Metta V, Pariante CM, et al. Neurogenic and anti-inflammatory effects of probiotics in Parkinson's disease: A systematic review of preclinical and clinical evidence. Brain Behav Immun. 2021;98:59–73. [DOI] [PubMed]

17. Tsao S, Nurrahma BA, Kumar R, Wu C, Yeh T, Chiu C, et al. Probiotic Enhancement of Antioxidant Capacity and Alterations of Gut Microbiota Composition in 6-Hydroxydopamin-Induced Parkinson's Disease Rats. Antioxidants (Basel). 2021;10:1823. [DOI] [PubMed] [PMC]
18. Castelli V, d'Angelo M, Lombardi F, Alfonsetti M, Antonosante A, Catanesi M, et al. Effects of the probiotic formulation SLAB51 in *in vitro* and *in vivo* Parkinson's disease models. Aging (Albany NY). 2020;12:4641–59. [DOI] [PubMed] [PMC]
19. Magistrelli L, Amoruso A, Mogna L, Graziano T, Cantello R, Pane M, et al. Probiotics May Have Beneficial Effects in Parkinson's Disease: *In vitro* Evidence. Front Immunol. 2019;10:969. [DOI] [PubMed] [PMC]
20. Ghyselinck J, Verstrepen L, Moens F, Ven Den Abbeele P, Bruggeman A, Said J, et al. Influence of probiotic bacteria on gut microbiota composition and gut wall function in an *in-vitro* model in patients with Parkinson's disease. Int J Pharm X. 2021;3:100087. [DOI] [PubMed] [PMC]
21. Hajare S, Kulkarni YA. Parkinson's disease and the gut-brain connection: unveiling pathways, mechanisms and promising therapies. Brain Res. 2025;1868:149975. [DOI] [PubMed]
22. Dos Santos JCC, Lima MPP, de Castro Brito GA, de Barros Viana GS. Role of enteric glia and microbiota-gut-brain axis in parkinson disease pathogenesis. Ageing Res Rev. 2023;84:101812. [DOI] [PubMed]
23. Socała K, Doboszewska U, Szopa A, Serefko A, Włodarczyk M, Zielińska A, et al. The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res. 2021;172: 105840. [DOI] [PubMed]
24. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol. 2015;21: 10609–20. [DOI] [PubMed] [PMC]
25. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6:263ra158. [DOI] [PubMed] [PMC]
26. Michel L, Prat A. One more role for the gut: microbiota and blood brain barrier. Ann Transl Med. 2016;4:15. [DOI] [PubMed] [PMC]
27. Kalyanaraman B, Cheng G, Hardy M. Gut microbiome, short-chain fatty acids, alpha-synuclein, neuroinflammation, and ROS/RNS: Relevance to Parkinson's disease and therapeutic implications. Redox Biol. 2024;71:103092. [DOI] [PubMed] [PMC]
28. Foster JA, Rinaman L, Cryan JF. Stress & the gut-brain axis: Regulation by the microbiome. Neurobiol Stress. 2017;7:124–36. [DOI] [PubMed] [PMC]
29. Lyte M. Microbial endocrinology: Host-microbiota neuroendocrine interactions influencing brain and behavior. Gut Microbes. 2014;5:381–9. [DOI] [PubMed] [PMC]
30. 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;13:937555. [DOI] [PubMed] [PMC]
31. Ghosh SS, Wang J, Yannie PJ, Ghosh S. Intestinal Barrier Dysfunction, LPS Translocation, and Disease Development. J Endocr Soc. 2020;4:bvz039. [DOI] [PubMed] [PMC]
32. Wang Q, Luo Y, Chaudhuri KR, Reynolds R, Tan E, Pettersson S. The role of gut dysbiosis in Parkinson's disease: mechanistic insights and therapeutic options. Brain. 2021;144:2571–93. [DOI] [PubMed]
33. Nie S, Ge Y. The link between the gut microbiome, inflammation, and Parkinson's disease. Appl Microbiol Biotechnol. 2023;107:6737–49. [DOI] [PubMed]
34. Rojo ND, Benítez MB, Cava R, Fuentes JM, Cortés SC, Polo RAG. Convergence of Neuroinflammation, Microbiota, and Parkinson's Disease: Therapeutic Insights and Prospects. Int J Mol Sci. 2024;25: 11629. [DOI] [PubMed] [PMC]
35. Obrenovich MEM. Leaky Gut, Leaky Brain? Microorganisms. 2018;6:107. [DOI] [PubMed] [PMC]
36. Dias V, Junn E, Mouradian MM. The role of oxidative stress in Parkinson's disease. J Parkinsons Dis. 2013;3:461–91. [DOI] [PubMed] [PMC]

37. Yoo BB, Mazmanian SK. The Enteric Network: Interactions between the Immune and Nervous Systems of the Gut. Immunity. 2017;46:910–26. [DOI] [PubMed] [PMC]
38. Brown GC, Camacho M, Williams-Gray CH. The Endotoxin Hypothesis of Parkinson's Disease. Mov Disord. 2023;38:1143–55. [DOI] [PubMed] [PMC]
39. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V. Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol. 2022;22:657–73. [DOI] [PubMed] [PMC]
40. Luczynski P, Whelan SO, O'Sullivan C, Clarke G, Shanahan F, Dinan TG, et al. Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus. Eur J Neurosci. 2016;44:2654–66. [DOI] [PubMed] [PMC]
41. Heijtz RD, Wang S, Anuar F, Qian Y, Björkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci U S A. 2011;108:3047–52. [DOI] [PubMed] [PMC]
42. Kwon D, Zhang K, Paul KC, Folle AD, Rosario ID, Jacobs JP, et al. Diet and the gut microbiome in patients with Parkinson's disease. NPJ Parkinsons Dis. 2024;10:89. [DOI] [PubMed] [PMC]
43. Shen T, Yue Y, He T, Huang C, Qu B, Lv W, et al. The Association Between the Gut Microbiota and Parkinson's Disease, a Meta-Analysis. Front Aging Neurosci. 2021;13:636545. [DOI] [PubMed] [PMC]
44. Toh TS, Chong CW, Lim S, Bowman J, Cirstea M, Lin C, et al. Gut microbiome in Parkinson's disease: New insights from meta-analysis. Parkinsonism Relat Disord. 2022;94:1–9. [DOI] [PubMed]
45. Nie S, Wang J, Deng Y, Ye Z, Ge Y. Inflammatory microbes and genes as potential biomarkers of Parkinson's disease. NPJ Biofilms Microbiomes. 2022;8:101. [DOI] [PubMed] [PMC]
46. Mahbub NU, Islam MM, Hong S, Chung H. Dysbiosis of the gut microbiota and its effect on α-synuclein and prion protein misfolding: consequences for neurodegeneration. Front Cell Infect Microbiol. 2024;14:1348279. [DOI] [PubMed] [PMC]
47. Schmitt V, Masanetz RK, Weidenfeller M, Ebbinghaus LS, Süß P, Rosshart SP, et al. Gut-to-brain spreading of pathology in synucleinopathies: A focus on molecular signalling mediators. Behav Brain Res. 2023;452:114574. [DOI] [PubMed]
48. FAO/WHO. Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. In: Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria; 2001 Oct 1–4; Córdoba, Argentina. Rome: FAO; 2002.
49. Kimber IK, Tremblay M. Food for thought: probiotic modulation of microglial activity in Parkinson's disease. Front Mol Neurosci. 2025;18:1690507. [DOI] [PubMed] [PMC]
50. Bi M, Liu C, Wang Y, Liu S. Therapeutic Prospect of New Probiotics in Neurodegenerative Diseases. Microorganisms. 2023;11:1527. [DOI] [PubMed] [PMC]
51. Lee YZ, Cheng S, Chang M, Lin Y, Wu C, Tsai Y. Neuroprotective Effects of *Lactobacillus plantarum* PS128 in a Mouse Model of Parkinson's Disease: The Role of Gut Microbiota and MicroRNAs. Int J Mol Sci. 2023;24:6794. [DOI] [PubMed] [PMC]
52. Liao J, Cheng Y, You S, Kuo W, Huang C, Chiou J, et al. *Lactobacillus plantarum* PS128 alleviates neurodegenerative progression in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse models of Parkinson's disease. Brain Behav Immun. 2020;90:26–46. [DOI] [PubMed]
53. Lu C, Chang H, Weng Y, Chen C, Kuo Y, Tsai Y. The Add-On Effect of *Lactobacillus plantarum* PS128 in Patients With Parkinson's Disease: A Pilot Study. Front Nutr. 2021;8:650053. [DOI] [PubMed] [PMC]
54. Reiriz M, Beltrán-Velasco AI, Echeverry-Alzate V, Martínez-Miguel E, Gómez-Senent S, Uceda S, et al. *Bifidobacterium infantis* and *Bifidobacterium breve* Improve Symptomatology and Neuronal Damage in Neurodegenerative Disease: A Systematic Review. Nutrients. 2025;17:391. [DOI] [PubMed] [PMC]
55. Georgescu D, Ancusa OE, Georgescu LA, Ionita I, Reisz D. Nonmotor gastrointestinal disorders in older patients with Parkinson's disease: is there hope? Clin Interv Aging. 2016;11:1601–8. [DOI] [PubMed] [PMC]

56. Sun J, Li H, Jin Y, Yu J, Mao S, Su K, et al. Probiotic *Clostridium butyricum* ameliorated motor deficits in a mouse model of Parkinson's disease via gut microbiota-GLP-1 pathway. Brain Behav Immun. 2021; 91:703–15. [DOI] [PubMed]
57. Liao B, Ding L, Chen W, Yue M, Wang Y, Hong D, et al. Engineered *Clostridium butyricum*-pMTL007-GLP-1 Delays Neurodegeneration in Prnp-SNCA*A53T Transgenic Mice Model by Suppressing Astrocyte Senescence. Probiotics Antimicrob Proteins. 2025;[Epub ahead of print].
58. Wang Y, Chen W, Han Y, Xu X, Yang A, Wei J, et al. Neuroprotective effect of engineered *Clostridium* butyricum-pMTL007-GLP-1 on Parkinson's disease mice models via promoting mitophagy. Bioeng Transl Med. 2023;8:e10505. [DOI] [PubMed] [PMC]
59. Nosrani EA, Tamtaji OR, Alibolandi Z, Sarkar P, Ghazanfari M, Tameh AA, et al. Neuroprotective effects of probiotics bacteria on animal model of Parkinson's disease induced by 6-hydroxydopamine: A behavioral, biochemical, and histological study. J Immunoassay Immunochem. 2021;42:106–20. [DOI] [PubMed]
60. Dong X, Yang T, Jin Z. *Lactobacillus reuteri*-derived γ-amino butyric acid alleviates MPTP-induced Parkinson's disease through inhibiting ferroptosis via the AKT-GSK3β-GPX4 axis. NPJ Parkinsons Dis. 2025;11:149. [DOI] [PubMed] [PMC]
61. Castelli V, d'Angelo M, Quintiliani M, Benedetti E, Cifone MG, Cimini A. The emerging role of probiotics in neurodegenerative diseases: new hope for Parkinson's disease? Neural Regen Res. 2021;16:628–34. [DOI] [PubMed] [PMC]
62. Visñuk DP, de Giori GS, LeBlanc JG, de Moreno de LeBlanc. Neuroprotective effects associated with immune modulation by selected lactic acid bacteria in a Parkinson's disease model. Nutrition. 2020; 79–80:110995. [DOI] [PubMed]
63. Liu J, Chen Q, Su R. Interplay of human gastrointestinal microbiota metabolites: Short-chain fatty acids and their correlation with Parkinson's disease. Medicine (Baltimore). 2024;103:e37960. [DOI] [PubMed] [PMC]
64. Kumar D, Bishnoi M, Kondepudi KK, Sharma SS. Gut Microbiota-Based Interventions for Parkinson's Disease: Neuroprotective Mechanisms and Current Perspective. Probiotics Antimicrob Proteins. 2025;17:2438–60. [DOI] [PubMed]
65. Elford JD, Becht N, Garssen J, Kraneveld AD, Perez-Pardo P. Buty and the beast: the complex role of butyrate in Parkinson's disease. Front Pharmacol. 2024;15:1388401. [DOI] [PubMed] [PMC]
66. Aho VTE, Houser MC, Pereira PAB, Chang J, Rudi K, Paulin L, et al. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. Mol Neurodegener. 2021;16:6. [DOI] [PubMed] [PMC]
67. Hall DA, Voigt RM, Cantu-Jungles TM, Hamaker B, Engen PA, Shaikh M, et al. An open label, non-randomized study assessing a prebiotic fiber intervention in a small cohort of Parkinson's disease participants. Nat Commun. 2023;14:926. [DOI] [PubMed] [PMC]
68. DuPont HL, Suescun J, Jiang Z, Brown EL, Essigmann HT, Alexander AS, et al. Fecal microbiota transplantation in Parkinson's disease-A randomized repeat-dose, placebo-controlled clinical pilot study. Front Neurol. 2023;14:1104759. [DOI] [PubMed] [PMC]
69. Cheng Y, Tan G, Zhu Q, Wang C, Ruan G, Ying S, et al. Efficacy of fecal microbiota transplantation in patients with Parkinson's disease: clinical trial results from a randomized, placebo-controlled design. Gut Microbes. 2023;15:2284247. [DOI] [PubMed] [PMC]
70. Hamilton AM, Krout IN, White AC, Sampson TR. Microbiome-based therapeutics for Parkinson's disease. Neurotherapeutics. 2024;21:e00462. [DOI] [PubMed] [PMC]
71. Magalhães KT, da Silva RNA, Borges AS, Siqueira AEB, Puerari C, Bento JAC. Smart and Functional Probiotic Microorganisms: Emerging Roles in Health-Oriented Fermentation. Fermentation. 2025; 11:537. [DOI]

72. Hong C, Chen J, Huang T. Probiotics treatment for Parkinson disease: a systematic review and meta-analysis of clinical trials. Aging (Albany NY). 2022;14:7014–25. [DOI] [PubMed] [PMC]
73. Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015;386:896–912. [DOI]
74. Chaudhuri KR, Healy DG, Schapira AHV. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006;5:235–45. [DOI] [PubMed]
75. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008; 79:368–76. [DOI] [PubMed]
76. Yin S, Zhu F. Probiotics for constipation in Parkinson's: A systematic review and meta-analysis of randomized controlled trials. Front Cell Infect Microbiol. 2022;12:1038928. [DOI] [PubMed] [PMC]
77. Barichella M, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, et al. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: An RCT. Neurology. 2016;87:1274–80. [DOI] [PubMed]
78. Tan AH, Lim S, Chong KK, Manap MAAA, Hor JW, Lim JL, et al. Probiotics for Constipation in Parkinson Disease: A Randomized Placebo-Controlled Study. Neurology. 2021;96:e772–82. [DOI] [PubMed]
79. Ibrahim A, Ali RAR, Manaf MRA, Ahmad N, Tajurruddin FW, Qin WZ, et al. Multi-strain probiotics (Hexbio) containing MCP BCMC strains improved constipation and gut motility in Parkinson's disease: A randomised controlled trial. PLoS One. 2020;15:e0244680. [DOI] [PubMed] [PMC]
80. Ghalandari N, Assarzadegan F, Habibi SAH, Esmaily H, Malekpour H. Efficacy of Probiotics in Improving Motor Function and Alleviating Constipation in Parkinson's Disease: A Randomized Controlled Trial. Iran J Pharm Res. 2023;22:e137840. [DOI] [PubMed] [PMC]
81. Du Y, Li Y, Xu X, Li R, Zhang M, Cui Y, et al. Probiotics for constipation and gut microbiota in Parkinson's disease. Parkinsonism Relat Disord. 2022;103:92–7. [DOI] [PubMed]
82. Sun H, Zhao F, Liu Y, Ma T, Jin H, Quan K, et al. Probiotics synergized with conventional regimen in managing Parkinson's disease. NPJ Parkinsons Dis. 2022;8:62. [DOI] [PubMed] [PMC]
83. Chu C, Yu L, Li Y, Guo H, Zhai Q, Chen W, et al. *Lactobacillus plantarum* CCFM405 against Rotenone-Induced Parkinson's Disease Mice via Regulating Gut Microbiota and Branched-Chain Amino Acids Biosynthesis. Nutrients. 2023;15:1737. [DOI] [PubMed] [PMC]
84. Dong Y, Qi Y, Chen J, Han S, Su W, Ma X, et al. Neuroprotective Effects of *Bifidobacterium animalis* subsp. lactis NJ241 in a Mouse Model of Parkinson's Disease: Implications for Gut Microbiota and PGC-1α. Mol Neurobiol. 2024;61:7534–48. [DOI] [PubMed] [PMC]
85. Weintraub D, Aarsland D, Chaudhuri KR, Dobkin RD, Leentjens AF, Rodriguez-Violante M, et al. The neuropsychiatry of Parkinson's disease: advances and challenges. Lancet Neurol. 2022;21:89–102. [DOI] [PubMed] [PMC]
86. Cong S, Xiang C, Zhang S, Zhang T, Wang H, Cong S. Prevalence and clinical aspects of depression in Parkinson's disease: A systematic review and metaanalysis of 129 studies. Neurosci Biobehav Rev. 2022;141:104749. [DOI] [PubMed]
87. Chuquilín-Arista F, Álvarez-Avellón T, Menéndez-González M. Prevalence of Depression and Anxiety in Parkinson Disease and Impact on Quality of Life: A Community-Based Study in Spain. J Geriatr Psychiatry Neurol. 2020;33:207–13. [DOI] [PubMed]
88. Nisa A, Amalisa RN, Kristantya I, Haryono Y, Nugraha P. Probiotic Supplementation in Parkinson's Disease: Probiotic supplementation in Parkinson's diseases. Surabaya Med J. 2024;2:73–85. [DOI]
89. Park JM, Lee SC, Ham C, Kim YW. Effect of probiotic supplementation on gastrointestinal motility, inflammation, motor, non-motor symptoms and mental health in Parkinson's disease: a meta-analysis of randomized controlled trials. Gut Pathog. 2023;15:9. [DOI] [PubMed] [PMC]
90. Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. Mov Disord. 2009;24:2175–86. [DOI] [PubMed] [PMC]
91. Kim S, Guevarra RB, Kim Y, Kwon J, Kim H, Cho JH, et al. Role of Probiotics in Human Gut Microbiome-Associated Diseases. J Microbiol Biotechnol. 2019;29:1335–40. [DOI] [PubMed]

92. Yang X, He X, Xu S, Zhang Y, Mo C, Lai Y, et al. Effect of *Lacticaseibacillus paracasei* strain Shirota supplementation on clinical responses and gut microbiome in Parkinson's disease. Food Funct. 2023; 14:6828–39. [DOI] [PubMed]
93. Zeng T, Lin C, Deng Y, Zhu W. Effect of *BF* 839 + earthworm protein supplement on motor and some non-motor symptoms of Parkinson's disease: a randomized clinical trial. Front Neurol. 2024;15: 1371791. [DOI] [PubMed] [PMC]
94. Zandifar A, Badrfam R, Mohammaditabar M, Kargar B, Goodarzi S, Hajialigol A, et al. The Effect of Prebiotics and Probiotics on Levels of Depression, Anxiety, and Cognitive Function: A Meta-Analysis of Randomized Clinical Trials. Brain Behav. 2025;15:e70401. [DOI] [PubMed] [PMC]
95. Xie C, Prasad AA. Probiotics Treatment Improves Hippocampal Dependent Cognition in a Rodent Model of Parkinson's Disease. Microorganisms. 2020;8:1661. [DOI] [PubMed] [PMC]
96. Videnovic A, Golombek D. Circadian and sleep disorders in Parkinson's disease. Exp Neurol. 2013; 243:45–56. [DOI] [PubMed] [PMC]
97. Du Y, Wang L, Cui Y, Xu X, Zhang M, Li Y, et al. Effect of Probiotics Supplementation on REM Sleep Behavior Disorder and Motor Symptoms in Parkinson's Disease: A Pilot Study. CNS Neurosci Ther. 2025;31:e70541. [DOI] [PubMed] [PMC]
98. Tan AH, Hor JW, Chong CW, Lim S. Probiotics for Parkinson's disease: Current evidence and future directions. JGH Open. 2020;5:414–9. [DOI] [PubMed] [PMC]
99. Xiang S, Ji J, Li S, Cao X, Xu W, Tan L, et al. 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. Front Aging Neurosci. 2022;14:730036. [DOI] [PubMed] [PMC]
100. Valvaikar S, Vaidya B, Sharma S, Bishnoi M, Kondepudi KK, Sharma SS. Supplementation of probiotic *Bifidobacterium breve Bif11* reverses neurobehavioural deficits, inflammatory changes and oxidative stress in Parkinson's disease model. Neurochem Int. 2024;174:105691. [DOI] [PubMed]
101. Loh JS, Mak WQ, Tan LKS, Ng CX, Chan HH, Yeow SH, et al. Microbiota-gut-brain axis and its therapeutic applications in neurodegenerative diseases. Signal Transduct Target Ther. 2024;9:37. [DOI] [PubMed] [PMC]
102. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23:2129–70. [DOI] [PubMed]
103. Andreozzi V, Cuoco S, Balestrieri M, Fierro F, Ferrara N, Erro R, et al. Synbiotic supplementation may globally improve non-motor symptoms in patients with stable Parkinson's disease: results from an open label single-arm study. Sci Rep. 2024;14:23095. [DOI] [PubMed] [PMC]
104. Zali A, Hajyani S, Salari M, Tajabadi-Ebrahimi M, Mortazavian AM, Pakpour B. Co-administration of probiotics and vitamin D reduced disease severity and complications in patients with Parkinson's disease: a randomized controlled clinical trial. Psychopharmacology (Berl). 2024;241:1905–14. [DOI] [PubMed]
105. Hsieh T, Kuo C, Hsieh K, Shieh M, Peng C, Chen Y, et al. Probiotics Alleviate the Progressive Deterioration of Motor Functions in a Mouse Model of Parkinson's Disease. Brain Sci. 2020;10:206. [DOI] [PubMed] [PMC]
106. Parra I, Martínez I, Vásquez-Celaya L, Gongora-Alfaro JL, Tizabi Y, Mendieta L. Neuroprotective and Immunomodulatory Effects of Probiotics in a Rat Model of Parkinson's Disease. Neurotox Res. 2023; 41:187–200. [DOI] [PubMed]
107. Leta V, Mandal G, Zinzalias P, Staunton J, Batzu L, Trivedi D, et al. Effects of a four-strain probiotic on inflammatory markers in Parkinson's disease: a multicentre randomised controlled trial (the SymPD study) (N5.001). Neurology. 2024;102:7_supplement_1. [DOI]

108. Atak ES, Yıldız D, Kocatürk RR, Temizyürek A, Özcan ÖÖ, Ergüzel TT, et al. Therapeutic Targets of Probiotics in Parkinson Disease: A Systematic Review of Randomized Controlled Trials. Basic Clin Neurosci. 2024;15:165–74. [DOI] [PubMed] [PMC]
109. Brusnic O, Adrian B, Sorin-Radu F, Grama B, Sofonea F, Roman-Filip C, et al. Importance of Fecal Microbiota Transplantation and Molecular Regulation as Therapeutic Strategies in Inflammatory Bowel Diseases. Nutrients. 2024;16:4411. [DOI] [PubMed] [PMC]
110. Eslami M, Adampour Z, Dowlat BF, Yaghmayee S, Tabaei FM, Oksenych V, et al. A Novel Frontier in Gut-Brain Axis Research: The Transplantation of Fecal Microbiota in Neurodegenerative Disorders. Biomedicines. 2025;13:915. [DOI] [PubMed] [PMC]
111. Bruggeman A, Vandendriessche C, Hamerlinck H, Looze DD, Tate DJ, Vuylsteke M, 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] [PubMed] [PMC]
112. Scheperjans F, Levo R, Bosch B, Lääperi M, Pereira PAB, Smolander O, et al. Fecal Microbiota Transplantation for Treatment of Parkinson Disease: A Randomized Clinical Trial. JAMA Neurol. 2024;81:925–38. [DOI] [PubMed] [PMC]
113. Chen K, Sun L, Liu Y, Chen R. Safety and efficacy of fecal microbiota transplantation in the treatment of Parkinson's disease: a systematic review of clinical trials. Front Neurosci. 2025;19:1639911. [DOI] [PubMed] [PMC]
114. Nagpal R, Wang S, Woods LCS, Seshie O, Chung ST, Shively CA, et al. Comparative Microbiome Signatures and Short-Chain Fatty Acids in Mouse, Rat, Non-human Primate, and Human Feces. Front Microbiol. 2018;9:2897. [DOI] [PubMed] [PMC]
115. Mestas J, Hughes CCW. Of mice and not men: differences between mouse and human immunology. J Immunol. 2004;172:2731–8. [DOI] [PubMed]
116. MacLean EL. Unraveling the evolution of uniquely human cognition. Proc Natl Acad Sci U S A. 2016; 113:6348–54. [DOI] [PubMed] [PMC]
117. Menozzi E, Schapira AHV. The Gut Microbiota in Parkinson Disease: Interactions with Drugs and Potential for Therapeutic Applications. CNS Drugs. 2024;38:315–31. [DOI] [PubMed] [PMC]
118. Zheng Y, Zhang Z, Tang P, Wu Y, Zhang A, Li D, et al. Probiotics fortify intestinal barrier function: a systematic review and meta-analysis of randomized trials. Front Immunol. 2023;14:1143548. [DOI] [PubMed] [PMC]
119. Chuang Y, Fan K, Su Y, Wu M, Chiu Y, Liu Y, et al. Precision probiotics supplement strategy in aging population based on gut microbiome composition. Brief Bioinform. 2024;25:bbae351. [DOI] [PubMed] [PMC]
120. de Almeida Brasiel PG, Luquetti SCPD. Effects of Probiotics Supplementation on Short-Chain Fatty Acids: A Systematic Review of Randomized Controlled Trials. Nutr Rev. 2025;83:1892–907. [DOI] [PubMed]
121. Sreenikitha K, Das S, Andrighetti T, Sudhakar P. Comparative study of the gut microbiomes between Western and Indigenous cultures – Implications for health and disease. The Microbe. 2025;7: 100310. [DOI]
122. Low DY, Hejndorf S, Tharmabalan RT, Poppema S, Pettersson S. Regional Diets Targeting Gut Microbial Dynamics to Support Prolonged Healthspan. Front Microbiol. 2021;12:659465. [DOI] [PubMed] [PMC]
123. Gu X, Tang J, Chen C. Efficacy of gut microbiota-targeted therapies in Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. Front Cell Infect Microbiol. 2025;15:1627406. [DOI] [PubMed] [PMC]