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SYSTEMATIC REVIEW

Probiotic Supplementation in Parkinson's Disease

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ABSTRACT

Background: Parkinson's disease (PD) is a prevalent neurodegenerative disease with both motor and non-motor symptoms. It has been postulated that dysbiosis and gut infections may have metabolic consequences that go unchecked and exacerbate the neurodegenerative process or peripheral inflammation in PD. **Objective**: This meta-analysis aims to elucidate the potential benefits of of probiotics as supplemental therapy for PD. **Materials and Method**: PRISMA 2020 was used for literature search. Multiple databases, such as PubMed, Science Direct, and CINAHL Plus, as well as Full Text, Sage Journals, and Web of Science, and clinical registries were investigated. The quality assessment and statistical analysis were conducted using the Jadad scale and the Review Manager software version 5.4.1. **Results**: Ten randomized controlled trials (RCTs) were included in this systematic review, six of which were quantitative studies. The results indicated that probiotic treatment significantly improved cognitive function based on the MMSE (mean difference [MD] = 0.4, 95% CI [-0.17, 0.97], I2 = 0%). Probiotic treatment also improved gastrointestinal symptoms as evidenced by the Bristol stool score (MD = 0.28, 95% CI [-0.40, 0.97], I2 = 93%) and the bowel movement score (MD = 1.25, 95% CI [0.74, 1.75], I2 = 0%). Significant effects were observed in the depression scale and quality of life, including the Patient Assessment of Constipation Quality of Life (PACQoL) and the Parkinson's Disease Questionnaire (PDQ39). **Conclusion**: Probiotic supplementation significantly improved disease progression, gastrointestinal effects, mental health, and quality of life in patients with PD. This improvement may be attributed to a reduction in the inflammatory response and an increase in the activity of gut-brain axis.

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Highlights

1. The role of probiotics for treatment in Parkinson's disease (PD) is still on clinical trials.
2. Probiotics can be used as an additional therapy for PD to enhance intestinal motility, psychological well-being, and quality of life.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive degenerative illness of the central nervous system that affects the basal ganglia pathologically (Ramesh and Arachchige, 2023). The disease progresses from the degeneration of substantia nigra, the presence of Lewy bodies, and the depletion of dopamine in the substantia nigra pars compacta and the striatum (Sahay and Sutiono, 2018). With the increasing age of the U.S. population, it is anticipated that the prevalence of PD will increase significantly. Currently, PD is the second most common neurodegenerative disease after Alzheimer's disease. It is projected that the prevalence of PD in the U.S. will increase two-fold by 2040. In Indonesia, approximately 10 individuals are diagnosed with PD annually. To date, the number of individuals suffering from PD is estimated to be between 200,000 and 400,000 individuals. It is estimated that 876,665 from 238,452.952 Indonesians are diagnosed with PD. The mortality rate is ranked 12th globally and 5th in the Asia region, with a prevalence of 1,100 deaths in 2002 (Ray Dorsey et al., 2018).

Gut microbiota influences the gut-brain axis, which connects the central and enteric neural systems. In mammals, these systems communicate via the vagus and pelvic nerves, with enteroendocrine cells serving as a communication channel. The neurological and immunological systems maintain the complex microbial environment of the gastrointestinal tract in order to optimize host advantages such as protection, nourishment, and psychological well-being (Montanari et al., 2023; Santos García et al., 2021; Santos et al., 2019).

Previous studies have indicated a correlation between the gut-brain axis and PD, with diet, gut microbiome, and metabolites playing significant environmental roles. Lewy pathology discovered in the 1980s has prompted further research (Salim et al., 2023). The neurodegenerative process of PD can be exacerbated by peripheral inflammation or metabolic effects caused by dysbiotic and gut pathogens. Many preclinical and clinical studies have shown the disruption of gut permeability, gut inflammation, changes in gut microbiome, and a decrease in fecal short-chain fatty acids in PD (Tan et al., 2021).

A recent therapeutic target for PD treatment is α-Synuclein. Drugs targeting α-synuclein played role in inhibiting α-Synuclein misfolding, producing antisense oligonucleotides (ASOs) to reduce the expression of SCNA (α-Syn gene), regulating the α-Syn gene through β2AR agonists, or using LAG3 for binding to exogenous α-Syn (Gouda et al., 2022). A previous study demonstrated the inhibitory and clearance effects of the probiotic strain *B. subtilis* PXN21 on α-Synuclein aggregation in a *C. elegans* model through the production of metabolites and the creation of biofilm (Goya et al., 2020). Clinical trials and animal studies also demonstrated the benefits of probiotics in PD. As a result, probiotic supplementation therapy in PD has increased (Mirzaei et al., 2022). To address these scientific gaps, we conducted an analytical systematic review using more recent clinical studies to assess the effect of probiotic supplementation on PD.

OBJECTIVE

This study aims to elucidate the potential benefits of probiotics as supplemental therapy for PD patients.

MATERIALS AND METHODS

Study design

The Preferred Reporting Items of the Systematic Review and Meta-Analysis (PRISMA) guidelines were used throughout the course of this study.

Data collection

A search was conducted in PubMed, Science Direct, CINAHL Plus, as well as Full Text, Sage Journals, Web of Science and clinical registries using the following keywords: ("probiotic*" OR "probiotic supplementation*" OR "lactobacillus" OR "Bifidobacterium" OR "yeast*" OR "yogurt*" OR "fermented product*" OR "synbiotic*" OR "cultured milk product*" OR "fermented milk*") AND ("Parkinson" OR "Parkinson's disease" OR "parkinsonism"). An additional search was conducted in clinical registries such as clinicaltrial.gov and ISCRTN. The downloaded articles were sorted and reviewed. The inclusion criteria for the literature search were: (1) randomized and placebo-controlled trial of PD patients in accordance with the standardized diagnostic criteria; (2) reporting at least one primary outcome such as gastrointestinal effect, disease progression, inflammation biomarker, or mental health score; (3) available in full-text and written in English; (4) primary studies; and (5) published within ten years. The exclusion criteria for the literature search were: (1) not primary studies; (2) not full-text manuscripts; (3) using languages other than English; and (5) using animal models or in vivo studies.

Data analysis

A statistical analysis was performed, with continuous data used for the primary outcomes and dichotomous data for the side effects. The heterogeneity of the literature data was tested using I2. The statistical results were considered significant at a p-value of less than 0.05.

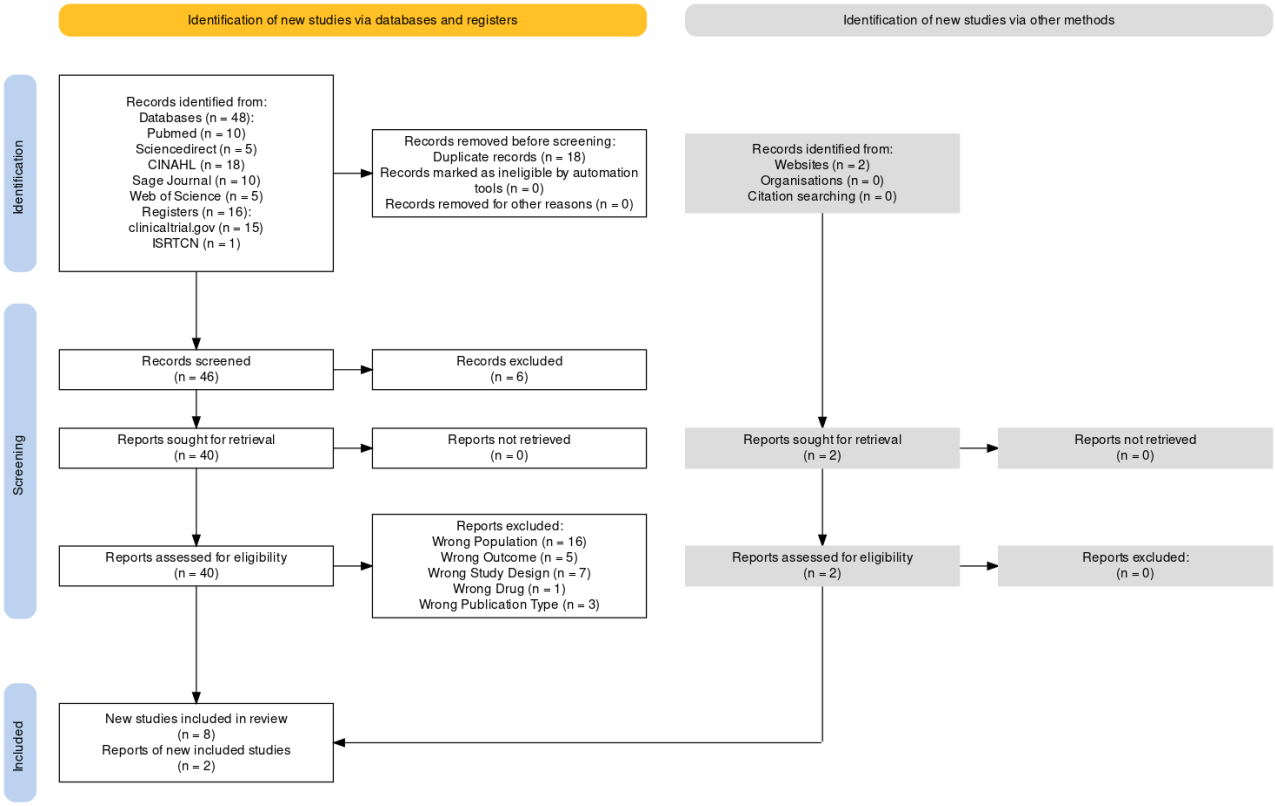

Figure 1. PRISMA Flowchart

RESULTS

A total of 48 studies were identified from the databases, while 16 studies were identified from the registries. A total of 18 studies were identified as duplicates and 46 studies were screened. Subsequently, 40 studies were assessed for eligibility, with 30 studies excluded. This meta-analysis and systematic review included ten relevant studies. The baseline features of the studies were compiled in Table 1. Three studies were conducted in Iran (Ghalandari et al., 2023b; Mehrabani et al., 2023; Tamtaji et al., 2019), two in China (Sun et al., 2022; Yang et al., 2023), one in Italy (Barichella et al., 2016), one in Malaysia (Ibrahim et al., 2020), one in Taiwan (Lu et al., 2021), one in Rumania (Georgescu et al., 2016) and one in the U.S. (Htoo, 2022). The study by Tamtaji et al. included 60 patients with PD

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who had been diagnosed according to the clinical criteria set forth by the U.K. PD Society Brain Bank. The intervention group was administered with a multistrain probiotic capsule containing 2 x 10^9 CFU/g of *Lactobacillus reuteri, Lactobacillus acidophilus, Bifidobacterium bifidum,* and *Lactobacillus fermentum* within 12 weeks. The mean age of the probiotic group was 68.2 ± 7.8 years, while that of the placebo group was 67.7 ± 10.2 years (Tamtaji et al., 2019). The study by Barichella et al. included 120 patients with functional constipation according to the ROME III criteria and the U.K. PD Society Brain Bank criteria. The intervention group was administered with multistrain probiotic milk containing 250 x10^9 CFU/g of *bifidobacterium (breve and animalis subsp lactis), Streptococcus salivarius subsp thermophilus, Lactobacillus plantarum, Enterococcus faecium, Lactobacillus paracasei, Lactobacillus rhamnosus GG, Lactobacillus acidophilus,* and *Lactobacillus delbrueckii subsp bulgaricus* within four weeks. The mean age of the probiotic group was 71.8 ± 7.7 years, while that of the placebo group was 69.5 ± 10.3 years (Barichella et al., 2016). The study conducted by Ghalandari *et al*. included 30 patients with idiopathic PD and functional constipation based on the ROME IV criteria. Multistrain probiotic capsules containing 4 x1011 CFU/g of *Lactobacillus plantarum, Bifidobacterium longum, Lactobacillus casei, Lactobacillus bulgaricus, Bifidobacterium infantis, Bifidobacterium breve, Lactobacillus acidophilus,* and *Streptococcus thermophilus* were administered to the intervention group within eight weeks. The mean age of the probiotic group was 68.07 ± 6.68 years, while that of the placebo group was 68.54 ± 6.92 years (Ghalandari et al., 2023b).

Table 1. Details of included study

Author	Sample Size	Intervention	Comparison	Outcome	Jadad Score
Tamtaji (2018)	60	Multistrain capsule	Placebo capsule	Inflammatory biomarker (such as GSH and TAC), MDS-UPDRS, FPG, lipid profile and BMI	8
Barichella (2016)	120	Multistrain fermented milk	Pasteurized fermented milk	Bowel movement, sensation of complete bowel emptying, stool consistency, rescue medication, and satisfaction scale	8
Ghalandari (2023)	30	Multistrain capsule	Placebo capsule	Sense of complete evacuation, frequency of defecation, Bristol stool, laxative use, and UPDRS	8
Ibrahim (2020)	55	Multistrain capsule	Placebo capsule	MDS-UPDRS, Garrigues Questionnaire, GTT, PDQ39-SI, and NMSS	8
Lu (2021)	25	Capsule of *Lactobacillus plantarum* PS128	None (single arm study)	Beck depression inventory-II, UPDRS, non-motor symptoms questionnaire, PDQ-39, patient assessment of constipation symptom, and PGI-C	8
Mehrabani (2023)	80	Multistrain sachet	Maltodextrin	Inflammatory biomarker (such as GSH and MDA), PDQ39, BDI-II, HADS, and FSS	7
Sun (2022)	82	Capsule of *Probio-M8*	Benserazide combined with agonist of dopamine	HAMD, Bristol stool, PACQOL, MMSE, UPDRS-III, HAMA, and PDSS	8
Yang (2023)	128	Fermented milk of *Lacticaseibacillus paracasei* YIT 9029; LcS	Placebo acidified milk without Lc	Bristol stool, bowel movement, PACQOL, MDS-UPDRS, NMSS, HAMA, HAMD, PDQ-39 and MMSE	8
Htoo (2022)	38	Multistrain capsule	Placebo	Constipation score, depression and anxiety score, PDQ-39, BMI	7
Georgescu (2016)	40	Multistrain tablet	Trimebutine 200 mg	Severity score of abdominal pain, bloating, and constipation	8

The study by Ibrahim *et al*. included 55 patients with idiopathic PD in stages 1 to 4 of the Hoehn and Yahr scale and functional constipation according to the ROME III criteria. The intervention group was administered with a multistrain probiotic capsule containing 3 x10^{10} CFU/g of Bifidobacterium infantis (BCMC1 02129) and 107 mg of *Lactobacillus casei, Bifidobacterium longum, Lactobacillus acidophilus,* and *Lactobacillus lactis* within eight weeks. The mean age (range) of the probiotic group was 69.0 (64.0–74.0) years, while that of the placebo group was 70.5 (62.0–70.3) years (Ibrahim et al.,

2020). The study by Lu *et al*. included 25 patients with idiopathic PD in a single arm study. All patients were administered with a single strain probiotic capsule containing 6 $x10^{10}$ CFU/g of *Lactobacillus plantarum PS128* within eight weeks. The mean age of the patients was 61.84 ± 5.74 years. The study by Mehrabani et al. included 80 patients with PD according to the criteria from the U.K. PD Society Brain Bank. The intervention group was administered with a symbiotic sachet containing 5 $x10^{9}$ oFU/*g* of *Bifiobacterium longum (BIA-8), Streptococcus thermophilus, Lactobacillus acidophilus (LAA-5), Lactobacillus plantarum (LAP-10),* and *Lactobacillus rhamnosus (LAR-7)* within 12 weeks. The mean age of the probiotic group was 69 years, while that of the placebo group was 69.05 ± 8.23 years. The study by Sun et al. included 82 patients with PD. The intervention group was administered with a single strain capsule of *Bifidobacterium animalis subsp. lactis Probio-M8 (Probio-M8)* within 12 weeks. The mean age of the probiotic group was 66.46 ± 6.98 years, while that of the placebo group was 68.76 ± 6.91 years (Lu et al., 2021).

The study by Yang *et al*. included 128 patients with PD according to the Queen Square Brain Bank criteria. The intervention group was administered with single strain fermented milk containing 1 $x10^{10}$ CFU/g of *Lacticaseibacillus paracasei strain Shirota (L. paracasei YIT 9029; LcS)* within 12 weeks. The mean age of the probiotic group was 67.22 ± 6.46 years, while that of the placebo group was 69.64 ± 6.41 years (Yang et al., 2023). The study by Htoo (2022) included 38 patients with PD. The intervention group was administered with a multistrain probiotic capsule containing 5.2$x10^{9}$ CFU of *Bacillus, Bifidobacterium, Lactobacillus,* and *Saccharomyces* within six weeks. The mean age of the probiotic and vitamin B3 combination group was 71 ± 9 years, while that of the placebo group was 74 ± 6 years old and that of the probiotic group was 71 ± 9 years old. The study by Georgescu et al. included 40 patients with PD. The intervention group was administered with a multistrain probiotic tablet containing *Lactobacillus acidophilus* and *Bifidobacterium infantis* within 12 weeks. The mean age of the total patients was 76.05 ± 2.09 years (Htoo, 2022).

DISCUSSION

The International Scientific Association for Probiotics and Prebiotics (ISAPP) defines probiotics as living microorganisms that, when administered in the appropriate quantity, positively influence the host, following guidelines from the World Health Organization and the Food and Agriculture Organization (Hill et al., 2014; Ibrahim et al., 2023). The probiotic potential is specifically associated with certain strains of microorganisms, rather than being determined by the genus or species. In vitro tests can be conducted to determine if the microbial strains meet the aforementioned criteria. It is important to base the probiotic dose (CFU/g) of the final product on those shown to be effective in human clinical trials. Although the minimum effective quantity remains unknown, it is widely agreed that probiotic products should contain at least 106 CFU/ml or gram, and that daily consumption of 108 to 109 probiotic microbes is necessary to elicit probiotic effects (Ibrahim et al., 2023). Most probiotic strains are lactic acid bacteria (LAB), with *Lactobacillus* being the most significant, followed by *Streptococcus* and *Lactococcus*. Some *Enterococcus* and *Escherichia coli* species are also probiotics. LAB, or gram-positive, nonsporulating, catalase-negative organisms, are found in many places. Gut-related organisms are found in dairy products, meats, vegetables, and commercial fermented goods (Ibrahim et al., 2023).

A comparison of the gut microbiomes of PD patients with healthy controls revealed significant differences. A previous meta-analysis revealed that the bacterial families of *Lachnospiraceae,* which was more abundant in control samples, as well as *Bifidobacteriaceae* and *Akkermansiaceae*, which were more abundant in PD patients, were the main causes of the divergence between PD and controls. Other families including *Clostridium methylpentosum*, *Christensenellaceae*, *Porphyromonadaceae*, *Oscillospiraceae*, and *Rikenellaeae* were also more abundant in PD (Romano et al., 2021). In line with this, a meta-analysis reviewed different species in PD. The study revealed that *Bifidobacteriaceae, Ruminococcaceae, Verrucomicrobiaceae,* and *Christensenellaceae* were more abundant in the gut microbiota in PD patients compared to healthy controls. These variations might contribute to the pathogenesis of PD by decreasing the production of short-chain fatty acids, the metabolism of lipids, immunoregulatory activity, and the permeability of the intestinal tract (Shen et al., 2021). A study conducted at an Egyptian hospital found that the PD group had considerably higher levels of lactic acid bacteria, *Clostridium* cluster IV, *Akkermansia, Bifidobacterium,* and a lower level of *Firmicutes* than the control group (Khedr et al., 2021). In early-stage PD patients, a study found considerably lower level of *Prevotellacopri*, supporting prior findings indicating that advanced PD patients had lower level

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of *Prevotellaceae*. *Prevotella* produces short-chain fatty acids (SCFAs) such as butyrate. As a result, a decrease in SCFAs may contribute to the development of intestinal barrier leakiness and immunological dysfunction during the progression of PD (Hashish and Salama, 2023).

Table 2. The results of overall effect and heterogeneity tests

Outcome	Pooled Effect				Heterogeneity		
	Overall Effect	95% CI	z	p	df	I^2	p
Disease progression							
MDS-UPDRS	-0.67	-7.62 to 6.27	0.19	0.85	1	0%	0.32
UPDRS III	-0.51	-2.95 to 1.94	0.41	0.68	2	0%	0.88
MMSE	0.40	-0.17 to 0.97	1.38	0.17	2	0%	0.88
Gastrointestinal effect							
Bristol score	0.28	-0.40 to 0.97	0.81	0.42	2	93%	< 0.00001
Bowel movement	1.25	0.74 to 1.75	4.85	< 0.00001	1	0%	0.61
Mental health							
HAMD	-1.89	-3.31 to -0.47	2.62	0.009	2	0%	0.66
Metabolic effect							
GSH	11.01	-49.68 to 71.71	0.36	0.72	1	69%	0.07
TAC	52.71	0.13 to 105.3	1.96	0.05	1	10%	0.29
BMI	1.15	-0.07 to 2.36	1.85	0.06	4	0%	0.99
Quality of life							
PDQ 39	-2.14	-3.83 to -0.44	2.47	0.01	5	32%	0.19
PacQOL	-12.13	-15.43 to-8.83	7.2	< 0.00001	2	0%	0.55

A previous meta-analysis found that probiotic intervention significantly improved motor symptoms, constipation, quality of life (QoL), anxiety, and depression parameters in PD patients (Park et al., 2023; Xie et al., 2023). Additionally, probiotic supplements boosted glutathione levels (GSH) in the serum of PD patients and decreased their reliance on laxatives. The study discovered that probiotic therapy significantly reduced motor clinical presentation as well as constipation-related quality of life and mood-related measures. Overall, probiotic treatment has shown potential for improving the quality of life and overall well-being of PD patients (Chu et al., 2023). Another quantitative meta-analysis of three studies showed that probiotic treatment significantly increased the frequency of bowel movements among people with PD and normalized stool consistency (Hong et al., 2022). Furthermore, probiotics reduced triglycerides, VLDL, HDL, insulin, MDA, CRP, HOMA-IR, but only triglycerides in patients with neurological illness (Tamtaji et al., 2020). Compared to the control group, probiotics increased weekly defecation frequency in PD patients. In contrast, PD patients treated with probiotics had similar stool consistency to those given a placebo (Yin and Zhu, 2022). Another meta-analysis of eleven trials found compelling evidence of age-related reductions in both motor and non-motor symptoms, depression, and gastrointestinal motility. The results showed a moderate to low level of improvement in the quality of life, anxiety, serum inflammatory markers, and diabetes risk. However, the Bristol stool scale scores, antioxidant capacity, constipation, and dyslipidemia risk did not improve. In addition, probiotic pills improved gastrointestinal motility over fermented milk (Park et al., 2023). A study by Ghalandari et al. showed that probiotics significantly increased weekly bowel movement (Ghalandari et al., 2023b). Another study found that probiotic therapy resulted in the amelioration of constipation symptoms, such as enhanced stool frequency, improved texture, decreased use of laxatives, and decreased Parkinson's UPDRS III score, without any notable variance in overall adverse effects (Xie et al., 2023).

Disease progression

Parkinson's disease progresses gradually and is distinguished by both motor and non-motor symptoms (Martin, 2010). A correlation has been established between PD and changes in the gut flora, thereby opening up a new avenue for investigation (Yang et al., 2019). The progression of the disease, whether motor or non-motor symptoms, is evaluated based on the MDS-UPDRS, UPDRS III, and MMSE

criteria. However, due to the limited number of studies and inconsistency of results among current studies, no significant conclusions can be drawn. showing non significance due to limited number of studies and inconsistence result among current studies (Helmy et al., 2022). For a significant period of time, the Unified Parkinson's Disease Rating Scale (UPDRS) was the primary means of assessing the progression of PD. The Movement Disorders Society (MDS-UPDRS) introduced and published the updated version of the UPDRS in 2008. The MDS-UPDRS is increasingly being employed for the assessment of motor dysfunction. (Yamamoto et al., 2023).

No significant difference was observed between the placebo and probiotic intervention for Parkinson's disease in UPDRS III ($p = 0.68$) and MDS-UPDRS ($p = 0.05$) with mean differences of -0.51 (95% CI [-2.95, 1.94[) and -1.90 (95% CI [-3.77, - 0.04]), respectively (Xie et al., 2023). A study of mice showed that the administration of multi-strain probiotics on a regular basis within six months resulted in a significant reduction in the motor deficits that were present in motor coordination, balance, and gait pattern. An immunohistochemical examination revealed that the substantia nigra of the PD animals treated with probiotics contained a highly conserved tyrosine hydroxylase (TH)-positive cell. According to the study, administering probiotics to mice over an extended period of time may have neuroprotective effects on dopamine neurons and slow the development of motor dysfunctions (Hsieh et al., 2020). Another study was conducted to assess motor function using a rotarod test and to examine cytokines and neurotransmitters in the cerebellum. Probiotics was shown to enhance motor skills during moderate and high-intensity exercises and to alleviate inflammatory reactions in the brain (Park et al., 2023). Supplementing probiotics in elderly individuals without health issues might enhance cognitive abilities, lower Aβ levels in the hippocampus, preserve the structural integrity of neurons, and mitigate neuroinflammation by modifying gut microbiota. This could potentially forestall the onset of neuroinflammation, which is associated with Alzheimer's disease (Handajani et al., 2023; Liu et al., 2023).

Non-motor symptoms associated with PD include sensory impairments, neurobehavioral alterations, disturbances in autonomic regulation, and disruptions in sleep patterns (Poewe, 2008). Cognitive impairments in early-stage PD are prevalent and progress over time. These entail difficulties in switching between tasks, impaired executive functions, decreased verbal fluency, and visuospatial skills. Dementia, affecting up to 80% of PD patients, may also occur (Gupta and Shukla, 2021). Two studies using the Mini-Mental State Examination (MMSE) found no significant difference in cognitive function (MD = 0.40, 95% CI [0.17, 0.97[, $p = 0.17$) (Sun et al., 2022; Yang et al., 2023). Furthermore, an animal model trial demonstrated that the supplementation of *Lacticaseibacillus rhamnosus* HA-114 for six weeks enhanced cognitive impairments related to the hippocampus (Xie and Prasad, 2020). An earlier study found that a 12-week probiotic intervention significantly improved the MMSE score and the total MoCA score of elderly individuals with mild cognitive impairment, compared to those of the placebo group, and a significant increase in the probiotic group (Fei et al., 2023).

Gastrointestinal effect

The pathology of Parkinson's disease begins in the enteric nervous system (ENS) and extends to the central nervous system (CNS) through the vagus nerve, as evidenced by the injection of human α-Synuclein fibrils into the gastrointestinal tissue of mice (Zhu et al., 2022). Fecal metabolites, including bioactive molecules such as SCFAs, have been associated with neurodegeneration. SCFAs, produced by gut bacteria fermentation, play a crucial role in the pathogenesis of neurological diseases such as multiple sclerosis, Alzheimer's disease, and PD. Low SCFA levels in PD patients are associated with an increase in endotoxin and neurotoxin, potentially contributing to the development of PD. SCFAs also facilitate digestive tract movement and control the ENS, potentially contributing to constipation in PD. Microbial SCFAs play a key role in microbiota-gut-brain axis signal communication (Zhu et al., 2022). A decrease in SCFA-producing bacteria and an increase in mucin-degrading *Akkermansia* in PD result in increased intestinal permeability, exposing the neural plexus to toxins and causing abnormal α-Synuclein fibril aggregation. This is exacerbated by decreased serum LPS-binding protein in PD. Therapeutic intervention to modify these intestinal issues may be established, with metagenomic analyses using next-generation sequencers accelerating the understanding of taxonomic changes (Hirayama and Ohno, 2021). A study employing 16S rRNA gene sequencing discovered microbial compositions associated with PD, including a drop in SCFA-producing bacteria such as *Lachnospiraceae*. This might be a side effect of PD, rather than a cause or biomarker. Xenobiotics may

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cause gut microbial dysbiosis and dementia, since functional projections indicate an increase in xenobiotic degradation pathways. Another study discovered a lower level of the *Lachnospiraceae* family in patients with PD, as well as higher levels of *Christensenellaceae* and *Lactobacillaceae*, which were associated with poorer clinical outcomes. A Chinese PD patient exhibited a unique fecal microbiota with changes in biosynthesis, metabolism, and apoptotic pathways. These changes in the gut microbiota may influence the development of motor disease (Salim et al., 2023).

The results showed that the bowel movements of the probiotic group was significantly higher (pooled MD = -1.25, 95% CI [0.74, 1.75], p < 0.00001). However, based on the Bristol stool score, the probiotic group showed no significant therapeutic effect (pooled MD = 0.28, 95% CI [-0.40, 0.97], p = 0.42). In PD, the use of antiparkinsonian drugs may exacerbate constipation symptoms and cause sluggish bowel transit or puborectal dyssynergia (Stocchi and Torti, 2017). In addition, one of the non-motor symptoms of PD is constipation, which can significantly manifest 20 years before the onset of motor symptoms. The underlying mechanisms and pathophysiology of constipation are complex (Barrenschee et al., 2017; Fasano et al., 2015) The pathogenesis of Parkinson's disease may not always involve microbiological stimuli, and it is unclear whether abnormal peristalsis in PD patients is due to gut flora or disease changes (Nowak et al., 2022). A study found that the effect of probiotic administration could persist even when *L. plantarum* was discontinued (Ghalandari et al., 2023a). For patients with PD and constipation, probiotics may improve the Bristol stool scale. Decreased short-chain fatty acids (SCFAs) have been observed in PD patients. SCFAs have anti-inflammatory properties and are essential for the repair of the intestinal mucosal layer, modulation of the intestinal neural system activity, and promotion of the intestinal movement (Aho et al., 2021; Unger et al., 2016). Probiotics can increase SCFA production and relieve constipation through the production of mucus in the intestine, improve the intestinal mucosal layer, and increase intestinal motility (Dimidi et al., 2017; Suez et al., 2019).

Mental health

In this study, depression was evaluated based on the Hamilton Depression Rating Scale (HAMD). The results showed that the HAMD score was significantly lower in the probiotic group (pooled MD = -1.89, 95% CI [-3.31, -0.47], p = 0.009). Probiotics also have beneficial effects on mental health. Probiotics were found to markedly reduce the depression scale score (MD = −0.30, 95% CI [−0.51, −0.09], p = 0.005) (Huang et al., 2016). Probiotics not only affect gut flora, but they also assist healthy older individuals in experiencing less stress and exhibiting greater mental flexibility. The probiotic group outperformed the placebo group on the stress score and mental flexibility test. (Kim et al., 2021). The gut-brain axis connects the intestinal microbiota to the brain through central, autonomic, enteric, and hypothalamic-pituitary-adrenal neural systems. Effective communication between the gut and brain involves mucosal immune cell cytokines and endocrine cell hormones. The signaling between the brain and the body in response to stress requires neurotransmitter, neurochemical, and metabolite production. Studies have demonstrated that the colon and gut-brain axis produce over 90% of serotonin, which modulates the activation of receptors in enterocytes, gut neurons, and immune system cells (Cox and Weiner, 2018; Kali, 2016; Vera-Santander et al., 2023).

Metabolic effect

Two studies provided the results of glutathione (GSH) level measurement. A heterogeneity was observed (I2 = 69%, p = 0.07). This finding indicated that the GSH level in the probiotic group was not significantly increased (pooled MD = 11.01, 95% CI [-49.68 71.71], p = 0.72). In the analysis of the total antioxidant capacity (TAC) level, no heterogeneity was observed among the studies (I2 = 10%, p = 0.29), indicating that the TAC level of the probiotic group was not significantly different (pooled MD = 52.71, 95% CI [0.13, 105.30], p = 0.05). According to the results of the BMI measurement, no heterogeneity was observed among the studies (I2 = 0%, p = 0.99), indicating that the BMI of the probiotic group was not significantly higher compared to that of the control group (pooled MD = 1.15, 95% CI [-0.07, 2.36], p = 0.06). A previous meta-analysis showed that supplementation with probiotics significantly reduced the concentration of pro-inflammatory cytokines such as hs-CRP, TNF-a, IL-6, IL-4, IL-12, and TNF-a. However, IL-1B, IL-8, IL-17, and IF levels were not affected (Milajerdi et al., 2020). Probiotics can generate a number of metabolites, including glutathione (GSH), butyrate, and

folate, that have antioxidant properties. GSH, a significant non-enzymatic antioxidant in cells, primarily works in tandem with selenium-dependent glutathione peroxidase to remove radicals such as hydroxyl radicals, hydrogen peroxides, and peroxynitrite (Hoffmann et al., 2019; Wang et al., 2017). Total antioxidant capacity (TAC) was found to significantly increase following the administration of probiotics. However, in this study, an increase in the level of TAC was not significant because a longer supplementation period might be required to influence the TAC (Musazadeh et al., 2023). It has been suggested that probiotics and synbiotics reduce body weight in different ways. Probiotics facilitate in the restoration of the tight connections that separate epithelial cells, lowering intestinal permeability, preventing bacterial translocation, reducing inflammation induced by lipopolysaccharides (LPS), and elevating the levels of pancreatic polypeptide (PPY) in the gut, leptin, and glucagon-like peptide (GLP-1) (Álvarez-Arraño and Martín-Peláez, 2021).

Quality of life

The quality of life assessed using the PDQ39 questionnaire showed significant difference in favor of the probiotic group compared to the placebo group (MD = -2.14; 95% CI [-3.83, -0.44]; p = 0.01). This study used the Patient Assessment of Constipation Quality of Life (PACQoL) questionnaire to assess patient well-being, and found that probiotic supplementation significantly reduced symptoms and improved the quality of life of PD patients. The analysis showed a mean difference of -12.13 (95% CI [-15.43, -8.83], $p < 0.00001$). A study conducted in Saudi Arabia revealed that several domain-based variables influenced the quality of life (QOL) of individuals with PD, including frequent hospitalizations, education level, and marriage status (Al-Khammash et al., 2023). A meta-analysis study found that PD patients had significantly poorer quality of life (QOL) compared to healthy controls, highlighting the need for effective measures to improve QOL in this patient population (Zhao et al., 2021). This longitudinal follow-up study found that PD patients have short-term impairment in their health-related quality of life (HRQoL) due to motor status impairment during the OFF state (UPDRS-III), gait issues (FOGQ), and NMS burden. The findings further suggest that clinically severe deterioration in HRQoL in women and younger patients should be monitored closely (Santos García et al., 2021).

Limitations

Limited studies were available for analysis.

CONCLUSION

There is a growing interest in and some promising findings regarding the potential therapeutic benefits of probiotics in PD. The results of this meta-analysis indicated significant changes in patients with PD after probiotic supplementation as evidenced by bowel movements, mental health, and quality of life.

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Conflict of Interest

The authors have no conflict of interest to declare.

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Author Contribution

Conceptualization: AIM., RNA., I.K.; methodology: AIM., RNA., I.K.; data collection and extraction: AIM., RNA., I.K.; data analysis and interpretation: AIM., RNA., I.K.; manuscript writing: AIM., RNA., I.K.; critical revision: Y.H., P.N.; statistical analysis: AIM., Y.H., P.N.

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