

Review Paper



Therapeutic Targets of Probiotics in Parkinson Disease: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Introduction: Parkinson disease is the world's second most prevalent neurological disease. In this disease, intracytoplasmic neuronal inclusions are observed in enteric neurons in the gastrointestinal tract, and the composition of the intestinal microbiome is altered. These changes correlate with the motor phenotype. A systematic review was conducted to determine the effect of using probiotics in Parkinson disease.

Methods: Scopus, PubMed, Web of Science, the Cochrane Library, ScienceDirect, and Ovid-LWW were searched until April 2021. A total of 27395 records were found according to inclusion and exclusion criteria with the following outcomes: Parkinson disease rating, oxidative stress, and gastrointestinal system markers. Data search, article selection, and data extraction assessments were performed according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines. The Jadad scale was used to rate the evidence's quality.

Results: Our study information was gathered from 5 randomized controlled trials involving 350 individuals with Parkinson disease receiving probiotic supplements. Parkinson disease rating and non-motor symptoms test were performed in the samples. Also, oxidative stress (glutathione, malondialdehyde) and gastrointestinal system symptoms (bowel opening frequency, gut transit time, complete bowel movement, spontaneous bowel movements) were evaluated during 4-12 weeks of using probiotics in these patients.

Conclusion: While all high-quality studies demonstrate improvement in disease symptoms of the patients, currently sufficient data are not available to recommend the use of probiotics for people with Parkinson disease in clinical practice.

Keywords:

Parkinson disease,
Probiotics, Fermented foods,
Bifidobacterium, Lactobacillus

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Highlights

- Proving that probiotics may help by reducing the severity of Parkinson disease (PD) rating, selected gastrointestinal measurements, and oxidative stress parameters in PD.
- Modulation of the gut microbiome could be a therapeutic target for PD.
- Strategies to inhibit PD symptoms.

Plain Language Summary

Parkinson disease (PD) is a global concern. Pathologically, AD is characterized by the presence of reducing dopamine levels, oxidative stress, increased inflammatory cytokines and free radicals. It induces neuronal injury resulting with non-motor symptoms of PD are gastrointestinal (GI) dysfunction. In this review study, we investigated the therapeutic targets of probiotics in PD. This study reported the probiotic supplements were used for 4-12 weeks in PD can protect oxidative stress by increasing glutathione (GSH) levels and decreasing malondialdehyde (MDA), C- reactive protein (CRP) levels, Parkinson disease rating and GI dysfunction such as spontaneous bowel movement, bowel opening frequency (BOF), gut transit time (GTT) abdominal pain, bloating, constipation. Although the studies included in this study have high methodological quality, the number of studies is quite insufficient. It also varied greatly in terms of the number of people treated, treatment durations, gender differences, disease degree, age and types of probiotics administered. We suggest that future studies should have investigate the probiotic effects on pathological lesions in PD patients.

1. Introduction

Parkinson disease (PD) is a neurological disease whose prevalence is rapidly rising. The disease incidence and prevalence were reported to be 11–19 and 108–257 per 100000 in Europe, respectively. The loss of dopaminergic neurons in the substantia nigra and pars compacta, as well as the accumulation of tender folded-synuclein termed Lewy bodies in the intracytoplasmic space, are the clinical features of PD. Mitochondrial dysfunction, oxidative stress, increased inflammatory cytokines and free radicals, and genetic and environmental variables are associated with this clinical condition (Balestrino & Schapira, 2020). These factors commonly cause motor symptoms, including bradykinesia, tremor, and postural disorder. However, the clinical side also includes non-motor symptoms (Ding et al., 2017). The most common non-motor symptoms of PD are gastrointestinal (GI) dysfunction, such as constipation, bloating, abdominal pain, stool consistency, and bowel movements (Schrag et al., 2000). Many factors can be associated with neurodegenerative disorders, including gut microbiota and functions related to the blood-brain barrier (Shoemark & Allen, 2015). Probiotic supplementation has been reported to help relieve clinical and metabolic outcomes in PD (Parashar & Udayabanu, 2017). As a result, modulation of the gut microbiome could be a therapeutic target for PD.

Supplementing with probiotics reduces motor severity ratings (UPDRS), serum biomarkers, and body mass index (BMI) in people with PD (Tamtaji et al., 2019). However, there is a scarcity of evidence on the impact of probiotic supplementation on serum biomarkers in PD patients. Furthermore, only a few clinical studies have mentioned the influence of probiotics on PD management. This study aimed to investigate the effects of probiotic supplementation on BMI indices, gastrointestinal symptoms, and glutathione levels in people with PD.

2. Materials and Methods

Literature search

Electronic databases, including Scopus, PubMed, The Cochrane Library, Web of Science, Ovid-LWW, and ScienceDirect, were searched until April 2021. The following keywords and medical subject header (MeSH) phrases were used in the search strategy: “Probiotics,” “fermented foods,” “*Lactobacillus*,” and “*Bifidobacterium*,” combined with “Parkinson’s disease.” They were used with the boolean operators (‘AND’ and ‘OR’).

Inclusion and exclusion criteria

The selection process was conducted independently by two researchers. The inclusion and exclusion criteria were as follows: 1) Randomized controlled trials (RCTs)

with placebo groups included patients with Parkinson, supplemented live bacteria as probiotics; 2) Relevant data about the study's features and major outcomes, such as BMI, UPDRS, serum glutathione and gastrointestinal problems (constipation, bloating, abdominal pain, stool consistency, and bowel movements); 3) PD patients.

Irrelevant titles and abstracts, reviews, editorials, conference book chapters, books, letters, case reports, retracted articles, and case reports were included, and non-English articles and in vitro and in vivo studies were excluded. The articles that did not meet the inclusion criteria were also excluded.

Study selection

All 'titles' and 'abstracts' were recovered from the Zotero library to perform the research processes, and duplicate results were removed with Zotero reference manager software (Zotero, 2020). Then, the remaining 'Titles' and 'Abstracts' of studies were scanned for eligibility. The next stage was to go over the whole text of the remaining studies. The screening procedure was carried out separately by three researchers. There were no disagreements between the three researchers. The following data were documented using standardized tables: 1) Basic data, including first author, year of publication, research design, country, age, gender, weight, and BMI; 2) Interventions, including participant count, probiotic kind, methods, and study duration; 3) Outcomes of interest, including change in interested parameters in each article; and 4) Quality of the article.

Quality appraisal of included studies

The quality appraisal of included studies was assessed using the Jadad checklist (maximum 5 points) (Jadad et al., 1996). The following criteria were considered: 1) Randomization (2 points), 1 point if randomization is mentioned, 1 additional point if the method of randomization is appropriate or -1 point if it is inappropriate; 2) Blinding (2 points), 1 point if blinding is mentioned, 1 additional point if the method blinding is appropriate or -1 point if it is inappropriate; and 3) Withdrawals and dropouts (1 point), 1 point if the fate of all patients in the trial is known. Obtaining 4 to 5 points indicates good quality of studies.

3. Results

A total of 27395 records were identified using a search strategy from eight databases (PubMed, n=63; The Cochrane Library, n=50; Scopus, n=346; Web of Science,

n=112 [Korean Journal Database, Web of Science Core Collection, SciELO citation index, Russian science citation index]; ScienceDirect, n=2791; and Ovid-LWW, n=24033). Then, 16309 records were removed because they were duplicates. So, 11086 studies were available for screening. Of those, reviews (n=3402), book chapters and encyclopedia (n=637), non-research publications (letters, conference, index, editorial, and abstract) (n=3119), case reports (n=295), article retraction (n=81), irrelevant titles and abstracts (n=3418) were excluded based on screening the 'titles' and 'abstracts.' Finally, 134 articles were selected for full-text reading. Of those, 129 studies were excluded for the following reasons: Non-English (n=11), animals and in vivo and in vitro (n=79), no probiotic treatment provided (n=16), no placebo (n=1), no PD (n=8), and no available full text (n=14). The inclusion and exclusion process led to the inclusion of 5 randomized control trials (Figure 1).

There was significant variation between research studies regarding the number of participants. The number of PD patients in the study ranged from 48 to 120, totaling 350. The supplement duration was in the range of 4-12 weeks (Table 1).

PD rating

Movement disorder society-sponsored revision of the unified Parkinson disease rating scale (MDS-UPDRS) was used to monitor the longitudinal course of PD, with a point range from 0 to 199 (Goetz et al., 2008). Higher scores show worsening outcomes of the disease. In two studies, UPDRS was used. In both studies, UPDRS scores were dropped after 8 weeks use of *Lactobacillus Casei*, *Lactobacillus acidophilus*, *Bifidobacterium infantis*, *Lactobacillus lactis*, *Bifidobacterium longum* supplement and 12 weeks use of *L. acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum* 2×10^9 CFU (colony-forming unit/g) (Tamtaji et al., 2019; Ibrahim et al., 2020). Also, the non-motor symptoms score (NMSS) is a scale that informs the severity of the PD patient's non-motor symptoms. The score ranges from 0 to 360; higher scores define severe deterioration (Van Wamelen et al., 2021). Ibrahim et al. (2020) reported decreasing scores of NMSS after 8 weeks use of probiotics.

In other words, the probiotics used decreased these scales in PD, proving that probiotics may help by reducing the severity of the disease.

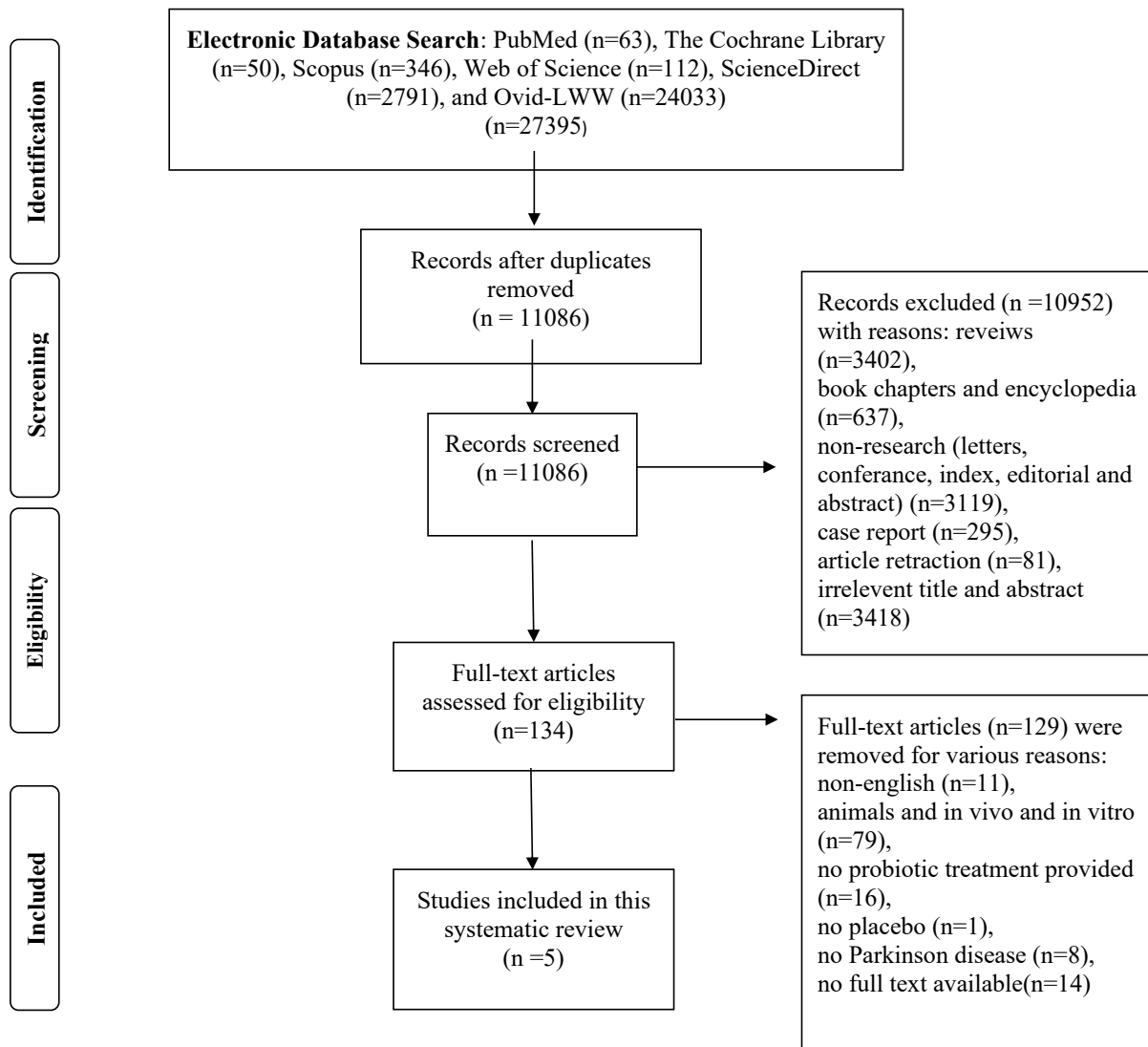


Figure 1. PRISMA flowchart (Moher et al., 2009)

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Oxidative stress

Glutathione (GSH) is a tripeptide amino acid and a powerful antioxidant in the cells and tissues of the body. It consists of the amino acids L-cysteine, L-glutamate, and glycine. Glutathione protects the organism by eliminating free radicals and reactive oxygen species (Smeyne & Smeyne, 2013). In two studies, GSH was measured. Tamtaji et al. (2019) reported that 12 weeks use of *B. bifidum*, *L. acidophilus*, *L. fermentum*, and *L. reuteri* (2×10^9 CFU/g) supplement increased GSH levels in plasma. Borzobadi et al. (2018) reported insignificant increases in GSH levels after 12 weeks use of *B. bifidum*, *L. acidophilus*, *L. fermentum*, and *Lactobacillus reuter* (8×10^9 CFU/d probiotic). Moreover, malondialdehyde (MDA) is a highly reactive molecule that is an oxidative stress biomarker. Tamtaji et al. (2019) reported decreases

in MDA after 12 weeks of probiotic use, and inflammation biomarker C- reactive protein (CRP) remarkably dropped.

This finding supported the idea that probiotics can protect oxidative stress by increasing GSH levels and decreasing MDA and CRP levels.

Gastrointestinal system

Gastrointestinal problems are frequent in PD, and the whole GI tract is affected mainly by numerous complications (Fasano et al., 2015).

Ibrahim et al. (2020) reported increased bowel opening frequency (BOF) and gut transit time (GTT) decreased in PD patients after 8 weeks of usage of *L. acidophilus*, *L. Casei*, *L. lactis*, *B. infantis*, *B. longum*. In addition,

Table 1. Characteristics and outcomes of the included studies

Study	Design	Time (wk)	Age (y)	Definition of Parkinson	Intervention of Experimental Group
Ibrahim, et al., 2020 Malaysia	RCT	8	I: 69.0 (64.0–74.0) C: 70.5 (62.0–70.3) [median (IQR)]	Hoehn–Yars scale	30×10 ⁹ CFU, 2% fructooligosaccharide (FOS), and lactose. The microbial composition of the probiotics were: <i>L. casei</i> , <i>L. acidophilus</i> , <i>L. lactis</i> , <i>B. infantis</i> , <i>B longum</i>
Tamtaji et al., 2019 Iran	RCT	12	I: 68.2±7.8 C: 67.7±10.2 (Mean±SD)	UK Parkinson's Disease Society Brain Bank	Probiotics containing <i>L. acidophilus</i> , <i>B. bifidum</i> , <i>L. fermentum</i> , and <i>L. reuteri</i> (2×10 ⁹ CFU/g)
Tan et al., 2020 Malaysia	RCT	4	I: 70.9±6.6 C: 68.6±6.7 (Mean±SD)	Queen Square Brain Bank Criteria	Ten billion CFU of eight commercially available bacterial strains were included in each probiotic pill (<i>L. reuteri</i> , <i>L. acidophilus</i> , <i>L. gasseri</i> , <i>B. bifidum</i> , <i>L. rhamnosus</i> , <i>B. longum</i> , <i>E. faecium</i> , <i>E. faecalis</i>).
Borzabadi et al., 2018 Iran	RCT	12	I:66.9±7.0 C:66.7±10.7 (Mean±SD)	UK Parkinson's Disease Society Brain Bank	8×10 ⁹ CFU/d probiotics containing <i>L. acidophilus</i> , <i>B. bifidum</i> , <i>L. reuteri</i> , and <i>L. fermentum</i>
Barichella et al., 2016 Italy	RCT	4	I: 71., 9±7.7 C: 69.5±10.3 (Mean±SD)	UK Parkinson's Disease Society Brain Bank	Fermented milk containing multiple probiotic strains and prebiotic fiber

Study	Intervention of Control Group	Study Sample	Outcomes	Jadad Score
Ibrahim, et al., 2020 Malaysia	Placebo (granulated milk with lactose but no fructooligosaccharide or microbial cells in an orange flavoring, comparable to probiotics)	N: 48 I: 22 C: 26	BOF ↑ *P<0.001, GTT ↓ *P<0.030, UPDRS II ↓ *P=0.040, UPDRS III ↓ *P<0.001, NMSS scores ↓ *P<0.001, BMI ↑ *P=0.010 (probiotic group)	4
Tamtaji et al., 2019 Iran	Placebo	N: 60 I: 30 C: 30	MDS-UPDRS ↓ *P<0.01, GSH ↑ *P=0.03, CRP ↓ *P<0.001, MDA ↓ *P= 0.006 (probiotic group)	5
Tan et al., 2020 Malaysia	Placebo (maltodextrin)	N: 72 I: 34 C: 38	SBM ↑*P<0.001, Stool consistency ↑ *P=0.009, Constipation ↓ *P=0,001, constipation related quality of life ↓ *P=0.001* (probiotic group)	5
Borzabadi et al., 2018 Iran	Placebo	N: 50 I: 25 C: 25	GSH ↑ *P=0.58 (probiotic group)	5
Barichella et al., 2016 Italy	Placebo (pasteurized, fermented, fiber-free milk)	N:120 I: 80 C: 40	CBM ↑ *P=0.002 (probiotic group)	4

Abbreviations: BOF: Bowel opening frequency; BMI: Body mass index; CBM: Complete bowel movement; CFU: Colony-forming unit; CRP: C-reactive protein; GTT: Gut transit time; Gsh; Plasma glutathione; IQR: Interquartile range; MDA: Malondialdehyde; NA: No applicable; NMSS: Non-motor symptoms score; RTC: Randomized controlled trial; SBM: Spontaneous bowel movements.

Table 2. Quality appraisal by Jadad scale of included studies

Study	Randomization	Blinding	An Account of All Patients	Total
Ibrahim et al., 2020, Malaysia	1+1	1+1	1	5
Tamtaji et al., 2019, Iran	1+1	1+1	1	5
Tan et al., 2020, Malaysia	1+1	1+1	1	5
Borzabadi et al., 2018, Iran	1+1	1+1	1	5
Barichella et al., 2016, Italy	1+1	1+0	1	4

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following 4 weeks of using fermented milk containing several probiotic strains and prebiotic fiber, Barichella et al. (2016) reported an increase in complete bowel movement. After 4 weeks of using a probiotic pill containing 10 billion CFU of eight different commercially available bacterial strains (*L. reuteri*, *L. acidophilus*, *Lactobacillus gasseri*, *B. bifidum*, *Lactobacillus rhamnosus*, *B. longum*, *Enterococcus faecium*, *Enterococcus faecalis*), spontaneous bowel movements increased. Also, probiotic supplements increased stool consistency and decreased constipation. On the other hand, the quality of life-related to constipation decreased (Tan et al., 2020).

As a result, supplements containing probiotics helped to regulate GI problems regardless of the time of administration but did not affect the quality of life due to constipation. However, the data in existing studies are very limited.

Quality appraisal of included studies

The average score obtained from the modified Jadad scale was calculated as 4.8 points (range 4-5 points). Five studies were classified as “good” methodological quality. Individual scores are shown in Table 2.

4. Discussion

This systematic review investigates the effects of probiotic/prebiotic consumption in PD patients, which is a priority study in this area. Despite little evidence, the included five trials in this systematic review of PD individuals recommended the beneficial effects of probiotics in the clinical setting. Also, GI functions are highly related to probiotics. However, the evidence obtained from the RTCs about PD is limited. Similar to our results, in a systematic review, certain probiotics are beneficial in treating GI tract problems. Specific probiotics have been demonstrated to alleviate irritable bowel syndrome and lower gastrointestinal symptoms, prevent diarrhea asso-

ciated with antibiotics and *H. pylori* eradication therapy, and demonstrate appropriate safety (Hungin et al., 2018). Kesika et al. (2020) reported the effect of probiotics on Alzheimer disease and the gut-brain axis; it was found that probiotic consumption prevented inflammation, reduced oxidative stress, and improved memory in Alzheimer patients. Amirani et al. (2020) conducted a systematic study of the effects of probiotic supplementation on mental health, inflammatory biomarkers, and oxidative stress in psychiatric patients. Probiotic supplementation has a beneficial impact on the Hamilton depression rating scale, CRP, interleukin-10, and MDA levels but no effect on inflammation and oxidative stress indicators. Similarly, another study showed that GSH levels increased, and MDA and CRP levels dropped by using probiotics (Tamtaji et al., 2019).

Although with low evidence, data from three RCTs involving 161 individuals with Alzheimer disease who received *Lactobacillus* and *Bifidobacterium* strains from the diet showed no benefit of probiotic supplementation on cognitive functions (standardized mean difference, 0.56; 95% CI, -0.06%, 1.18%) (Krüger et al., 2021). The MDA-UPDRS and NMSS were improved after usage of probiotics (Ibrahim et al., 2020). In the chronic phase of PD, cognition and brain functions may be associated. On the other hand, probiotic supplementation improved plasma triglycerides, very low-density lipoprotein cholesterol, insulin resistance, and plasma MDA in another trial. There were no RCTs that looked at synbiotic supplementation or microbiota compositions. The evidence for probiotics and synbiotics in treating dementia and cognition is insufficient to justify their use in clinical practice (Krüger et al., 2020).

On the other hand, although probiotics have many benefits, they can also cause some complications. A systematic review assessed probiotic use problems in 60 case reports and 7 case series involving 93 individuals. Fungi were the most common infectious complication in

35(37.6%) cases, with *Saccharomyces* genus being the most common genus with 47(50.6%) cases, followed by *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Pediococcus*, and *Escherichia coli* with 26(27.9%), 12(12.8%), 5(5.4%), 2(2.2%), and 1(1.1%) cases, respectively (Costa et al., 2018). Also, Rao et al. investigated brain foggiess (BF), gas, and bloating dependence with D-lactate in small intestinal bacterial overgrowth (SIBO). SIBO was more common in the BF group than in the non-BF group (68% vs 28%, $P=0.05$). Probiotics were used by everyone in the BF group. D-lactic acidosis was more common in the BF group than in the non-BF group (77% vs 25%, $P=0.006$). In 20/30 (66%) of the patients, BF was replicated. In 10/30 (33%) of patients with BF and 2/8 (25%) of those without, gastrointestinal transit was delayed. The results of the other metabolic tests were normal. However, BF was resolved, and gastrointestinal symptoms improved considerably ($P=0.005$) in 23/30 people after stopping probiotics and using antibiotics (77%). In a group without short bowel syndrome, BF, gas, and bloating may be linked to probiotic use, SIBO, and D-lactic acidosis (Rao et al., 2018). However, the probiotic does not include *Neisseria streptococcus*, *Staphylococcus*, or *Hemophilus* strains in the predominant organisms discovered by culture in duodenal aspirates. However, there is no data to confirm that the patients who applied are acidotic. It should be noted that many *Lactobacilli* and all *Bifidobacteria* exclusively create L-lactate and not D-lactate (Petrova et al., 2018; Quigley et al., 2018; Reid et al., 2019). Probiotics may trigger bacterial translocation and enterocyte damage in patients with acute pancreatitis, resulting in organ failure (Besselink et al., 2004; Besselink et al., 2009). Still, in a later study, it was found that probiotics did not cause any contraindications. Conversely, carbohydrates may worsen the situation with lactic acidosis caused by their fermentation (Bongaerts & Severijnen, 2016). Established tests and clinical guidelines in treating high-risk adults and children are essential, as probiotics can produce different effects in different health conditions (Sanders et al., 2016). More importantly, probiotic complications in PD are unknown, but the impact on neurological diseases may also be an indicator of PD.

Furthermore, it is essential to emphasize that there are some limitations to consider when designing future interventions (1). Although this study was conducted through a wide literature search (27395 records), the studies that could be included in probiotic use in PD patients were low and insufficient. Therefore, the systematically compiled parameters are limited and unsuitable for comparison (2). The probiotic and the active bacteria in its content are stated in our study. Still, it is impossible

to identify which bacteria can be better and provide more benefits to PD patients due to the lack of existing studies (3). Bacterial colony numbers vary from study to study, and since there is no standard yet, no interpretation of the amount of CFU could be made (4). Positive results in the researched area have been revealed so that this area can be pursued, and more profound research is needed (5). A comprehensive systematic review forms the basis of new studies on the amount of probiotic usage, duration, and variety of clinically supportive nutritional support for PD patients (6).

5. Conclusion

A growing body of data suggests that the gut-brain bidirectional connection and dysbiosis have a role in PD. A healthy gut microbiome may lower the chance of acquiring a variety of human diseases, including PD. α -synuclein build-up in PD has been shown to begin in the enteral nervous system and move to the central nervous system by trans-synaptic cell-to-cell transmission. As previously noted, creating a proinflammatory environment in dysbiosis can signal the brain via systemic routes and may cause a defective blood-brain barrier. Finally, it was suggested that an immune system imbalance in the host might be partially responsible for PD's motor and non-motor symptoms. The hunt for early biomarkers and innovative treatment methods has accelerated due to an improved understanding of PD pathophysiology.

In this systematic review, probiotics used in PD are reviewed. As a result, various probiotic supplements were used for 4-12 weeks in PD rating, oxidative stress, and GI tract symptoms such as spontaneous bowel movement, GTT, BOF, abdominal pain, bloating, constipation, and improvements in each parameter were observed. Although the studies included in this study are of high methodological quality, the number of studies is insufficient. Therefore, some issues need to be included in the literature, from different probiotic strains, parameters, and duration of use to clinical studies of probiotics in PD."

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research."

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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