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Accepted Manuscript (Uncorrected Proof)

**Title:** Effect of Probiotics on Parkinson's Disease Rating, Selected Gastrointestinal Measurements and Oxidative Stress Parameters in Parkinson's Disease: A Systematic Review of Randomized Controlled Trials

**Running title:** Probiotics in Parkinson's Disease

**Authors:** Elif Sina Atak<sup>1</sup>, Dilara Yıldız<sup>1</sup>, Rümeysa Rabia Kocatürk<sup>1</sup>, Arzu Temizyürek<sup>2</sup>, Öznur Özge Özcan<sup>3</sup>, Türker Tekin Ergüzel<sup>4</sup>, Mesut Karahan<sup>1,5\*</sup>, Nevzat Tarhan<sup>6,7</sup>

1. Nutrition and Dietetics, Faculty of Health Sciences, Üsküdar University, Istanbul, Turkey.
2. Physiology, School of Medicine, Koç University, Istanbul, Turkey.
3. Molecular Neuroscience, Health Sciences Institute, Üsküdar University, Istanbul, Turkey.
4. Software Engineering, Faculty of Engineering and Natural Sciences, Üsküdar University, Istanbul, Turkey.
5. Biomedical Device Technology, Vocational School of Health Sciences, Üsküdar University, Istanbul, Turkey.
6. Psychiatry, School of Medicine, Üsküdar University, Istanbul, Turkey.
7. NP Istanbul Brain Hospital, Istanbul, Turkey.

**\*Corresponding author:** Mesut Karahan, Nutrition and Dietetics, Faculty of Health Sciences, Üsküdar University, Istanbul, Turkey. E-mail: mesut.karahan@uskudar.edu.tr

To appear in: *Basic and Clinical Neuroscience*

**Received date:** 2021/03/07

**Revised date:** 2021/06/11

**Accepted date:** 2021/10/26

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**Please cite this article as:**

Atak, E. S., Yıldız, D., Kocatürk, R. R., Temizyürek, A., Özcan, O. O., & Ergüzel, T. T., et al. (In Press). Effect of Probiotics on Parkinson's Disease Rating, Selected Gastrointestinal Measurements and Oxidative Stress Parameters in Parkinson's Disease: A Systematic Review of Randomized Controlled Trials. *Basic and Clinical Neuroscience*. Just Accepted publication Nov. 1, 2022. Doi: <http://dx.doi.org/10.32598/bcn.2022.3665.1>

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## **Abstract**

**Introduction:** Parkinson's disease is the world's second most prevalent neurological disease. In Parkinson's 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 probiotics with individuals with Parkinson's disease.

**Methods:** Scopus, PubMed, Web of Science, The Cochrane Library, Science Direct and OVID-LWW were searched until April 2021 and total 27,395 records were reached according to inclusion and exclusion criteria with the following outcomes: Parkinson's disease rating; oxidative stress, and gastrointestinal system markers. Data searches, article selection and data extraction assessments were performed according to the PRISMA guidelines. The Jadad scale was used to rate the evidence's quality.

**Results:** The information gathered from 5 randomized controlled trials involving 350 individuals with Parkinson's disease receiving probiotic supplements. Parkinson's disease rating and non-motor symptoms test were performed. Oxidative stress (Glutathione, malondialdehyde) and gastrointestinal system symptoms (bowel opening frequency, gut transit time, complete bowel movement, spontaneous bowel movements) were evaluated for 4-12 weeks of usage.

**Conclusion:** While all high-quality studies demonstrate progress, there is currently insufficient data to recommend the use of probiotics for people with Parkinson's disease in clinical practice.

**Keywords:** Parkinson's Disease, Probiotics, Fermented Foods, Bifidobacterium, Lactobacillus

## Introduction

Parkinson's disease (PD) is a neurological disease that is rapidly progressing. The incidence was reported to be 11–19/100,000 and its prevalence was 108–257/100,000 in Europe. The loss of dopaminergic neurons in the substantia nigra (SN) and pars compacta, as well as the accumulation of tender folded-synuclein termed Lewy bodies (LBs) in the intrastoplasmic space, are the clinical features of PD. Mitochondrial dysfunction, oxidative stress, an increase in inflammatory cytokines and free radicals, as well as genetic and environmental variables, are linked to 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 (NMS) (Ding et al., 2017). The most common NMS problem of PD is gastrointestinal (GI) dysfunction such as constipation, bloating, abdominal pain, stool consistency and bowel movements (Schrag, Jahanshahi & Quinn, 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 benefit from 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 reduced motor severity ratings (UPDRS), serum biomarkers, and body mass index (BMI) in people with PD (Tamtaji et al., 2018). However, there is a scarcity of evidence on the impact of probiotic supplementation on serum biomarkers in PD patients. Furthermore, just a few clinical research have mentioned about the influence of probiotics on PD management. The goal of this study was to investigate the effects of probiotic supplementation on BMI indices, gastrointestinal, and glutathione levels in people with PD.

## **Materials and Methods**

### **Literature search**

Electronic databases Scopus, PubMed, The Cochrane Library, Web of Science, OVID-LWW and Science Direct were searched until April 2021. The following keywords and medical subject header (MeSH) phrases were used in the search strategy: “Probiotics,” “Fermented Foods,” “Lactobacillus,” “Bifidobacterium,” combined with “Parkinson’s Disease” using 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 Parkinson’s patients and 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 including 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, case reports were included, and non-English articles were excluded of *in vitro* and *in vivo* studies. The articles that do not meet inclusion criteria were also excluded.

### **Study selection**

To perform the research processes, all titles and abstracts were retrieved to Zotero library and duplicate results removed with Zotero reference manager software (Zotero 2020). The titles and/or 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 three researchers. The following data was documented using

standardized tables: (1) basic data: first author, year of publication, research design, country, age, gender, weight, and BMI; (2) interventions: participant count, probiotic kind, methods and duration and (3) outcomes of interest: Change in interested parameters in each article; (4) quality of the article.

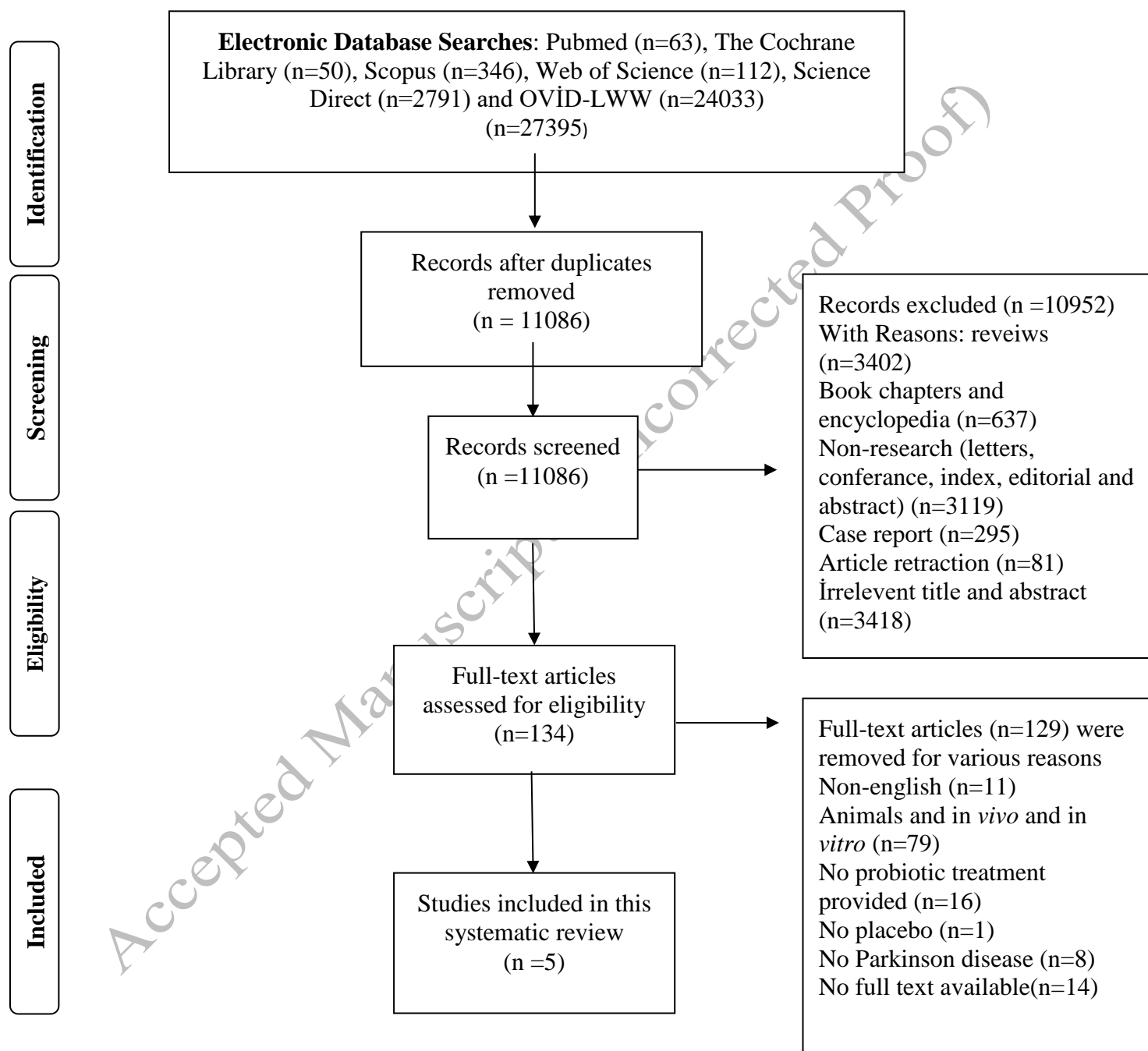
### **Quality appraisal of included studies**

The quality appraisal of included studies was assessed using the Jadad checklist (Max 5 point) (Jadad et al., 1996). 1) Randomization (2 point): 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 point): 1 point if blinding is mentioned, 1 additional point if the method blinding is appropriate or -1 point if it is inappropriate. 3) Withdrawals and dropouts (1point): 1 point if thhe fate of all patients in the trial is known. 5-4 points describe good quality of studies.

### **Results**

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), Science Direct (n=2791) and OVID-LWW (n=24033)]. 16309 records were removed while deduction of duplicates. 11086 studies were available for screening. Reviews (n=3402), book chapters and encyclopedia (n=637), non-research (letters, conference, index, editorial and abstract) (n=3119), case report (n=295), Article retraction (n=81), irrelevant title and abstracts (n=3418) were excluded based on title and abstract. 134 articles were selected for full-text reading. 129 studies were excluded for 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), no full text available (n=14). The inclusion and exclusion process led to the inclusion of five RTCs (Fig. 1).

**Fig. 1.** PRISMA Flowchart (Moher D et al., 2009).



In terms of the number of participants, there was significant variation between research. The number of Parkinson's patients in the study ranged from 48 to 120, totaling 350. The supplement duration was in range of 4-12 weeks.

## **PD Rating**

Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to monitor the longitudinal course of PD and point range was 0-199 (Goetz et al., 2008). Higher scores show worsening outcomes of the disease. In two studies, UPDRS was used. In both 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 *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum*  $2 \times 10^9$  CFU (Colony-forming unit)/g (Tamtaji et al., 2018; Ibrahim et al., 2020). Also, Non-Motor Symptoms Score (NMSS) is a scale that informs the severity of the Parkinson's patient's non-motor symptoms. The score range was 0-360 and higher scores define severe deterioration (Van Wamelen et al., 2021). Ibrahim et al. reported decreasing scores of NMSS after 8 weeks use of probiotics (Ibrahim et al., 2020).

In other words, the probiotics used actually caused reductions in these scales in PD, which provides evidence that it may help by reducing the severity of the disease.

Table 1.

## **Oxidative stress**

Glutathione (GSH) is a tripeptide amino acid that functions in the cells and tissues of the body and is a powerful antioxidant. It consists of the amino acids L-cysteine, L-glutamate and glycine. Glutathione protects the organism by eliminating free radicals and reactive oxygen molecules



(Smeyne & Smeyne, 2013). In two studies, GSH was measured. Tamtaji et al. reported 12 weeks use of *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus fermentum* and *Lactobacillus reuteri* ( $2 \times 10^9$  CFU/g) supplement increased GSH levels in plasma and Borzobadi et al. reported insignificant increases in GSH levels  $8 \times 10^9$  CFU/day probiotic, containing *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus fermentum* and *Lactobacillus reuteri* uses for 12 weeks (Tamtaji et al., 2018; Borzabadi et al., 2018). Moreover, malondialdehyde (MDA) is a highly reactive molecule that is an oxidative stress biomarker. Tamtaji et al. reported decreases of MDA after 12 weeks of probiotic use and inflammation biomarker C- reactive protein (CRP) extremely dropped (Tamtaji et al., 2020).

This reinforced the idea that, probiotics can be protective for oxidative stress by increasing of GSH levels and decreasing MDA and CRP levels.

### **Gastrointestinal System (GIS)**

GIS problems are frequent in PD and mostly the whole GIS tract is affected by numerous complications (Fasano, Visanji & Visanji, 2015).

Ibrahim et al. reported increased bowel opening frequency (BOF) and gut transit time (GTT) decreased in Parkinson's patients after 8 weeks usage of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus lactis*, *Bifidobacterium infantis*, *Bifidobacterium longum* (Ibrahim et al., 2020). In addition, following 4 weeks of using fermented milk containing several probiotic strains and prebiotic fiber, Barichella et al. showed an increase in complete bowel movement (CBM) (Barichella et al, 2016). After 4 weeks of using a probiotic pill containing 10 billion CFU of eight different commercially available bacterial strains (*Lactobacillus reuteri*, *Lactobacillus acidophilus*, *Lactobacillus gasseri*, *Bifidobacterium bifidum*, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, *Enterococcus faecium*, *Enterococcus faecalis*), spontaneous bowel movements (SBM) increased.

Also, probiotic supplement increased stool consistency and decreased constipation. On the other hand the life quality related to constipation decreased (Tan et al., 2020).

As a result, supplements containing probiotics helped to regulate GIS 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.

Table 2.

### **Quality appraisal of included studies**

The average score obtained from the Modified Jadad scale was calculated as 4,8 points (range 4-5 points). 5 studies were classified as "good" methodological quality. Individual scores are shown in Table 2.

### **Discussion**

This systematic review investigates the effects of probiotic/prebiotic consumption in PD and this study is a prioring study in this area. In the included 5 trials in this systematic review of PD individuals, probiotics were found to be beneficial in the clinical setting despite little evidence. Also, GIS functions are highly related with probiotics. However, the evidence obtained from the RTCs are limited in PD. Similarly to our results, in a systematic review certain probiotics have been shown to be beneficial in GIS problems. It has been demonstrated that specific probiotics can alleviate irritable bowel syndrome and lower gastrointestinal symptoms, prevent diarrhea associated with antibiotics and H. pylori eradication therapy, and demonstrate appropriate safety (Hungin et al., 2018). Periyanaiana Kesika et al. reported the effect of probiotics on Alzheimer's disease and the gut-brain axis, it was found that probiotic consumption prevented inflammation, reduced oxidative stress, and improved memory in Alzheimer's patients (Kesika, Suganthi & Sivamaruthi, 2020). Elaheh Amirani

et al. conducted a systematic study of the effects of probiotic supplementation on mental health, inflammatory biomarkers, and oxidative stress in psychiatric patients. Probiotic supplementation had a beneficial effect on the Hamilton depression rating scale, CRP, IL-10, and MDA levels were improved, but indicators of inflammation and oxidative stress were not affected (Amirani et al, 2020). Similarly in a previous study, it was shown that GSH levels increased, and MDA and CRP levels dropped by using probiotics (Tamtaji et al., 2018).

With very low certainty of evidence, data from three RCTs involving 161 individuals with Alzheimer's disease who received *Lactobacillus* and *Bifidobacterium* strains from the diet showed no benefit of probiotic supplementation on cognitive function (standardized mean difference, 0.56; 95% CI: -0.06 to 1.18) (Krüger, Hillesheim & Pereira, 2020). The MDA-UPDRS and NMSS were improved after usage of probiotics (Ibrahim et al., 2020). In chronic phase of PD, it is possible that cognition and brain functions are associated. Probiotic supplementation, on the other hand, 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 the treatment of 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. Probiotic use problems were assessed in 60 case reports and 7 case series involving a total of 93 individuals in a systematic review. 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 (percent 12,8), 5 (percent 5,4), 2 (percent 2,2), and 1 (1.1%) cases respectively (Costa et al., 2018). Also, Rao et al. investigated the 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 percent) of patients with BF and 2/8 (25%) of those without, gastrointestinal transit was delayed. The results of the other metabolic tests were ordinary. BF 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 strains of *Neisseria treptococcus*, *Staphylococcus* or *Hemophilus*, in the predominant organisms discovered by culture in duodenal aspirates. Although 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, 2009), but in a later study, it was found that probiotics did not cause any contraindications. Carbohydrates, on the other hand, may worsen the situation with lactic acidosis caused by its fermentation (Bongaerts and Severijnen, 2016). Established tests and clinical guidelines in the treatment of adults and children who are at high risk, as probiotics can produce different effects in different health conditions, are important (Sanders et al., 2016). More importantly, probiotic complications in PD is unknown, but the effect in neurological diseases may be indicator for PD as well.

Furthermore, it is significant to emphasize that there are some limitations to consider in the design of 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 Parkinson's patients were insufficient. Therefore, the systematically compiled parameters are limited and not suitable for comparison. (2) The type of probiotic and the active bacteria in its content are stated in our study, but it is not possible to identify which bacteria can be better and provide more benefits to Parkinson's 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 this area can be pursued, and deeper research is needed. (5) It is a comprehensive systematic review that forms the basis of new studies that can be done in terms of the probiotic usage amount, duration and variety of a clinically supportive nutritional support for Parkinson's patients. (6)

## 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.  $\alpha$ -synuclein build-up in PD has been shown to begin in the enteric nervous system and move to the CNS by trans-synaptic cell-to-cell transmission. As previously noted, the creation of a proinflammatory environment in dysbiosis can also 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 the motor and non-motor symptoms of PD. The hunt for early biomarkers and innovative treatment methods has accelerated as a result of this improved understanding of PD pathophysiology.

So, in this systematic review probiotics use in PD are reviewed. As a result, various probiotic supplements were used for 4-12 weeks in PD rating, oxidative stress, GIS symptoms as SBM, GTT, BOF, abdominal pain, bloating, constipation and improvements of each parameter was observed. Although the studies included in this study are high in methodological quality, but the number of studies is insufficient. Therefore, there are issues that need to be filled in the literature, from different probiotic strains, parameters, duration of use to CPU studies of probiotics in PD.

**Author Declarations****Grant Support**

No applicable

**Financial Interest**

There is no financial interest in a company or its competitor of a product discussed in the review.

**Conflicts of Interest**

There are no conflicts of interest declared by the authors.

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**Table 1.** Characteristic and outcomes of the included studies

Study	Design	Time (week)	Age	Definition of Parkinson	Intervention of experimental group	Intervention of control group	Study Sample	Outcomes	Jadad Score
Azliza et al., 2020, Malaysia	RCT	8 week	I:69.0 (64.0–74.0) C:70.5 (62.0–70.3) [median (IQR)]	Hoehn–Yars scale	30*10 <sup>9</sup> CFU, 2% fructooligosaccharide (FOS), and lactose. The microbial composition of the probiotics were: (Lactobacillus Casei, Lactobacillus acidophilus, Lactobacillus Lactis, bifidobacterium infantis, bifidobacterium longum)	Placebo (granulated milk with lactose but no fructo-oligosaccharide 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., 2018, Iran	RCT	12 week	I: 68.2 ± 7.8 C: 67.7 ± 10.2 (Mean ± SD)	UK Parkinson's Society Brain Bank	Probiotic containing Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus fermentum and Lactobacillus reuteri (2*10 <sup>9</sup> CFU/g)	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
Ai Huey Tan et al., 2020, Malaysia	RCT	4 week	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. (Lactobacillus reuteri, Lactobacillus acidophilus, Lactobacillus gasseri, Bifidobacterium bifidum, Lactobacillus rhamnosus, Bifidobacterium longum, Enterococcus faecium, Enterococcus faecalis)	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 RCT et al., 2018, Iran	12 week	I:66.9 ± 7.0 C:66.7 ± 10.7 (Mean ± SD)	UK Parkinson's Disease Society Brain Bank	8×10 <sup>9</sup> CFU/day probiotic, containing Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri, and Lactobacillus fermentum	Placebo	N:50 I:25 C:25	Gsh ↑ *p=0,58 (probiotic group)	5
Barichella RCT et al., 2016, Italy	4 week	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	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; SD: Standard derivation

**Table 2.** Quality appraisal by Jadad Scale of included studies

	<b>Randomization</b>	<b>Blinding</b>	<b>An account of all patients</b>	<b>Total</b>
Ibrahim et al., 2020, Malaysia	1+1	1+1	1	5
Tamtaji et al., 2018, Iran	1+1	1+1	1	5
Ai Huey 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