International Journal of General Medicine Dovepress

Open Access Full Text Article REVIEW

Effects of Probiotics on Neurodegenerative Disease-Related Symptoms and Systemic Inflammation: A Systematic Review

Fengya Zhu[1], Shao Yin[2], Yuan Wang[3], Yue Zhong[1], Qiang Ji[1], Jie Wu[2]

[1]Traditional Chinese Medicine Department, Zigong First People's Hospital, Zigong, People's Republic of China; [2]Department of Endocrinology, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China; [3]Acupuncture and Moxibustion School, Chengdu University of Traditional Chinese Medicine, Chengdu, People's Republic of China

Correspondence: Jie Wu, Email drwujie@163.com

Abstract: In recent years, probiotics, as a class of biologically active microorganisms, have increasingly attracted attention for their potential in treating neurodegenerative diseases (NDDs). To comprehensively assess the effects of probiotics on clinical symptoms and systemic inflammation regulation in various NDDs, this systematic review conducted a detailed search of the Cochrane Library, Embase, PubMed, and Web of Science databases, ultimately including 22 eligible randomized controlled trials (RCTs), with 4 RCTs for Alzheimer's Disease (AD), 10 RCTs for Parkinson's Disease (PD), 2 RCTs for Multiple Sclerosis (MS), and 2 RCTs for Mild Cognitive Impairment (MCI), and intervention durations ranging from 4 to 16 weeks. The comprehensive analysis indicates that probiotics help improve clinical symptoms related to NDDs, including gastrointestinal function, cognitive function, quality of life, and mental health. Additionally, probiotics generally have a positive effect on reducing systemic inflammation and enhancing antioxidant capacity in patients. In conclusion, existing evidence supports the promising potential of probiotics in treating NDDs. However, further large-scale, high-quality studies are needed to explore specific differences in efficacy among various probiotic strains, dosages, and modes of administration. Moreover, considering that lifestyle and dietary habits may modulate the effects of probiotics, these external factors should also be included in research considerations to gain a more comprehensive understanding of the mechanisms and application strategies of probiotics in NDDs treatment.

Keywords: probiotics, neurodegenerative disease, systemic inflammation, systematic review

Introduction

Neurodegenerative diseases (NDDs) are a group of complex, heterogeneous disorders, such as Alzheimer's Disease, Parkinson's Disease, Multiple Sclerosis, and Amyotrophic Lateral Sclerosis. They primarily manifest as axonal and neuronal damage in various regions of the central or peripheral nervous system,[1] leading to memory and cognitive impairments, as well as deficits in behavioral, sensory, and/or motor functions.[2] Among the numerous risk factors associated with NDDs, aging is undoubtedly the most fundamental cause,[3,4] as it is a natural process that cannot be avoided by any organism. With the increase in the global aging population, the prevalence of NDDs is rising continuously and is expected to surpass cancer, becoming the second leading cause of death after cardiovascular diseases.[5] Decades of research have identified eight genetic factors and biochemical pathways associated with NDDs, including pathological protein aggregation, synaptic and neuronal network dysfunction, abnormal protein balance, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation, and neuronal cell death[6] Among these factors, neuroinflammation plays a central role in the progression of NDDs, where inflammatory mediators such as cytokines, chemokines, and reactive oxygen species contribute to neuronal injury. Neuroinflammation is considered a key pathological process related to the progression of NDDs. Inflammatory responses cause direct or indirect damage to neurons by releasing inflammatory mediators, such as pro-inflammatory cytokines and chemokines (IL-1β, IL-6, TNF-α), anti-inflammatory cytokines (IL-4 and IL-10), and small molecules (NO, ROS), thereby promoting

Received: 5 October 2024
Accepted: 5 December 2024
Published: 10 December 2024

neuronal death and dysfunction.[7] Recent studies have highlighted the involvement of specific cell signaling pathways, such as NF-κB,[8] JAK-STAT,[9] and MAPK pathways,[10] in mediating the inflammatory responses during neurodegeneration. These signaling pathways not only regulate the inflammatory response but also contribute to the crosstalk between inflammation and neurodegeneration, exacerbating disease progression. Therefore, improving clinical symptoms and alleviating systemic inflammation have become central challenges in the treatment of NDDs.

Probiotics, defined by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host",[11] can impact systemic inflammation through various mechanisms, including modulation of gut microbiota balance, enhancement of gut barrier function, and regulation of immune responses.[12] A recent study[13] suggested that probiotics may have the potential to reduce inflammation and oxidative stress, improve gut microbiota composition, and enhance cognitive function in NDDs, thereby supporting their therapeutic potential. Some studies have investigated the effects of probiotics on various types of NDDs, including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Multiple Sclerosis (MS), focusing on areas such as cognitive function,[14–16] motor and non-motor symptoms,[17–19] oxidative stress and systemic inflammation,[20–22] metabolic responses,[23,24] and mood.[25] Prebiotics and synbiotics, as derivatives of probiotics, enhance the survival of probiotic microorganisms in the gut. Their effects may depend on the specific strains, doses, and components of the probiotic products.[26]

Despite the growing body of research, there has been no systematic evaluation of clinical trials investigating the effects of probiotics on various NDDs, and the differences in efficacy among different types of probiotics remain unknown. A comprehensive summary of these studies will help clarify the potential effects of probiotics. Therefore, this review aims to elucidate the impact of probiotics on symptoms related to NDDs and systemic inflammation, providing valuable insights for future research directions and clinical applications. By elucidating the impact of probiotics on symptoms related to NDDs and systemic inflammation, this review seeks to provide valuable insights that may guide the design of future randomized controlled trials and inform personalized therapeutic strategies in clinical settings.

Methods

This review strictly adhered to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and was pre-registered on the PROSPERO platform (CRD 42024557533).

Inclusion Criteria

1) The study is a randomized controlled trial; 2) Patients are clinically diagnosed with any neurodegenerative disease based on clinical evaluation and/or diagnostic criteria; 3) The intervention group must use probiotics as the primary intervention, with no restrictions on the form of probiotics, including capsules, tablets, or fermented foods; 4) The probiotic strains, doses, frequency, and duration of administration are clearly specified; 5) The control group does not include probiotic treatment and may consist of a placebo, waiting treatment, or standard care; 6) No consideration is given to age, gender, or racial differences; 7) The study must report outcomes related to neurodegenerative disease symptoms (eg, cognitive function, motor function, behavioral changes, quality of life) and systemic inflammation (eg, inflammatory biomarkers, peripheral inflammatory responses).

Exclusion Criteria

1) Non-randomized controlled studies, observational studies, case reports, and reviews; 2) Participants with acute neurological conditions unrelated to NDDs; 3) Different groups receiving interventions containing probiotics or other substances that could confound the results; 4) Studies with inadequate reporting of interventions or outcomes; 5) Insufficient information on probiotic interventions, such as unclear strains, doses, frequency, or duration of administration.

Search Strategy

Four databases, including Cochrane Library, Embase, PubMed, and Web of Science, were searched up to June 30, 2024, with no restrictions on language or publication date. In addition, references from relevant studies were manually searched

to identify other potentially eligible studies. A combination of subject headings and free terms was used, such as AD, PD, MS, MCI, probiotics, prebiotics, synbiotics, randomized controlled trials, and clinical trials. Grey literature and data from research registration platforms were not considered due to lack of access. The detailed search strategy is provided in the Supplementary material.

Study Selection

Two independent reviewers conducted the literature search according to the search strategy. After removing duplicate studies, they screened the remaining studies based on titles, abstracts, and full texts, and included all studies that met the criteria for final assessment. Any disagreements were resolved through discussion between the two reviewers, and if consensus could not be reached, a third reviewer made the final decision.

Data Extraction

Two independent reviewers extracted data from the included studies using standardized forms. The extracted content included study characteristics (such as authors, publication year, and study design), participant characteristics (such as sample size and demographics), intervention details (such as probiotic strains, dose, and duration), control group information, and outcomes. Any disagreements were resolved through discussion between the two reviewers, and if consensus could not be reached, a third reviewer made the final decision.

Assessment of Risk of Bias

The risk of bias in the included studies will be assessed using the Cochrane Risk of Bias Tool. The assessment will cover six aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each aspect will be rated as low, high, or unclear risk of bias. The assessment will be conducted independently by two reviewers, and any discrepancies will be resolved through discussion with a third reviewer if needed.

Results

We retrieved 487 articles from four databases and ultimately confirmed 22 randomized controlled trials (RCTs) that met the inclusion criteria. A detailed screening flow chart is shown in Figure 1, and the exclusion list and reasons for exclusion are shown in Supplementary material. Ten studies investigated PD, six studies examined MS (with two studies having identical PICOS but different outcomes), four studies focused on AD, and two studies researched MCI. This review included a total of 1287 patients diagnosed with NDDs. Among the 23 studies, one used a single probiotic strain,[27] two employed a combination of probiotics and other treatments,[28,29] and 18 used synbiotics. The control design primarily used placebos, with two studies using trimetazidine[23] and selenium[28] The intervention duration ranged from 4 to 16 weeks, with the basic characteristics of each study presented in Table 1. The following summarizes the findings by disease type.

Parkinson's Disease

Ten studies assessed the effects of probiotics on gastrointestinal function in PD patients, all using multi-strain probiotics. The results indicated that probiotic use (4 to 12 weeks) significantly improved weekly bowel movements,[30,32–36] stool consistency,[32,35,36] and stool characteristics,[34,35] reduced gastrointestinal transit time,[31] and improved quality of life in PD patients.[31–35] However, probiotics did not show significant benefits in the frequency of feeling complete bowel evacuation or the use of laxatives.[36] This is similar to the findings of a previous study.[19] Georgescu et al[23] compared trimetazidine and probiotics, finding that both had similar effects on alleviating abdominal pain and bloating, but probiotics were less effective than trimetazidine in improving constipation.

Four studies supported the role of probiotics in improving motor symptoms of PD.[17,31,33,35] However, Ghalandari et al[36] found no significant difference in UPDRS II scores after 8 weeks of intervention. Two additional studies reported positive effects of probiotics on cognitive and behavioral performance in PD patients.[31,33] Compared to healthy

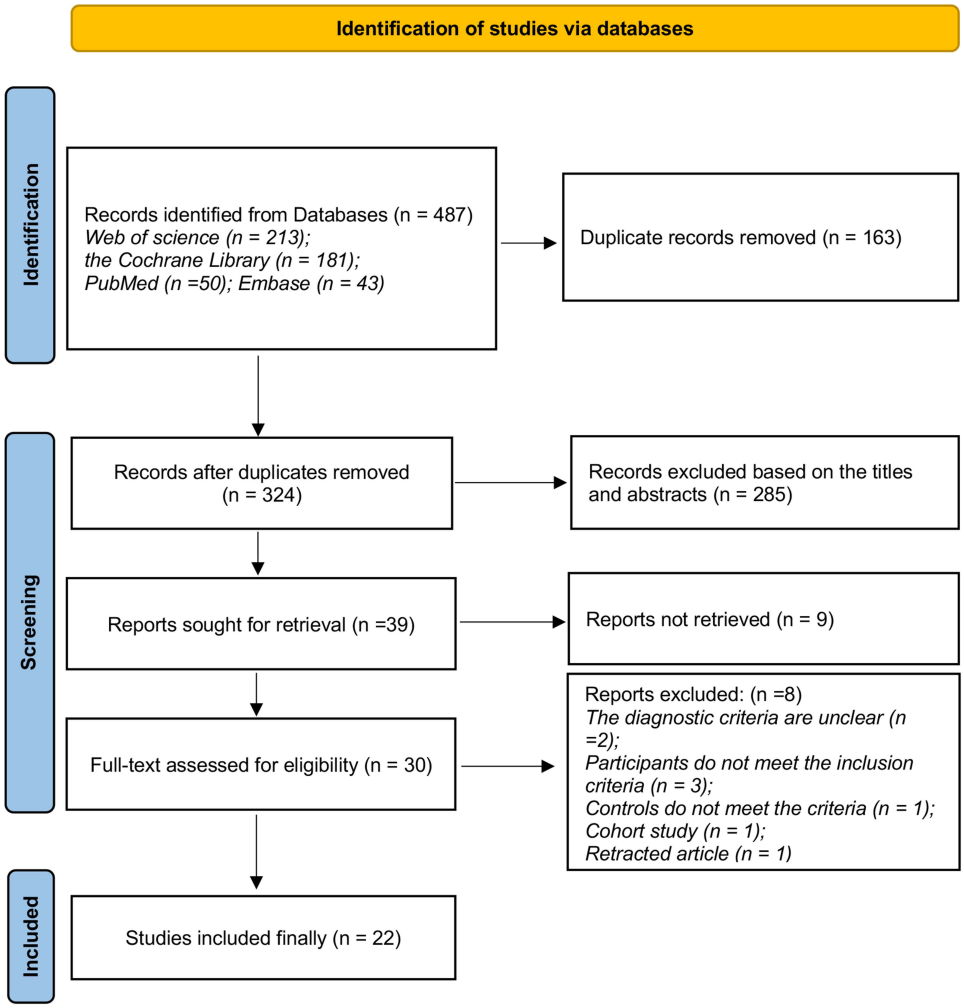


Figure 1 Literature search and studies selection flow chart.

individuals, PD patients have dysbiosis of the gut microbiota; probiotics have a positive impact on some microbial populations but do not cause major changes in the overall gut microbiota.[33–35]

Additionally, Tamtaji et al[17] focused on the metabolic levels in PD patients, finding that 12 weeks of probiotic use reduced high-sensitivity C-reactive protein and malondialdehyde while increasing glutathione levels. Probiotics also lowered insulin levels and insulin resistance while improving insulin sensitivity. Borzabadi et al[21] found that probiotics could modulate the gene expression of PPAR-γ in PD patients, but did not affect the gene expression of VEGF and LDLR or the biomarkers of oxidative stress. Another study[35] found that, compared to placebo, probiotics significantly improved sleep quality, anxiety, mental state, and depressive symptoms in PD patients. Lactobacillus fermentum was positively correlated with UPDRS-III, HAMA, HAMD-17 scores, and negatively correlated with MMS, while Klebsiella oxytoca was negatively correlated with feces hardness. Probiotics also altered the host's serum metabolites, including tryptophan, γ-aminobutyric acid, short-chain fatty acids, secondary bile acids, as well as serum acetate and dopamine levels.

Multiple Sclerosis

Six studies focused on MS. The study by Kouchaki et al[24] indicated that after 12 weeks of probiotic capsule use, MS patients showed improvements in EDSS scores, mental health, inflammatory factors, insulin resistance, and metabolic levels. One study focused on the mental health[40] and inflammatory status[20] of MS, finding that probiotic supplementation reduced inflammation levels and improved overall quality of life, depressive symptoms, fatigue, and pain in patients. These results were confirmed in the study by Asghari KM.[41] Moravejolahkami AR[42] found that combined treatment with

Table 1 Detailed Characteristics of Included Studies in the Systematic Review

Included Studies	Country/ Region	Disease Type	Sample Size (I/ C)	Age [y, mean (SD)] (I/C)	Sex (male/ female) (I, C)	Intervention	Comparison	Duration	Outcomes	Adverse Events (I/C)
Barichella M, 2016[30]	Italy	PD	80/40	71.8(7.7)/69.5 (10.3)	41/39, 24/16	Fermented milk containing probiotics and prebiotic fiber (125 g) Including the following strains: *Streptococcus salivarius subsp thermophilus, Enterococcus faecium, Lactobacillus rhamnosus GG, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp bulgaricus*, and *Bifidobacterium* (breve and animalis subsp lactis) /Qd	Placebo (a pasteurized, fermented, fiber-free milk) /Qd	4 w	number of complete bowel movements (CBMs) per week	1(abdominal pain and bloating)/1(abdominal pain and bloating)
Ibrahim A, 2020[31]	Malaysia	PD	27/28	69.0/70.5	16/9, 17/10	Probiotic (Hexbio®) in orange flavouring containing microbial cell preparation of (MCP®BCMC®) at 30×10^9 colony forming units (CFU), 2% fructo-oligosaccharide (FOS), and lactose. The microbial composition of the probiotics were: *Lactobacillus acidophilus* (BCMC® 12130)– 107mg, *Lactobacillus casei* (BCMC® 12313) −107mg, *Lactobacillus lactis* (BCMC® 12451)-107 mg, (BCMC® 02290) −107mg, *Bifidobacterium infantis* (BCMC® 02129) −107mg and *Bifidobacterium longum* (BCMC® 02120)-107mg. /Bid	Granulated milk of similar appearance to the probiotics containing lactose without fructo-oligosaccharide or microbial cells in orange flavouring/Bid	8 w	Constipation symptom and bowel opening frequency, gut transit time, MDS-UPDRS II and III scores, NMSS scores and PDQ-39SI scores	4(abdominal bloating, n=2; dizziness, n=2)/0
Georgescu D, 2016[23]	Romania	PD	20/20	69.80(5.64)/ 75.65(9.66)	10/10, 7/13	Mixture of two lactic bacteria: *Lactobacillus acidophilus* and *Bifidobacterium infantis*, 60 mg/ Bid	Trimebutine, 200mg/Tid	3 m	Abdominal pain, Bloating, Constipation	None

(*Continued*)

https://doi.org/10.2147/IJGM.S499406 DovePress

Table 1 (Continued).

Included Studies	Country/ Region	Disease Type	Sample Size (I/ C)	Age [y, mean (SD)] (I/C)	Sex (male/ female) (I, C)	Intervention	Comparison	Duration	Outcomes	Adverse Events (I/C)
Tamtaji OR, 2019[17]	Iran	PD	30/30	68.2(7.8)/67.7 (10.2)	-	Probiotic capsule contained *Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri*, and *Lactobacillus fermentum* (each 2×10^9 CFU/g)/Qd	Placebo capsules /Qd	12w	MDS-UPDRS, hs-CRP, GSH, MDA, insulin levels, HOMA-IR, QUICKI	None
Borzabadi S, 2018[21]	Iran	PD	25/25	66.9(7.0)/66.7 (10.7)	17/8, 16/9	8×10^9 CFU probiotic supplements/Qd	Placebo/Qd	12w	NO, GSH, IL-1, IL-8, TNF-α, TGF-β	None
Tan AH, 2021[32]	Malaysia	PD	34/38	63.1/61.5	20/24, 28/10	Probiotic capsule, contained 10 billion colony forming units (CFU) of eight different commercially available bacterial strains (*Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus gasseri, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Enterococcus faecalis, Enterococcus faecium*)/Qd	Placebo capsul: containing an inactive substance (maltodextrin) /Qd	4 w	Number of spontaneous bowel movements per week, changes in stool consistency, constipation severity score, quality of life related to constipation, Change in levels of fecal calprotectin	1(lethargy)/0
Yang X, 2023[33]	China	PD	65/63	67.22(6.46), 69.64(6.41)	31/34, 42/21	LcS fermented milk (100 mL, containing 1×10^{10} living LcS cells)/Qd	Placebo/Qd	12w	MDS-UPDRS, MMSE, MoCA, PAC-QOL, bowel movements	None
Du Y, 2022[34]	China	PD	23/23	68.39(7.55)/ 66.65(8.66)	-	Probiotics containing Bacillus licheniformis *(Bacillus licheniformis*, 2.5×10^9 CFU, 2 capsules each time, three times daily), *Lactobacillus acidophilus, Bifidobacterium longum, Enterococcus faecalis* (BIFICO, 1.0×10^7 CFU per strain, 4 capsules each time, twice daily)	Conventional PD treatment	12w	Average number of complete bowel movements per week, degree of defecation effort, BSS, PAC-SYM, PAC-QOL	None
Sun H, 2022[35]	China	PD	48/34	-	-	Probio-M8 complex probiotics [including *Bifidobacterium (B). bifidum, B. longum, Lactobacillus (L). rhamnosus GG*]/Qd	Placebo/Qd	16w	PAC-QOL, MDS-UPDRS, NMSS, MMSE	None

Ghalandari N, 2023[36]	Iran	PD	14/13	68.07(6.68)/ 68.54(6.92)	6/8, 6/7	Comflor® (Fara Daroo Fanavar Mehr Co) capsules containing a total of 4.5×1011 CFU of *Lactobacillus plantarum, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus bulgaricus, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium breve*, and *Streptococcus thermophilus* (each genus accounting for 1.5×10^{11} CFU) without a prebiotic component/Qd	Placebo capsules/Qd	8w	Defecation per week, UPDRS II III, Times needed to use laxative per week, Times of defecation with a sense of complete evacuation per week	0/polydipsia and polyuria(n=2)
Akhgarjand C, 2024a[27]	Iran	AD	30/30	67.90(7.9), 67.77(7.9)	16/14, 16/14	B. longum R0175 (7.5×10^9/ capsule)/Bid	Placebo (malic acid, xylitol, and maltodextrin)/Bid	12w	GSH, MDA, 8-OHdG, TNF-α, IL-6, IL-10, LPS, QoL, physical activity	None
Akhgarjand C, 2024b[27]	Iran	AD	30/30	67.93(7.8), 67.77(7.9)	16/14, 16/14	L. rhamnosus HA-114 (7.5×10^9/ capsule /Bid)	Placebo (malic acid, xylitol, and maltodextrin)/Bid	12w	GSH, MDA, 8-OHdG, TNF-α, IL-6, IL-10, LPS, QoL, physical activity	None
Agahi A, 2018[14]	Iran	AD	25/23	79.70(1.72)/ 80.57(1.79)	7/18, 10/13	Two types of capsules each containing 3 bacteria (with a total dosage of 3×10^9 CFU) including either *Lactobacillus fermentum, Lactobacillus plantarum*, and *Bifidobacterium lactis* (provided by Zist Takhmir Company, Tehran, Iran) or Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium longum (provided by Milad Farmed Company, Tehran, Iran)/Qod	Placebo capsules containing 500 mg maltodextrine/Qod	12w	TYM test, TNF-aT, IL-6, IL-10, GSH, NO, MDA; TAC, 8-OHdG	None
Akbari E, 2016[37]	Iran	AD	30/30	77.67(2.62)/ 82.00(1.69)	6/24, 6/24	200 mL/day probiotic milk containing *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum*, and *Lactobacillus fermentum* (2×10^9 CFU/g for each) /Qd	Milk (200 mL/) day	12w	MMSE, hs-CRP, HOMA-IR, HOMA-B, QUICKI, MDA, FPG, GSH, TAC, NO, FPG, TG, VLDL, LDL, HDL, Total cholesterol	None

(*Continued*)

https://doi.org/10.2147/IJGM.S499406 DovePress

Table 1 (Continued).

Included Studies	Country/ Region	Disease Type	Sample Size (I/ C)	Age [y, mean (SD)] (I/C)	Sex (male/ female) (I, C)	Intervention	Comparison	Duration	Outcomes	Adverse Events (I/C)
Tamtaji OR, 2019[28]	Iran	AD	27/26	76.2(8.1)/78.8 (10.2)	-	Selenium (200 μg/day) plus probiotic containing *Lactobacillus acidophilus, Bifidobacterium bifidum*, and *Bifidobacterium longum* (2×10^9 CFU/day each)	Selenium (200 μg/day), Placebo (starch 200 μg/ day)	12w	MMSE, hs-CRP, HOMA-IR, Insulin, QUICKI, TNF-α, NO, TAC, GSH, MDA, FPG, LDL, HDL, TG, VLDL, Total cholesterol	None
Fei Y, 2023[38]	China	MCI	21/21	76.40(9.61)/ 75.30(9.75)	10/11, 11/10	The probiotic mixture included *Lactobacillus plantarum BioF-228, Lactococcus lactis BioF-224, Bifidobacterium lactis CP-9, Lactobacillus rhamnosus Bv-77, Lactobacillus johnsonii MH-68, Lactobacillus paracasei MP137, Lactobacillus salivarius AP-32, Lactobacillus acidophilus TYCA06, Lactococcus lactis LY-66, Bifidobacterium lactis HNO19, Lactobacillus rhamnosus HNO01, Lactobacillus paracasei GL-156, Bifidobacterium animalis BB-115, Lactobacillus casei CS-773, Lactobacillus reuteri TSR332, Lactobacillus fermentum TSF331, Bifidobacterium infantis BLI-02*, and *Lactobacillus plantarum CN2018*. The probiotics contained active cultures >2*10^{10} CFU/g/2g/Qd	Placebo capsules/2g/Qd	12w	MMSE, MoCA, PSQI, GSRS	None
Hwang YH, 2019[39]	Korea	MCI	50/50	68.0(5.12)/69.2 (7.00)	20/30, 14/36	*Lactobacillus plantarum* C29-fermented soybean (1.25×10^{10} CFU/g or more of Lactobacillus plantarum C29) 800 mg/Qd	Placebo capsules (800 mg)/Qd	12w	computerized neurocognitive function tests, BDNF	dizziness, stomach aches, headaches, gastritis, erectile dysfunction and seborrheic dermatitis/ irregular bowel movement, stomach aches, and erectile dysfunction

Kouchaki E, 2017[24]	Iran	MS	30/30	34.4(9.2)/33.8 (8.9)	25/5, 25/5	Probiotic capsules: *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum* and *Lactobacillus fermentum* (each 2×10^9 CFU/g)/Qd	Placebo capsules (starch)/Qd	12w	EDSS, BDI, GHQ-28, DASS, hs-CRP, NO, MDA, insulin, HOMA-IR, QUICKI, HDL	None
Rahimlou M, 2022a[40]	Iran	MS	32/33	39.9(8.76)/ 42.15(11.98)	6/26, 12/21	2 multi-strain probiotic capsules: Each probiotic capsule (Protexin) contained minimum 2 billion live microorganisms (2×10^9 CFU/capsule), equivalent to 10 billion live microorganisms per gram (1×10^{10} CFU/gram) of 14 strains (Bacillus subtilis PXN 21, Bifidobacterium bifidum PXN 23, Bifidobacterium breve PXN 25, Bifidobacterium infantis PXN 27, Bifidobacterium longum PXN 30, Lactobacillus acidophilus PXN 35, Lactobacillus delbrueckii ssp. bulgaricus PXN 39, Lactobacillus casei PXN 37, Lactobacillus plantarum PXN 47, Lactobacillus rhamnosus PXN 54, Lactobacillus helveticus PXN 45, Lactobacillus salivarius PXN 57, Lactococcus lactis ssp. lactis PXN 63, Streptococcus thermophilus PXN 66), cellulose (bulking agent) and vegetable capsule (Hydroxypropylmethyl Cellulose) /Qd	Two placebo capsules(maltodextrin) / Qd	12w	BDNF, NGF, IL-6, EDSS, GHQ-28, BDI, FSS, PRI	None

(*Continued*)

https://doi.org/10.2147/IJGM.S499406

Table 1 (Continued).

Included Studies	Country/ Region	Disease Type	Sample Size (I/ C)	Age [y, mean (SD)] (I/C)	Sex (male/ female) (I, C)	Intervention	Comparison	Duration	Outcomes	Adverse Events (I/C)
Rahimlou M, 2022b[20]	Iran	MS	32/33	39.9(8.76)/ 42.15(11.98)	6/26, 12/21	2 multi-strain probiotic capsules: Each probiotic capsule (Protexin) contained minimum 2 billion live microorganisms (2 × 10^9 CFU/capsule), equivalent to 10 billion live microorganisms per gram (1 × 10^{10} CFU/gram) of 14 strains (Bacillus subtilis PXN 21, Bifidobacterium bifidum PXN 23, Bifidobacterium breve PXN 25, Bifidobacterium infantis PXN 27, Bifidobacterium longum PXN 30, Lactobacillus acidophilus PXN 35, Lactobacillus delbrueckii ssp. bulgaricus PXN 39, Lactobacillus casei PXN 37, Lactobacillus plantarum PXN 47, Lactobacillus rhamnosus PXN 54, Lactobacillus helveticus PXN 45, Lactobacillus salivarius PXN 57, Lactococcus lactis ssp. lactis PXN 63, Streptococcus thermophilus PXN 66), cellulose (bulking agent) and vegetable capsule (Hydroxypropylmethyl Cellulose) /Qd	Two placebo capsules(maltodextrin) / Qd	12w	CRP, IFN-γ, IL-17, IL-35, TNF-α, TGF-β, FOXP3	None
Asghari KM, 2023[41]	Iran	MS	25/25	33.80(1.37)/ 34.95(7.03)	7/18, 8/17	Probiotic capsule containing 250 mg of SB (10^{10} CFU), a lactose filler, and a magnesium acetate oil/Qd	Placebo capsules/Qd	4m	GHQ-28, VAS, FSS, SF-36, hs-CRP, TAC, MDA	None

Moravejolahkami AR, 2023a[42]	Iran	MS	34/35	39.0(9.2)/37.8 (10.1)	8/26, 8/27	Probiotic capsule containing *L. casei, L. acidophilus, L. plantarum, L. bulgaricus, Bifidobacterium (B). breve, B. infantis, B. longum*, and *streptococcus thermophiles*, with a total dose of 4.5×1011 Colony Forming Unit (CFU), along with 100 mg concentrated fructooligosaccharide/Qd and anti-inflammatory-antioxidant-rich diet	Placebo capsules/Qd and usual diet	4m	MFIS, GPS, BLCS, BWCS, SSS	None
Moravejolahkami AR, 2023b[29]	Iran	MS	34/35	39.0(9.2)/37.8 (10.1)	8/26, 8/27	Probiotic capsule containing *L. casei, L. acidophilus, L. plantarum, L. bulgaricus, Bifidobacterium (B). breve, B. infantis, B. longum*, and *streptococcus thermophiles*, with a total dose of 4.5×10^{11} Colony Forming Unit (CFU), along with 100 mg concentrated fructooligosaccharide/Qd and anti-inflammatory-antioxidant-rich diet	Placebo capsules/Qd and usual diet	4m	Faecal calprotectin level, IVI, GSRS, anthropometric measurements (BW, BMI, WC, HC, WHR, MAC, cAMA, TSF, BF)	None

Abbreviations: AD, Alzheimer's disease; MCI, Mild cognitive impairment; MS, multiple sclerosis; PD, Parkinson's disease; I, intervention group; C, comparison group; F, Frequencies; m, months; w, week; Qd, Once a day; Bid, Twice a day.

https://doi.org/10.2147/IJGM.S499406 DovePress

a diet rich in anti-inflammatory and antioxidant agents and synbiotics improved fatigue, pain, sexual function, bowel, and bladder conditions in progressive MS patients. This treatment also reduced fecal calprotectin levels, improved visual impairment, and gastrointestinal function, without causing any changes in basic physiological indicators such as weight, BMI, waist circumference, hip circumference, or mid-arm circumference.[29]

Alzheimer's Disease

Four studies focused on the impact of probiotics on oxidative stress, inflammation, and metabolic levels in AD patients, with all treatment periods being 12 weeks, though the frequency of administration varied. Research by Akbari E[37] and Tamtaji OR[28] similarly found that both composite probiotics and probiotics combined with selenium can enhance cognitive function, improve metabolic status and antioxidant capacity, and reduce inflammation levels in AD patients. Probiotics improved oxidative damage in patients with mild to moderate AD[27] as indicated by increased serum GSH and decreased levels of 8-OHdG and MDA. This treatment also enhanced quality of life and physical activity, with no significant difference in efficacy between the two types of probiotics. However, cognitive function, inflammation, and oxidative stress responses to probiotic supplementation were insensitive in patients with severe AD.[14]

Mild Cognitive Impairment

Two studies focused on the effects of probiotics on MCI after 12 weeks of treatment. Fei et al[38] found that probiotic treatment could enhance cognitive function and sleep quality in elderly MCI patients, and improve gastrointestinal function. Another study[39] using computerized neurocognitive tests found that probiotics significantly improved overall cognitive function, especially in attention, compared to the placebo group. Cognitive improvement was associated with increased serum BDNF levels, and a significant increase in Lactobacillus numbers in MCI patients was also observed.

Safety Evaluation

For PD, two studies reported that the probiotic group experienced abdominal pain, bloating, dizziness[30,31] and drowsiness.[32] One study reported increased thirst and urination in the control group.[36] In MCI, the probiotic group experienced dizziness, stomach aches, headaches, gastritis, erectile dysfunction, and seborrheic dermatitis, while the control group had irregular bowel movements, stomach aches, and erectile dysfunction.[39] No adverse events were reported in AD and MS.

Bias Risk Assessment

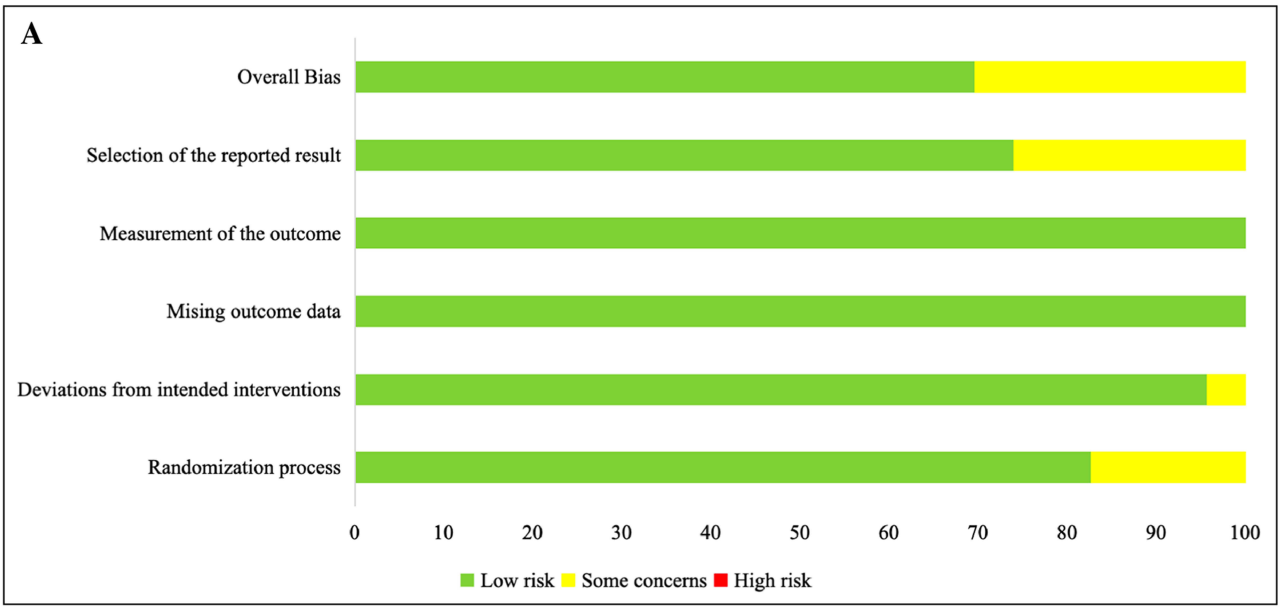
We used the Cochrane RoB 2 tool to conduct a comprehensive bias risk assessment of 22 RCTs (23 items). The assessment results indicate that 6 studies had issues in several key areas, including insufficient description of allocation concealment procedures, inadequate blinding information, or other potential sources of bias. Consequently, these studies were rated as having "some concerns". The remaining studies were considered to have a low risk of bias and were rated as "low risk". The detailed information and classification results of the bias risk are shown in Figure 2.

Discussion

Summary of Main Results

This study reviewed various NDDs and reported different outcomes of probiotic treatment for PD, MS, AD, and MCI. These RCTs primarily employed mixed probiotic strains with treatment durations ranging from 4 to 16 weeks. The summary results highlight several points: (a) Probiotics significantly improve gastrointestinal function (eg, weekly bowel movements) and quality of life in PD. (b) Probiotics can enhance cognitive function in MCI and mild to moderate AD patients, but evidence supporting their effectiveness in severe AD is lacking. (c) A few studies confirmed the analgesic effects of probiotics and their value in promoting mental health in MS. (d) In PD, MS, and AD, probiotics are beneficial in reducing systemic inflammation, improving metabolic status, and enhancing antioxidant capacity.

Most common NDDs share amyloid protein deposition and brain network degeneration as common pathological features.[43] The enteric nervous system (ENS) is a complex network of neurons and enteric glial cells that spans the entire



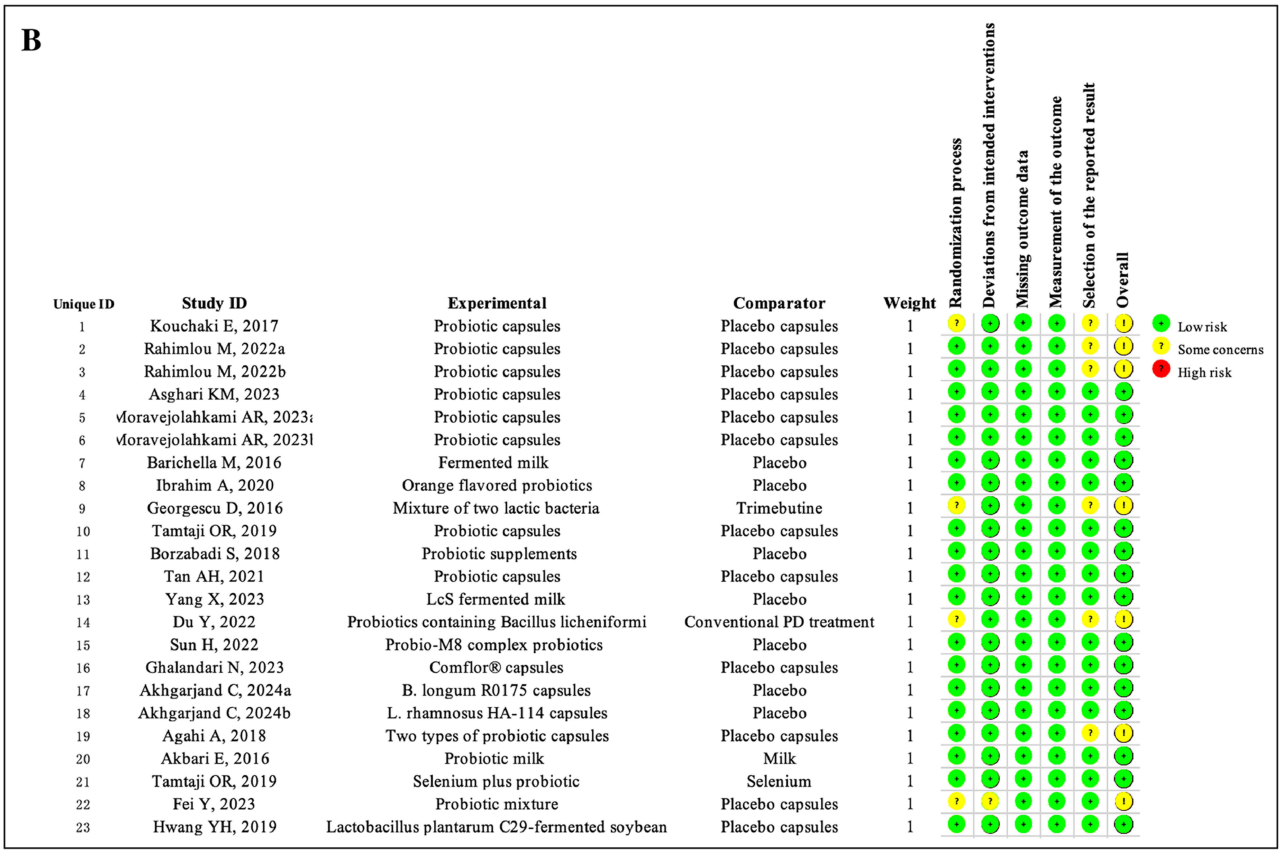


Figure 2 Overall summary of risk of bias in the included studies. (**A**) Risk of bias item presented as percentages across all included RCTs. (**B**) Risk of bias item for included RCTs.

gastrointestinal tract and participates in regulating gut functions; it is also known as the "second brain".[44] The ENS and the central nervous system (CNS) are intricately connected through the gut-brain axis signaling network. When the gut microbiota becomes dysregulated, related signals are transmitted to the central brain, manifesting as systemic low-grade

inflammation, immune damage, metabolic disorders, and oxidative stress.[45] Consequently, probiotics are receiving increasing attention for their potential in treating NDDs by regulating the gut-brain axis.

Although the etiology of NDDs is unclear and each NDD is considered a distinct entity, their pathological mechanisms often overlap.[46] Oxidative stress and inflammation are two major causes of NDDs. their pathological accumulation forms a vicious cycle that worsens with age,[47] a process known as "inflammaging". Inflammaging is a common foundation for various age-related pathologies, including neurodegeneration,[48] characterized by elevated levels of cytokines and inflammatory mediators, with no clear triggering factors.[47] In recent years, probiotics, as live microorganisms, have been shown to benefit health when consumed appropriately, with confirmed effects in anti-inflammatory and antioxidant activities.[49] Previous studies have shown that probiotics can improve cognitive and gastrointestinal symptoms in patients with AD, MCI, and PD, which may be related to reducing inflammatory responses and improving lipid metabolism.[50] Our study further extends these findings based on evidence from 23 clinical trials. Next, we will further discuss the results of probiotics on systemic inflammation in NDDs.

Increasing evidence suggests that neuroinflammation is not only an accompanying phenomenon in AD but also a core component of its pathogenesis.[51,52] Misfolded and aggregated proteins bind to pattern recognition receptors on microglia and astrocytes, triggering an innate immune response characterized by the release of inflammatory mediators, which contributes to disease progression and severity.[53] Microglia and astrocytes, as resident immune cells in the brain, are normally responsible for monitoring and clearing damaged cells and pathogens.[54] However, in AD patients, the behavior of these cells undergoes significant changes. They become excessively activated and produce large amounts of pro-inflammatory cytokines and chemokines, such as IL-1β, IL-6, and TNF-α,[55,56] exacerbating local inflammation. Additionally, they directly accelerate the pathological progression of AD by disrupting synaptic connections between neurons, promoting β-amyloid (Aβ) deposition, and tau protein hyperphosphorylation.[57,58] Conversely, IL-4, IL-10, IL-13, and TGF-β can activate neuroprotective microglia, inhibiting the release of pro-inflammatory cytokines.

As our understanding of the relationship between neuroinflammation and AD, scientists have begun to explore indirect approaches to influencing neuroinflammation through gut microbiota modulation and metabolic state improvement, thereby opening new avenues for AD treatment.[28,37] Our systematic review results show that in AD patients taking probiotics, the level of hs-CRP was significantly reduced. Another study found that using two single-strain probiotics (Bifidobacterium longum and Lactobacillus casei) compared to placebo significantly increased IL-10 levels and reduced TNF-α and IL-6 levels in patients with mild and moderate AD.[27] However, probiotics did not improve TNF-α, IL-6, and IL-10 levels in patients with severe AD.[14]

MS is a result of an imbalance between inflammatory and anti-inflammatory conditions.[59] hs-CRP is a highly sensitive systemic marker of inflammation and tissue damage. Nazeri et al reported that MS patients, especially those with cerebellar and brainstem symptoms, have higher hs-CRP levels.[60] Other studies also found significantly elevated levels of hs-CRP, IFN-γ, and TNF-α in the serum of MS patients.[61] This is consistent with the results from the studies included in our review. After probiotic treatment, there was a significant difference in hs-CRP levels between the probiotic and placebo groups.[20,24,41] Probiotics also significantly reduced other pro-inflammatory cytokines and chemokines (such as TNF-α and IFN-γ) while increasing anti-inflammatory cytokines (such as FOXP3 and TGF-β). However, there were no significant differences in IL-17 and IL-35 concentrations.[20] Animal studies further confirmed that probiotics can alleviate the severity of MS, which is related to the bidirectional modulation of the body's anti-inflammatory and pro-inflammatory mechanisms.[62,63]

The crosstalk between the gut and brain is a pathway for PD pathology to propagate either from the bottom up or from the top down.[64] Abnormal aggregation of α-synuclein and pathological spread between the gut, brainstem, and higher brain regions may be fundamental causes of PD development and progression.[65] α-Synuclein peptides may play a dual role in PD. On one hand, it may act as an antigenic epitope and drive immune responses.[66] On the other hand, pro-inflammatory immune activity can increase the levels and aggregation of α-synuclein in the gut and brain,[67] with this positive inflammatory loop ultimately leading to neuronal death. Although only three studies have assessed the inflammatory state in PD patients. Borzabadi S noted that after 12 weeks of probiotic treatment, the gene expression of IL-1, IL-8, and TNF-α was downregulated, while TGF-β was upregulated in the peripheral blood mononuclear cells

(PBMCs) of PD patients.[21] Probiotics were also associated with a reduction in hs-CRP levels in PD.[17] However, probiotics did not cause a significant change in fecal calprotectin levels.[32]

Strengths and Limitations

This systematic review has several limitations. First, almost all studies involved the use of two or more strains in combination, administered in forms such as capsules, tablets, or emulsions. However, the variation in strains, forms, and dosages complicates the assessment of their effects, particularly in determining the specific benefits of individual or combined use. A study on probiotics for IBS explicitly identified that variations in bacterial strains, combinations, and dosages are major sources of heterogeneity in the results.[68] Second, changes in the gut microbiota are closely related to lifestyle and dietary habits. However, these potential factors were not accounted for in the 23 studies. Furthermore, only three studies focused on changes in the gut microbiota. After 12 weeks of probiotic treatment, the number of Lactobacillus in MCI patients significantly increased, while the quantities of Bifidobacterium and Clostridium remained unchanged,[39] and the relative abundance of Lactobacillus in PD patients significantly increased.[33] Another study observed probiotics in PG patients caused PD patients g_Christensenella_sp._Marseille-P2437 significantly increased, while g_Eubacterium_oxidoreducens_group, g_Eubacterium_hallii_group and s_Odoribacter_sp._N54.MGS-14 decreased,[34] but the research on the mechanism of probiotics is limited, and the further therapeutic mechanism and gut-brain axis mechanism need to be verified.

Finally, the strengths of this systematic review are outlined. First, we conducted a thorough literature search and identified a total of 18 RCTs across four types of NDDs—AD (4 RCTs), PD (10 RCTs), MS (2 RCTs), and MCI (2 RCTs)—making this the most comprehensive evaluation on the topic. Second, we detailed the specific strains, dosages, and administration frequencies used in each study. This concrete evidence aids researchers in further exploring the clinical value of different probiotic strains. Third, this review explored the role of neuroinflammation in various NDDs and discussed the anti-inflammatory effects of probiotics in detail, providing a basis for further investigation into the neuroprotective effects of probiotics. Fourth, we addressed safety issues related to probiotics, such as abdominal pain, bloating, dizziness, stomach pain, headache, and gastritis, with the need to clarify whether these adverse effects are caused by probiotics. Finally, we assessed the risk of bias for all studies using RoB2, and the results suggested that none of the studies had a high risk of bias, providing greater confidence in the summary results of this review. This review also provides guidance for the design of future RCTs and points to new research directions for clinical applications. Future RCTs in this field should place greater emphasis on research design, particularly on implementing allocation concealment and blinding, to ensure more objective and unbiased results.

Conclusion

Probiotics have shown potential in improving symptoms and quality of life in NDDs, including benefits for gastrointestinal function, cognitive performance, pain relief, and inflammation. These findings suggest probiotics as a promising complementary approach, though further high-quality studies are needed to confirm their efficacy.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Taghizadeh Ghassab F, Shamlou Mahmoudi F, Taheri Tinjani R, Emami Meibodi A, Zali MR, Yadegar A. Probiotics and the microbiota-gut-brain axis in neurodegeneration: beneficial effects and mechanistic insights. *Life Sci*. 2024;350:122748. doi:10.1016/j.lfs.2024.122748
2. Gitler AD, Dhillon P, Shorter J. Neurodegenerative disease: models, mechanisms, and a new hope. *Dis Model Mech*. 2017;10(5):499–502. doi:10.1242/dmm.030205
3. Wyss-Coray T. Ageing, neurodegeneration and brain rejuvenation. *Nature*. 2016;539(7628):180–186. doi:10.1038/nature20411
4. Kritsilis M, Rizou S, Koutsoudaki PN, Evangelou K, Gorgoulis VG, Papadopoulos D. Ageing, Cellular Senescence and Neurodegenerative Disease. *Int J Mol Sci*. 2018;19(10). doi:10.3390/ijms19102937
5. Gammon K. Neurodegenerative disease: brain windfall. *Nature*. 2014;515(7526):299–300. doi:10.1038/nj7526-299a
6. Wilson DM, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. *Cell*. 2023;186(4):693–714. doi:10.1016/j.cell.2022.12.032

7. Cai P, Li W, Xu Y, Wang H. Drp1 and neuroinflammation: deciphering the interplay between mitochondrial dynamics imbalance and inflammation in neurodegenerative diseases. *Neurobiol Dis*. 2024;198:106561.
8. Esmaealzadeh N, Miri MS, Mavaddat H, et al. The regulating effect of curcumin on NF-κB pathway in neurodegenerative diseases: a review of the underlying mechanisms. *Inflammopharmacology*. 2024;32(4):2125–2151.
9. Lashgari NA, Roudsari NM, Momtaz S, Sathyapalan T, Abdolghaffari AH, Sahebkar A. The involvement of JAK/STAT signaling pathway in the treatment of Parkinson's disease. *J Neuroimmunol*. 2021;361:577758. doi:10.1016/j.jneuroim.2021.577758
10. Bernhardi R. Neurodegenerative diseases – MAPK signalling pathways in neuroinflammation. In: Binder MD, Hirokawa N, Windhorst U, editors. *Encyclopedia of Neuroscience*. Berlin Heidelberg: Springer; 2009:2614–2620.
11. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506–514. doi:10.1038/nrgastro.2014.66
12. Kerry RG, Patra JK, Gouda S, Park Y, Shin HS, Das G. Benefaction of probiotics for human health. *A Rev J Food Drug Anal*. 2018;26(3):927–939. doi:10.1016/j.jfda.2018.01.002
13. Ojha S, Patil N, Jain M, Kole C, Kaushik P. Probiotics for neurodegenerative diseases: a systemic review. *Microorganisms*. 2023;11(4):1083. doi:10.3390/microorganisms11041083
14. Agahi A, Hamidi GA, Daneshvar R, et al. Does severity of Alzheimer's disease contribute to its responsiveness to modifying gut microbiota? A double blind clinical trial. *Front Neurol*. 2018;9:662. doi:10.3389/fneur.2018.00662
15. Liu N, Yang D, Sun J, Li Y. Probiotic supplements are effective in people with cognitive impairment: a meta-analysis of randomized controlled trials. *Nutr Rev*. 2023;81(9):1091–1104. doi:10.1093/nutrit/nuac113
16. Krüger JF, Hillesheim E, Pereira A, Camargo CQ, Rabito EI. Probiotics for dementia: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev*. 2021;79(2):160–170. doi:10.1093/nutrit/nuaa037
17. Tamtaji OR, Taghizadeh M, Daneshvar Kakhaki R, et al. Clinical and metabolic response to probiotic administration in people with Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Clin Nutr*. 2019;38(3):1031–1035. doi:10.1016/j.clnu.2018.05.018
18. Chu C, Yu L, Li Y, et al. Meta-analysis of randomized controlled trials of the effects of probiotics in Parkinson's disease. *Food Funct*. 2023;14(8):3406–3422. doi:10.1039/D2FO03825K
19. 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:10.3389/fcimb.2022.1038928
20. Rahimlou M, Nematollahi S, Husain D, Banaei-Jahromi N, Majdinasab N, Hosseini SA. Probiotic supplementation and systemic inflammation in relapsing-remitting multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Front Neurosci*. 2022;16:901846. doi:10.3389/fnins.2022.901846
21. Borzabadi S, Oryan S, Eidi A, et al. The effects of probiotic supplementation on gene expression related to inflammation, insulin and lipid in patients with Parkinson's disease: a randomized, double-blind, placebocontrolled trial. *Arch Iran Med*. 2018;21(7):289–295.
22. Jiang J, Chu C, Wu C, et al. Efficacy of probiotics in multiple sclerosis: a systematic review of preclinical trials and meta-analysis of randomized controlled trials. *Food Funct*. 2021;12(6):2354–2377. doi:10.1039/D0FO03203D
23. 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;11:1601–1608. doi:10.2147/CIA.S106284
24. Kouchaki E, Tamtaji OR, Salami M, et al. Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Clin Nutr*. 2017;36(5):1245–1249. doi:10.1016/j.clnu.2016.08.015
25. Mirashrafi S, Hejazi Taghanaki SZ, Sarlak F, Moravejolahkami AR, Hojjati Kermani MA, Haratian M. Effect of probiotics supplementation on disease progression, depression, general health, and anthropometric measurements in relapsing-remitting multiple sclerosis patients: a systematic review and meta-analysis of clinical trials. *Int J Clin Pract*. 2021;75(11):e14724. doi:10.1111/ijcp.14724
26. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*. 2017;9(9):1021. doi:10.3390/nu9091021
27. Akhgarjand C, Vahabi Z, Shab-Bidar S, Anoushirvani A, Djafarian K. The effects of probiotic supplements on oxidative stress and inflammation in subjects with mild and moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled study. *Inflammopharmacology*. 2024;32(2):1413–1420. doi:10.1007/s10787-023-01427-2
28. Tamtaji OR, Heidari-Soureshjani R, Mirhosseini N, et al. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: a randomized, double-blind, controlled trial. *Clin Nutr*. 2019;38(6):2569–2575. doi:10.1016/j.clnu.2018.11.034
29. Moravejolahkami AR, Chitsaz A, Hassanzadeh A, Paknahad Z. Effects of anti-Inflammatory-antioxidant-rich diet and co-supplemented synbiotics intervention in patients with progressive forms of multiple sclerosis: a single-center, single-blind randomized clinical trial. *Nutr Neurosci*. 2023;26(11):1078–1089. doi:10.1080/1028415X.2022.2128010
30. Barichella M, Pacchetti C, Bolliri C, et al. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: an RCT. *Neurology*. 2016;87(12):1274–1280. doi:10.1212/WNL.0000000000003127
31. Ibrahim A, Ali RAR, Manaf MRA, 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(12):e0244680. doi:10.1371/journal.pone.0244680
32. Tan AH, Lim SY, Chong KK, et al. Probiotics for constipation in Parkinson Disease: a randomized placebo-controlled study. *Neurology*. 2021;96(5):e772–e82. doi:10.1212/WNL.0000000000010998
33. Yang X, He X, Xu S, et al. Effect of Lacticaseibacillus paracasei strain Shirota supplementation on clinical responses and gut microbiome in Parkinson's disease. *Food Funct*. 2023;14(15):6828–6839. doi:10.1039/D3FO00728F
34. Du Y, Li Y, Xu X, et al. Probiotics for constipation and gut microbiota in Parkinson's disease. *Parkinsonism Relat Disord*. 2022;103:92–97. doi:10.1016/j.parkreldis.2022.08.022
35. Sun H, Zhao F, Liu Y, et al. Probiotics synergized with conventional regimen in managing Parkinson's disease. *NPJ Parkinsons Dis*. 2022;8(1):62. doi:10.1038/s41531-022-00327-6
36. 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(1):e137840. doi:10.5812/ijpr-137840

37. Akbari E, Asemi Z, Daneshvar Kakhaki R, et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Front Aging Neurosci*. 2016;8:256. doi:10.3389/fnagi.2016.00256
38. Fei Y, Wang R, Lu J, et al. Probiotic intervention benefits multiple neural behaviors in older adults with mild cognitive impairment. *Geriatr Nurs*. 2023;51:167–175. doi:10.1016/j.gerinurse.2023.03.006
39. Hwang YH, Park S, Paik JW, et al. Efficacy and safety of lactobacillus plantarum C29-fermented soybean (DW2009) in individuals with mild cognitive impairment: a 12-week, multi-center, randomized, double-blind, placebo-controlled clinical trial. *Nutrients*. 2019;11(2):305. doi:10.3390/nu11020305
40. Rahimlou M, Hosseini SA, Majdinasab N, Haghighizadeh MH, Husain D. Effects of long-term administration of Multi-Strain Probiotic on circulating levels of BDNF, NGF, IL-6 and mental health in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled trial. *Nutr Neurosci*. 2022;25(2):411–422. doi:10.1080/1028415X.2020.1758887
41. Asghari KM, Dolatkhah N, Ayromlou H, Mirnasiri F, Dadfar T, Hashemian M. The effect of probiotic supplementation on the clinical and para-clinical findings of multiple sclerosis: a randomized clinical trial. *Sci Rep*. 2023;13(1):18577. doi:10.1038/s41598-023-46047-6
42. Moravejolahkami AR, Chitsaz A, Hassanzadeh A, Paknahad Z. Anti-inflammatory-antioxidant modifications and synbiotics improved health-related conditions in patients with progressive forms of multiple sclerosis: a single-center, randomized clinical trial. *Complement Ther Clin Pract*. 2023;53:101794. doi:10.1016/j.ctcp.2023.101794
43. Vaquer-Alicea J, Diamond MI. Propagation of protein aggregation in neurodegenerative diseases. *Annu Rev Biochem*. 2019;88(1):785–810. doi:10.1146/annurev-biochem-061516-045049
44. Baghdadi MB, Kim TH. The multiple roles of enteric glial cells in intestinal homeostasis and regeneration. *Semin Cell Dev Biol*. 2023;150–-151:43–49. doi:10.1016/j.semcdb.2023.01.005
45. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. *Cell Mol Life Sci*. 2017;74(20):3769–3787. doi:10.1007/s00018-017-2550-9
46. Dugger BN, Dickson DW. Pathology of Neurodegenerative Diseases. *Cold Spring Harb Perspect Biol*. 2017;9(7):a028035. doi:10.1101/cshperspect.a028035
47. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol a Biol Sci Med Sci*. 2014;69(Suppl 1):S4–9. doi:10.1093/gerona/glu057
48. Biagi E, Nylund L, Candela M, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. *PLoS One*. 2010;5(5):e10667. doi:10.1371/journal.pone.0010667
49. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. *N Engl J Med*. 2016;375(24):2369–2379. doi:10.1056/NEJMra1600266
50. Xiang S, Ji JL, Li S, 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:10.3389/fnagi.2022.730036
51. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease. *Curr Evid Future Directions Alzheimers Dement*. 2016;12(6):719–732. doi:10.1016/j.jalz.2016.02.010
52. Sun W, Gong J, Li S, et al. Bibliometric analysis of neuroinflammation and Alzheimer's disease. *Front Aging Neurosci*. 2024;16:1423139. doi:10.3389/fnagi.2024.1423139
53. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015;14(4):388–405. doi:10.1016/S1474-4422(15)70016-5
54. Ennerfelt HE, Lukens JR. The role of innate immunity in Alzheimer's disease. *Immunol Rev*. 2020;297(1):225–246. doi:10.1111/imr.12896
55. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell*. 2010;140(6):918–934.
56. Liddelow SA, Barres BA. Reactive astrocytes: production, function, and therapeutic potential. *Immunity*. 2017;46(6):957–967.
57. Kwon HS, Koh SH. Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. *Transl Neurodegener*. 2020;9(1):42. doi:10.1186/s40035-020-00221-2
58. Uddin MS, Kabir MT, Mamun AA, et al. Pharmacological approaches to mitigate neuroinflammation in Alzheimer's disease. *Int Immunopharmacol*. 2020;84:106479. doi:10.1016/j.intimp.2020.106479
59. Loma I, Heyman R. Multiple sclerosis: pathogenesis and treatment. *Curr Neuropharmacol*. 2011;9(3):409–416. doi:10.2174/157015911796557911
60. Nazeri M, Bazrafshan H, Abolhasani Foroughi A. Serum inflammatory markers in patients with multiple sclerosis and their association with clinical manifestations and MRI findings. *Acta Neurol Belg*. 2022;122(5):1187–1193. doi:10.1007/s13760-021-01647-9
61. Polachini CR, Spanevello RM, Casali EA, et al. Alterations in the cholinesterase and adenosine deaminase activities and inflammation biomarker levels in patients with multiple sclerosis. *Neuroscience*. 2014;266:266–274. doi:10.1016/j.neuroscience.2014.01.048
62. Salehipour Z, Haghmorad D, Sankian M, et al. Bifidobacterium animalis in combination with human origin of Lactobacillus plantarum ameliorate neuroinflammation in experimental model of multiple sclerosis by altering CD4+ T cell subset balance. *Biomed Pharmacother*. 2017;95:1535–1548. doi:10.1016/j.biopha.2017.08.117
63. Secher T, Kassem S, Benamar M, et al. Oral administration of the probiotic strain Escherichia coli nissle 1917 reduces susceptibility to neuroinflammation and repairs experimental autoimmune encephalomyelitis-induced intestinal barrier dysfunction. *Front Immunol*. 2017;8:1096. doi:10.3389/fimmu.2017.01096
64. Salim S, Ahmad F, Banu A, Mohammad F. Gut microbiome and Parkinson's disease: perspective on pathogenesis and treatment. *J Adv Res*. 2023;50:83–105. doi:10.1016/j.jare.2022.10.013
65. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH. The pathogenesis of Parkinson's disease. *Lancet*. 2024;403(10423):293–304.
66. Williams GP, Michaelis T, Lima-Junior JR, et al. PINK1 is a target of T cell responses in Parkinson's disease. *bioRxiv*. 2024. doi:10.1101/2024.02.09.579465
67. Kelly LP, Carvey PM, Keshavarzian A, et al. Progression of intestinal permeability changes and alpha-synuclein expression in a mouse model of Parkinson's disease. *Mov Disord*. 2014;29(8):999–1009. doi:10.1002/mds.25736
68. Mazurak N, Broelz E, Storr M, Enck P. Probiotic therapy of the irritable bowel syndrome: why is the evidence still poor and what can be done about it? *J Neurogastroenterol Motil*. 2015;21(4):471–485.