Exploration of Neuroprotective Therapy

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Analyzing the therapeutic and preventive potential of probiotics in Alzheimer's disease: a scoping review

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, neuroinflammation, and accumulation of amyloid-beta plaques and tau tangles. Emerging research emphasizes the gut-brain axis as a key modulator of AD pathogenesis, with gut microbiota influencing neuroimmune, neurochemical, and metabolic pathways. This review examines the therapeutic and preventive potential of probiotics, live beneficial microorganisms, in modulating the gut-brain axis to mitigate AD progression. Modifying gut microbiota presents a novel, potentially modifiable approach to influence AD pathophysiology and improve cognitive outcomes, offering insights for adjunctive clinical strategies. A systematic literature search was conducted across PubMed, Scopus, Web of Science, Google Scholar, and Cochrane Library for studies published up to July 2025. Studies were classified by design, sample size, follow-up duration, cognitive and biomarker outcomes, and risk of bias, following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility. Preclinical studies indicate that probiotics can regulate gut microbiota, reduce oxidative stress, suppress neuroinflammation, and enhance synaptic plasticity, improving cognition in animal models. Clinical trials suggest potential benefits in humans, including improved memory scores and reduced inflammatory biomarkers, though limited sample sizes, trial duration, and strain variability constrain conclusions. Overall, probiotics demonstrate promise as an adjunctive intervention in AD. Further long-term, strain-specific, and large-scale clinical studies are needed to confirm efficacy, establish causality, and optimize therapeutic strategies.

Keywords

Alzheimer's disease, probiotics, gut-brain axis, neuroinflammation

Introduction

Alzheimer's disease (AD) is a progressive neurological disorder marked by cognitive decline, memory loss, and behavioral abnormalities. It is the leading cause of dementia globally. Despite tremendous advances in understanding AD's biology, effective therapeutic options are still restricted. The gut-brain axis has recently received a lot of attention as a potential contribution to the development and progression of AD. The gut microbiota, a diverse community of bacteria that live in the gastrointestinal tract, has been linked to altered brain function via immunological, metabolic, and neurological mechanisms [1–3].

Emerging data suggest that dysbiosis, or gut microbial imbalance, may aggravate neuroinflammation and amyloid-beta (Aβ) accumulation, both of which are hallmarks of AD. Probiotics, or live microorganisms that provide health benefits to the host, have shown promise in restoring gut microbial balance and lowering systemic inflammation. Preclinical research has shown that probiotic administration can improve cognitive function, reduce oxidative stress, and modify neurotransmitter levels in AD animal models. Although limited, human clinical trials have shown that probiotic therapy in AD patients improves cognitive function and metabolic profiles [4, 5].

Scientific evidence for probiotics' therapeutic and preventive potential in AD is growing. Probiotics can affect the central nervous system by generating neuroactive chemicals, reinforcing the intestinal barrier, and altering the immune response. Furthermore, probiotic treatment may lower systemic inflammation, which contributes to neurodegeneration. However, bigger, well-designed randomized controlled studies are needed to show causality and find the best probiotic strains, doses, and therapy durations for AD care [6–10].

This review will examine existing information on the function of probiotics in the prevention and treatment of AD, with a special emphasis on underlying processes and clinical consequences, in order to guide future research and therapeutic options.

Methods

Literature search and study selection [Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow]: A comprehensive literature search was performed across five electronic databases, PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Library, covering publications from January 2000 to July 2025. The search initially retrieved 512 records, of which 112 duplicates were removed. An additional 50 records were automatically excluded based on pre-defined filters for publication date, language (English), and title relevance. Further exclusions for editorials, conference abstracts, and animal-only studies (n = 18) resulted in 332 records screened at the title and abstract level, with 220 excluded for irrelevance. Full texts of 112 reports were sought, with 2 not retrieved, leaving 110 full texts assessed for eligibility. Ultimately, 58 studies were included in the final synthesis, comprising 46 for qualitative analysis and 12 randomized controlled trials (RCTs) for quantitative/meta-analytic synthesis. The PRISMA flowchart (Figure 1) summarizes the study selection process and ensures transparency and reproducibility.

Evidence framework: Included studies were systematically categorized according to study design, sample size, follow-up duration, cognitive outcomes, biomarker outcomes, strength of causality, and risk of bias. RCTs were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, while observational studies were appraised for methodological rigor and strength of association. Observational studies were appraised for methodological structured evidence framework. Table 1 was developed to summarize these dimensions, differentiating between associations derived from observational studies and causal inferences supported by RCTs or mechanistic studies. This framework allowed stratification of evidence strength and facilitated synthesis of probiotic interventions in AD and mild cognitive impairment (MCI).

Data extraction and quality control: Data extraction was independently performed by two researchers to ensure accuracy and consistency, with discrepancies resolved by consensus. Extracted variables included probiotic strains, doses [colony-forming units (CFU)], administration frequency and duration, cognitive outcomes [e.g., mini-mental state examination (MMSE), Montreal Cognitive Assessment (MoCA)],

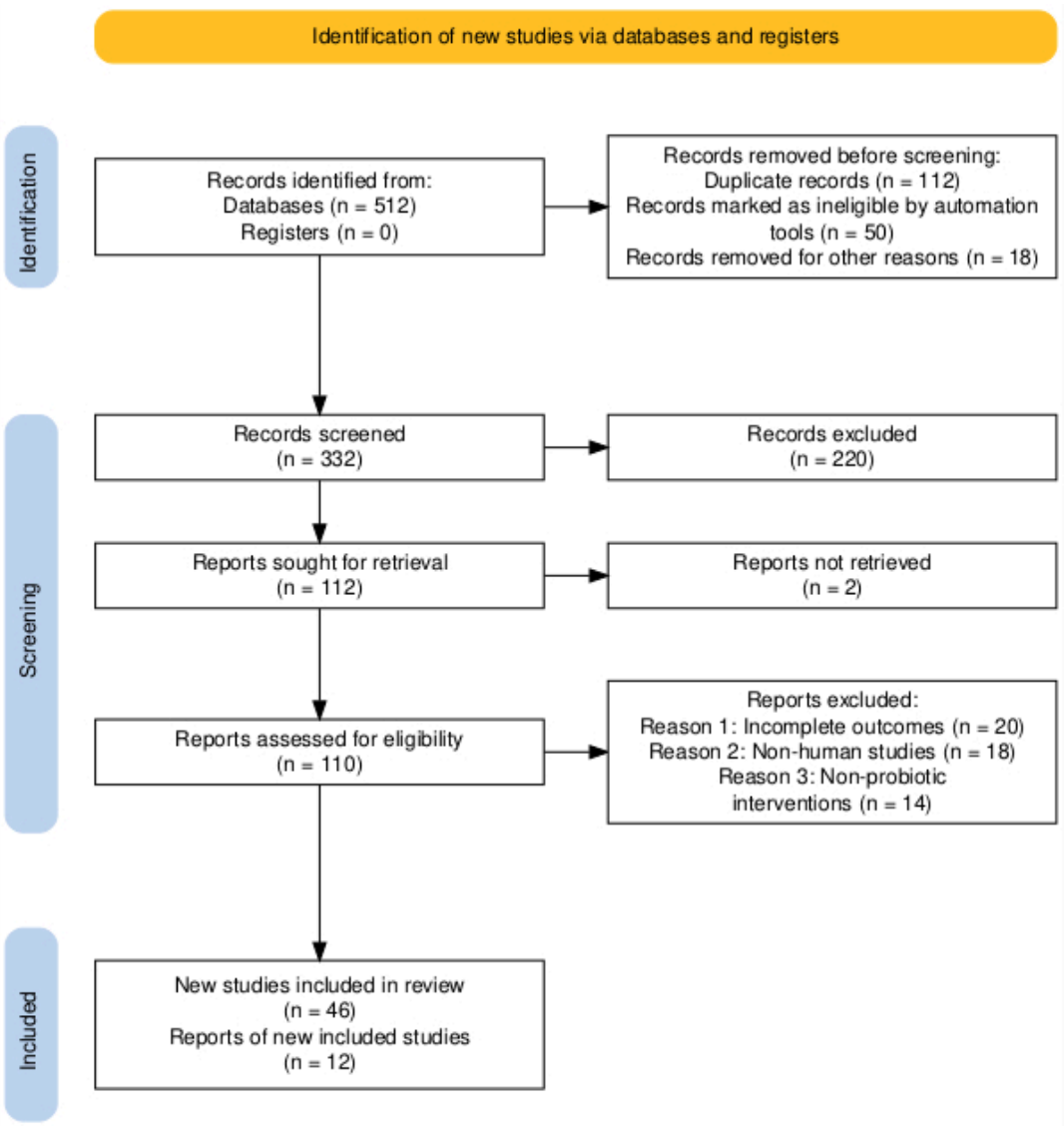

Figure 1. PRISMA flowchart. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses. Taken from https://www.prisma-statement.org/ without modification. Accessed August 30, 2025. © 2024-2025 the PRISMA Executive. Distributed under the terms of the Creative Commons Attribution License (CC BY 4.0).

Table 1. Evidence framework for probiotic interventions in Alzheimer's disease and mild cognitive impairment.

Study (author, year)	Study type	Sample size	Follow-up	Cognitive outcome	Biomarker outcome	Strength of causality
Akbari et al. [3], 2016	RCT	60	12 weeks	↑ MMSE	↓ IL-6	Moderate
Hsu et al. [41], 2024	RCT	80	8 weeks	↑ MoCA	↑ BDNF	Moderate
Akhgarjand et al. [40], 2022	RCT	70	12 weeks	↑ MMSE	↓ TNF-α	Moderate
Guo et al. [1], 2021	Systematic review	N/A	N/A	N/A	N/A	Low
Leblhuber et al. [2], 2018	Cohort	50	24 weeks	Association only	N/A	Low
Tripathi et al. [8], 2024	Meta-analysis	400	Varies	↑ Cognitive domains	↑ BDNF/↓ IL-6	Moderate

RCT: randomized controlled trial; MMSE: mini-mental state examination; IL-6: interleukin-6; MoCA: Montreal Cognitive Assessment; BDNF: brain-derived neurotrophic factor; TNF-α: tumor necrosis factor-alpha.

biomarker outcomes [e.g., brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6)], and follow-up periods. Mechanistic evidence from animal and in vitro studies was incorporated to contextualize clinical findings. Inclusion criteria required studies to assess probiotic interventions in adults with AD or MCI and

report cognitive or relevant biomarker outcomes. Studies were excluded if outcomes were incomplete, interventions were non-probiotic, or they were non-human investigations. This methodology adheres to PRISMA 2020 guidelines, ensuring transparency, reproducibility, and robust classification of clinical evidence.

Discussion

Pathophysiology of AD

The formation of Aβ plaques and neurofibrillary tangles made up of hyperphosphorylated tau protein are the most distinguishing pathogenic hallmarks. Senile plaques are caused by Aβ aggregation, which produces toxic oligomers, protofibrils, and insoluble fibrils. An imbalance in Aβ production and clearance contributes to its deposition, although the specific pathways are unknown. Peptide sequence, concentration, and environmental factors all influence Aβ aggregation [11, 12]. Neurofibrillary tangles form when tau protein is hyperphosphorylated, destabilizing microtubules necessary for intracellular transport. The spread of aberrant tau throughout the brain is related to gradual cognitive deterioration and is used to determine disease severity. Oxidative stress is a major component of AD, with higher reactive oxygen species (ROS) associated with amyloid deposition, tau phosphorylation, lipid peroxidation, and DNA damage. Copper, zinc, and iron interact with Aβ, exacerbating the oxidative damage [5, 13].

Chronic neuroinflammation is another key aspect of AD. Microglial cells, which were originally protective by removing Aβ, become permanently activated, releasing pro-inflammatory cytokines, chemokines, and ROS. This chronic inflammation promotes synaptic dysfunction, tau pathology, and neuronal death. Mutations in immune-regulating genes, including *TREM2* and *CD33*, impair microglial function, worsening amyloid buildup and inflammation. Complement system overactivation contributes to synapse loss [14–16].

Neurodegeneration in AD is characterized by extensive synapse loss, neuronal death, and cerebral atrophy, notably in memory-related brain regions like the hippocampus and cortex. Emerging research links the gut-brain axis to AD etiology. Gut dysbiosis, defined by lower microbial diversity, higher pro-inflammatory bacteria, and fewer beneficial taxa, has been linked to systemic inflammation, amyloid buildup, and neuroinflammation. Bacterial amyloids and endotoxins produced by some gut bacteria can pass the blood-brain barrier, activate microglia, and activate pro-inflammatory pathways such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [17, 18].

This expanding understanding of the intricate interplay between Aβ, tau pathology, oxidative stress, immunological dysregulation, neurodegeneration, and gut microbiota opens up new possibilities for potential therapeutic approaches targeting many pathways in AD [19].

Gut-brain axis: mechanisms and relevance to AD

The gastrointestinal system and brain have a dynamic, two-way communication network that affects important physiological functions like immunity, sleep, and appetite, as illustrated in Figure 2 [20]. The central nervous system, enteric nervous system, immune system, and gut microbiome all interact in complicated ways along the gut-brain axis. In recent years, research has expanded on this paradigm to include the gut microbiome as an important component, resulting in the gut-brain-microbiome axis. Alterations in this axis are increasingly being linked to neurological illnesses, such as AD, where alterations in gut microbiota composition and gut barrier integrity contribute to disease development [21–23].

AD is a neurodegenerative disorder that causes memory loss, cognitive decline, and motor dysfunction. Its pathologies include extracellular Aβ plaques and intracellular neurofibrillary tangles made of hyperphosphorylated tau protein. The disease is caused by complicated molecular processes, including amyloid precursor protein (APP) processing, oxidative stress, calcium dysregulation, and neuroinflammation, which eventually lead to synaptic failure and neuron death [24, 25].

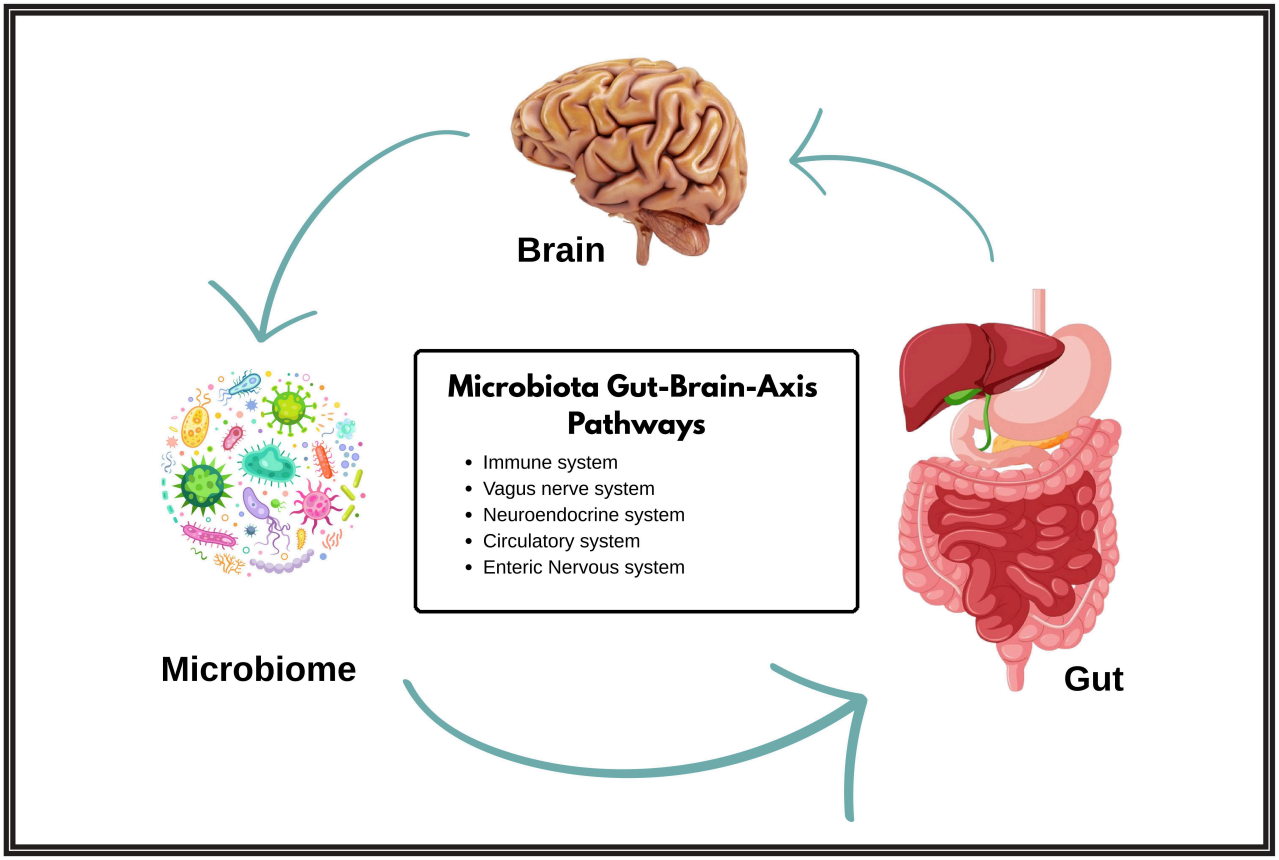

Figure 2. The gut-brain-microbiome axis and its mechanistic links to Alzheimer's disease. Adapted from [20]. © 2023 Yuan, He, Xie, Feng, Gao and Cai. Distributed under the terms of the Creative Commons Attribution License (CC BY). The brain icon: Designed by Freepik (https://www.freepik.com/free-photo/brain-s-side_870197.htm#fromView=keyword&page=1&position=7&uuid=76a18736-54a3-41bd-a26c-a414c611da2e&query=Human+Brain). The digestive system icon: Designed by Freepik (https://www.freepik.com/free-vector/gastrointestinal-tract-anatomy-education_24093235.htm#fromView=keyword&page=1&position=0&uuid=f84534a0-5059-4212-8c6e-254c6532d5bb&query=Intestinal). The microbe icon: Designed by Freepik (https://www.freepik.com/free-vector/pathogen-microorganisms-set_8610271.htm#fromView=search&page=2&position=43&uuid=d1621c36-2a41-4f4f-850a-24d33d9f6b91&query=Microbe).

Emerging research suggests that the gut microbiota influences AD pathogenesis via a variety of methods. Dysbiosis, characterized by an imbalance in bacterial populations such as an increased Firmicutes to Bacteroidetes ratio, can enhance intestine APP buildup and increase Aβ synthesis inside the gut, resulting in central nervous system dysfunction. Intestinal barrier disruption leads to the transfer of bacterial lipopolysaccharides (LPS) and Aβ oligomers into the systemic circulation, prompting neuroinflammatory reactions. Microbial metabolites such as short-chain fatty acids (SCFAs) and trimethylamine *N*-oxide (TMAO) influence amyloid formation, inflammatory signaling, and vascular dysfunction, aggravating AD progression [26–28].

Bacterial gut-derived amyloid proteins can cross-seed with host amyloids, causing pathological aggregation in the brain. Furthermore, bile acids affected by gut microorganisms may disrupt blood-brain barrier integrity, increasing cholesterol buildup and accelerating amyloidogenic protein processing within the brain. The gut microbiota influences central immune function by controlling microglial development and activation. Reduced microbial diversity or changed transmission can compromise the function of microglia, which are responsible for clearing Aβ plaques and maintaining brain homeostasis, leading to persistent neuroinflammation and dementia [5, 29].

Neurotransmitter imbalances in AD are influenced in part by gut microbial synthesis of neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin, dopamine, and noradrenaline. Changes in microbial populations influence neurotransmitter levels, affecting synapse function and cognitive processes. Furthermore, oxidative stress caused by ROS produced during microbial metabolism speeds up brain damage and amyloid disease [7, 16, 30–32].

Probiotics and cognitive function: insights from preclinical studies

Preclinical investigations on the influence of probiotics on cognitive function have yielded important molecular insights into their potential neuroprotective effects. Animal models of AD, aging, and other cognitive deficits have helped researchers understand how probiotics affect neuroinflammation, oxidative stress, synaptic plasticity, and gut-brain axis signaling [7, 33]. Several studies show that probiotic supplementation improves learning and memory in mouse models. Mice given multi-strain probiotics, for example, performed better in maze-based spatial memory tasks, which was linked to less Aβ deposition and neuroinflammation in the hippocampus. Modulating microglial activation and reducing pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and IL-6 are common side effects of these treatments. Furthermore, probiotic supplementation was demonstrated to restore antioxidant enzyme function, such as superoxide dismutase (SOD) and glutathione peroxidase, thereby minimizing oxidative damage to neural tissues [33, 34].

The gut microbiota is critical to these cognitive gains because probiotics help restore microbial balance, increase production of neuroactive metabolites like SCFAs, and control intestinal barrier integrity. Butyrate and other SCFAs have been demonstrated to enhance neurogenesis, inhibit histone deacetylases, and alter microglial function, all of which help to slow neurodegeneration [35, 36]. Emerging data suggest that probiotics alter neurotransmitter systems important for cognition, such as the GABA, serotonin, and dopamine pathways. These neurochemical changes are associated with better synaptic plasticity markers such as BDNF, which is required for learning and memory [36, 37].

Despite promising outcomes, diversity in probiotic strains, doses, and treatment durations makes comparisons between research difficult. Nonetheless, preclinical studies consistently support the concept that probiotics improve brain function in multiple ways, including immunological control, antioxidant effects, and microbiota-gut-brain axis modulation [38, 39].

Future research combining improved molecular approaches with longitudinal animal investigations will help to elucidate mechanisms and develop probiotic formulations for translational uses.

Clinical evidence: probiotics in AD and cognitive impairment

Emerging clinical evidence suggests that probiotics may help manage AD and MCI by improving cognitive function, reducing inflammation, and activating antioxidant systems. Several RCTs and meta-analyses have looked into the effects of probiotic supplementation on these groups, with consistently positive results [3, 40]. Three major RCTs investigated the effects of probiotics on cognitive outcomes in people with AD or MCI. Akbari et al. [3] administered a multi-strain probiotic formulation containing *Lactobacillus acidophilus*, *L. casei*, *Bifidobacterium bifidum*, and *L. fermentum* over a 12-week period and found a significant 27.9% improvement in MMSE scores compared to a 5% decline in controls. Similarly, Akhgarjand et al. [40] investigated *L. rhamnosus* HA-114 or *B. longum* R0175 and found a mean rise of 4.86 points in MMSE scores as well as improvements in instrumental activities of daily living (IADLs). Hsu et al. [41] discovered that a multi-strain probiotic intervention slowed cognitive decline, improved BDNF levels, reduced IL-1β, and increased antioxidant capacity.

Two systematic reviews and meta-analyses provide additional support for these conclusions. Den et al. [42] examined data from 297 AD and MCI patients, finding a moderate but statistically significant cognitive benefit (standardized mean difference = 0.37, $p = 0.002$) as well as reductions in inflammatory markers. Liu et al. [12] conducted a meta-analysis of 386 AD patients, finding improvements in cognitive ability, memory, and everyday functioning after probiotic therapy [42]. Aside from cognitive benefits, probiotic supplementation has been linked to considerable decreases in systemic inflammation, as demonstrated by lower high-sensitivity C-reactive protein (hs-CRP) and oxidative stress indicators such as malondialdehyde. The observed increases in BDNF suggest neuroprotective effects, which could lead to delayed cognitive deterioration [2].

Overall, these trials suggest that probiotics are a safe and well-tolerated supplementary therapy with the potential to improve cognitive performance, reduce neuroinflammation, and improve quality of life in AD and MCI patients. While the current evidence is encouraging, larger and longer-term studies are needed to provide clear clinical recommendations. Kindly refer to Table 2 for a summarized overview of all the studies mentioned here [43–46]. To further clarify strain-specific outcomes, a strain-efficacy mapping is provided in Table 3, readers are suggested to kindly refer to it. Additionally, a risk-of-bias assessment of included RCTs was performed using the Cochrane RoB 2 tool, kindly refer to Table 4.

Table 2. Key clinical studies investigating the cognitive and biological effects of probiotics in Alzheimer's disease and mild cognitive impairment.

Study (author, year)	Study design	Population	Probiotic intervention	Duration	Key cognitive outcomes	Biomarker/other outcomes
Akbari et al. [3], 2016	RCT	60 AD patients	*Lactobacillus acidophilus*, *L. casei*, *Bifidobacterium bifidum*, *L. fermentum* (2 × 10^9 CFU each)	12 weeks	MMSE ↑ 27.9% vs. ↓ 5.03% in controls	hs-CRP ↓ 17.6%, MDA ↓ 22%
Akhgarjand et al. [40], 2022	RCT	70 mild-to-moderate AD patients	*L. rhamnosus* HA-114 or *B. longum* R0175 (10^{15} CFU)	12 weeks	MMSE ↑ by 4.86 points, IADLs improved	No significant change in basic ADLs
Hsu et al. [41], 2024	RCT	Number not specified (AD patients)	Multi-strain probiotics including *Lactobacillus* and *Bifidobacterium* species (5 × 10^7–1 × 10^{10} CFU)	12 weeks	Trend toward reduced cognitive decline	IL-1β ↓, SOD ↑, BDNF ↑ by 36%
Den et al. [42], 2020	Systematic review and meta-analysis	297 AD/MCI patients	Various probiotic interventions across studies	Varied	Significant cognitive improvement (SMD = 0.37, p = 0.002)	Reduction in inflammation (SMD = –0.57)
Liu et al. [56], 2020	Systematic review and meta-analysis	386 AD patients	Various probiotic formulations	Varied	Improved cognitive function, memory, daily functioning	Not specified

RCT: randomized controlled trial; AD: Alzheimer's disease; CFU: colony-forming units; MMSE: mini-mental state examination; hs-CRP: high-sensitivity C-reactive protein; MDA: malondialdehyde; IADLs: instrumental activities of daily living; IL-1β: interleukin-1 beta; SOD: superoxide dismutase; BDNF: brain-derived neurotrophic factor; MCI: mild cognitive impairment; SMD: standardized mean difference.

Table 3. Strain-efficacy mapping of probiotics in Alzheimer's disease and mild cognitive impairment.

Study (author, year)	Strain(s) used	Dose (CFU)	Route & Duration	Cognitive outcomes	Biomarker outcomes
Akbari et al. [3], 2016	*L. acidophilus*, *L. casei*, *B. bifidum*, *L. fermentum*	2 × 10^9 each/day	Oral, 12 weeks	MMSE ↑ 27.9% vs. ↓ 5.03% in controls	hs-CRP ↓, MDA ↓
Akhgarjand et al. [40], 2022	*L. rhamnosus* HA-114 or *B. longum* R0175	10^{15}/day	Oral, 12 weeks	MMSE ↑ by 4.86 points, IADLs improved	No change in basic ADLs
Hsu et al. [41], 2024	Multi-strain *Lactobacillus* + *Bifidobacterium*	5 × 10^7–1 × 10^{10}/day	Oral, 12 weeks	Slowed cognitive decline	IL-1β ↓, SOD ↑, BDNF ↑
Kobayashi et al. [44], 2017	*Bifidobacterium breve* A1	2 × 10^{10}/day	Oral, 12 weeks	Cognitive impairment reduced	Not specified
Agahi et al. [45], 2018	Mixed *Lactobacillus* + *Bifidobacterium* strains	Not specified	Oral, 12 weeks	Mild cognitive improvement (stage-dependent)	Not specified

CFU: colony-forming units; MMSE: mini-mental state examination; hs-CRP: high-sensitivity C-reactive protein; MDA: malondialdehyde; IADLs: instrumental activities of daily living; IL-1β: interleukin-1 beta; SOD: superoxide dismutase; BDNF: brain-derived neurotrophic factor.

Mechanistic pathways underlying the therapeutic role of probiotics in AD

Probiotic therapies are becoming increasingly popular as a holistic therapeutic approach to AD. One important process is the restoration of gut microbial equilibrium. In preclinical (animal) models of AD, beneficial microorganisms (e.g., *Lactobacillus*, *Bifidobacterium*) are typically reduced, while pro-inflammatory strains (e.g., *Escherichia coli*) proliferate. This dysbiosis contributes to increased intestinal permeability, allowing bacterial endotoxins such as LPS to enter the bloodstream and cause systemic and

Table 4. Risk of bias assessment of key randomized controlled trials on probiotics in Alzheimer's disease and mild cognitive impairment (adapted using Cochrane RoB 2 tool).

Study (author, year)	Randomization process	Allocation concealment	Blinding (participants/personnel)	Incomplete outcome data	Selective reporting	Overall risk of bias
Akbari et al. [3], 2016	Low—random sequence generation clearly described	Low—allocation adequately concealed	Low—blinding of participants and personnel ensured	Low—no missing outcome data	Low—all prespecified outcomes reported	Low
Akhgarjand et al. [40], 2022	Low—random sequence generation described	Unclear—allocation concealment not clearly described	Low—blinding reported, method not specified	Low—complete outcome data reported	Unclear—study protocol not available, possible selective reporting	Mostly low, with unclear allocation concealment and potential selective reporting
Hsu et al. [41], 2024	Low—random sequence generation described	Low—allocation adequately concealed	Low—blinding ensured	Low—complete outcome data reported	Low—all prespecified outcomes reported	Low

RoB 2: Risk of Bias 2.

neurological inflammation [47]. Probiotics reduce gut leakiness, lower circulating LPS levels, and modify immunological responses, which reduces microglial activation and cytokine production in the brain. Emerging research demonstrates their diverse involvement in influencing neuroinflammation, oxidative stress, gut integrity, and immunological responses, all of which contribute to improved neurological outcomes, as mentioned in Table 5.

Table 5. Potential mechanisms of action of probiotics in Alzheimer's disease.

Mechanism	Key actions
Reduced neuroinflammation and oxidative stress	↓ Pro-inflammatory cytokines (TNF-α, IL-1, IL-6), ↓ ROS, ↑ SOD, ↓ NF-κB activation
Gut-brain axis modulation	↑ Gut barrier integrity, ↓ LPS translocation, ↓ intestinal inflammation
Boosting neuroactive metabolites	↑ SCFAs (butyrate, propionate), ↓ Aβ deposition, ↑ cognitive performance
Synergistic multifactorial effects	Modulates neuroendocrine, neuroimmune, neurometabolic pathways→↑ memory

TNF-α: tumor necrosis factor-alpha; IL-1: interleukin-1; ROS: reactive oxygen species; SOD: superoxide dismutase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; LPS: lipopolysaccharides; SCFAs: short-chain fatty acids; Aβ: amyloid-beta.

AD is characterized by neuroinflammation and high levels of ILs (IL-1β, IL-6) and TNF-α, which contribute to amyloidogenesis and tau pathology. Probiotic strains affect the immune system by balancing T-helper cell activity and increasing regulatory T cell responses. This reduces NF-κB activation and pro-inflammatory cytokine levels. Furthermore, probiotics may reduce microglial overactivation and astrocytic reactivity, both of which are major causes of neuronal damage. Oxidative stress is another major cause of neuronal damage in AD. ROS are produced as a result of mitochondrial malfunction and inflammation, which impede synaptic plasticity and hasten neurodegeneration. Probiotics activate antioxidant enzymes such as SOD, catalase, and glutathione peroxidase, which help eliminate ROS and maintain redox balance. Certain strains may stimulate mitochondrial biogenesis by activating the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and NRF1 pathways [48–51].

Recent research indicates that probiotics may lower Aβ buildup and tau phosphorylation. They may affect APP processing by altering the activities of β- and γ-secretases. Butyrate, a SCFA generated by gut bacteria, can inhibit GSK-3β, a crucial enzyme involved in tau phosphorylation. Probiotics may lower tau pathology and aid in the removal of misfolded proteins via this mechanism [33, 52–54]. Another important component of probiotic action is the improvement of neurotrophic support. BDNF, which is required for neuronal survival and synaptic function, is typically downregulated in AD. Probiotic supplementation has

been linked to higher BDNF expression and improved synaptic plasticity. For example, Hsu et al. [41] (2024) found that a 12-week probiotic treatment dramatically boosted blood BDNF levels and lowered inflammatory markers in AD patients, resulting in improved cognitive performance [4, 52]. The protein kinase B (AKT)/GSK-3β signaling pathway plays a key function in neuronal survival and tau control. Qian et al. [55] (2024) found that multi-strain probiotics activated AKT signaling and inhibited GSK-3β in senescence-accelerated mouse prone 8 (SAMP8) models, reducing Alzheimer-like disease and improving cognition. These conclusions are confirmed by meta-analytic research. Mo et al.'s [43] (2024) meta-analysis found that probiotic supplementation improved global cognition scores in persons with MCI and AD. This shows that introducing probiotics early in the disease course may be a safe and effective therapy for preventing cognitive loss [33, 41, 43, 54, 55].

Probiotics have neuroprotective effects through a convergence of channels, including lowering neuroinflammation, buffering oxidative stress, improving neurotrophic signaling, and correcting microbial imbalances, making them a promising choice for multimodal AD therapy.

Challenges, limitations, and future directions

Despite promising data for probiotics' efficacy in AD, various difficulties and constraints prevent their clinical use. One important concern is the variety in probiotic strains, doses, and treatment durations employed in different trials, which makes it difficult to draw consistent conclusions or create standard methods. Many clinical trials have small sample numbers and short follow-up periods, which limit our understanding of the long-term safety and efficacy of probiotic therapies [53, 56]. The complexity of the gut-brain axis, as well as individual variances in gut microbiota composition, make it difficult to design targeted probiotic therapy. Variability in patient microbiomes influences treatment outcomes, emphasizing the importance of tailored methods. Furthermore, conventional cognitive testing techniques may be insufficiently sensitive to detect small improvements, particularly in the early stages of AD or MCI [57–59].

Future research should focus on large-scale, well-designed RCTs using standardized probiotic formulations and outcome measurements. Combinations such as synbiotics and postbiotics are being investigated for their potential to boost therapeutic benefits via synergistic processes. Using modern technologies like genomics and metabolomics can assist in elucidating host-microbiome interactions and finding biomarkers that predict therapy response. Exploring probiotics as adjuncts to existing AD treatments has the potential to improve patient outcomes.

Conclusion

AD is a complicated neurodegenerative condition marked by Aβ accumulation, tau hyperphosphorylation, oxidative stress, neuroinflammation, and gradual cognitive impairment. Emerging data suggest that the gut-brain axis plays a significant role in AD pathogenesis, with gut dysbiosis driving systemic inflammation, neuroimmune dysregulation, and neuronal impairment. Probiotics, as living beneficial microorganisms, provide a promising therapeutic and preventive strategy by restoring microbial balance, improving intestinal barrier integrity, producing neuroactive metabolites including SCFAs, and reducing neuroinflammation. Preclinical studies consistently show that probiotic administration improves cognition, lowers oxidative stress, regulates microglial activation, and boosts neurotrophic support in AD models. Early clinical trials, despite their limited breadth and duration, support these findings, with reports of improved cognition scores, lower inflammatory markers, and higher BDNF levels. These findings indicate that probiotics are a safe and effective supplementary therapy for slowing cognitive decline in AD and MCI. However, the variability of probiotic strains, dosages, and treatment regimens, as well as individual differences in gut microbiota, limit generalizability. Future studies should concentrate on large-scale, multicenter, RCTs with standardized interventions and long-term follow-up. Incorporating omics technologies may enable individualized probiotic therapy based on individual microbiome patterns. Overall, probiotics are a novel, multimodal method to halt disease progression, improve cognitive function, and enhance quality of life in AD.

Abbreviations

AD: Alzheimer's disease

AKT: protein kinase B

APP: amyloid precursor protein

Aβ: amyloid-beta

BDNF: brain-derived neurotrophic factor

GABA: gamma-aminobutyric acid

IL-6: interleukin-6

LPS: lipopolysaccharides

MCI: mild cognitive impairment

MMSE: mini-mental state examination

NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

RCTs: randomized controlled trials

RoB 2: Risk of Bias 2

ROS: reactive oxygen species

SCFAs: short-chain fatty acids

SOD: superoxide dismutase

TNF-α: tumor necrosis factor-alpha

Declarations

Author contributions

AAS: Conceptualization, Investigation, Data curation, Writing—original draft. HSW: Conceptualization, Supervision, Writing—review & editing, Methodology. AP: Investigation, Writing—original draft, Writing—review & editing. ST: Data curation, Writing—review & editing. BS: Data curation, Writing—review & editing. NN: Investigation, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

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Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

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