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Editorial Article

Probiotics as adjunctive therapy for Alzheimer disease

Olia Hamzeh [1,2], and Mehrdad Halaji [3*]

[1] Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R. Iran
[2] Department of Clinical Biochemistry, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
[3] Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R. Iran

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*** Corresponding Author:**
Dr. Mehrdad Halaji (Ph.D)

E-mail:
Mehrdad.md69@gmail.com
Tel: +989393043764
Postal Code: 1449614535

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Abstract

Probiotics have attracted interest as potential adjunctive interventions for Alzheimer's disease (AD) through their effects on the microbiota–gut–brain axis. This letter critically examines the translational relevance of experimental and clinical evidence, emphasizing the distinction between biological activity and therapeutic efficacy. Preclinical studies report improvements in cognition, neuroinflammation, oxidative stress, and barrier integrity; however, prophylactic administration and differences between aging models and AD limit clinical extrapolation. Human trials yield inconsistent findings, with some reporting cognitive improvement and others demonstrating biomarker changes without significant cognitive or functional benefit. Variation in disease severity, strain composition, comparator selection, and methodological quality complicates interpretation. Current evidence does not establish a generalizable therapeutic effect or sustained disease modification. Adequately powered, multicenter trials should evaluate defined probiotic preparations alongside standard care, prioritize cognitive and functional outcomes, and assess safety and durability. Integrating longitudinal microbiome and metabolomic analyses may clarify mechanisms and identify patients most likely to benefit.

Keywords: Alzheimer's disease, Probiotics, Microbiota–gut–brain axis, Neuroinflammation, Cognitive function

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Introduction

The involvement of the gut microbiota in Alzheimer's disease (AD) has prompted considerable interest in probiotics as a potential adjunct to pharmacological treatment. Recent literature describe several mechanisms through which microbial interventions may influence neuroinflammation, oxidative injury, and synaptic function [1, 2]. Translating these observations into a therapeutic strategy, however, requires closer examination of the clinical evidence. Although some trials have reported cognitive improvement, others have demonstrated biochemical changes without corresponding functional benefit. This discrepancy deserves particular attention when considering whether probiotic supplementation can appreciably alter the course of AD.

Much of the rationale for probiotic therapy derives from interactions among intestinal permeability, microbial metabolites, and host immune responses. Disruption of these processes may contribute to systemic inflammation, blood–brain barrier dysfunction, and glial activation. Accordingly, attenuation of inflammatory signaling and reinforcement of endogenous antioxidant defenses have emerged as candidate mechanisms of probiotic action [1, 2]. These findings are relevant to AD pathophysiology, but their interpretation requires caution. Changes in circulating cytokines or brain-derived neurotrophic factor (BDNF) indicate biological activity; they do not, by themselves, establish neuronal preservation or clinically remarkable cognitive improvement. Similarly, alterations in microbial abundance require corroboration through functional and metabolic analyses.

Experimental studies nevertheless provide useful grounds for further investigation. Prajapati et al. administered a human-origin cocktail comprising ten Lactobacillus and Enterococcus strains to APP/PS1 mice for 16 weeks [3]. Supplementation improved spatial learning and attenuated amyloid accumulation and neuroinflammatory measures, with accompanying changes in intestinal permeability and barrier-associated markers. The observation of sex-dependent responses is also relevant to subsequent study design. Because administration began in young mice before substantial pathology had developed, these results primarily concern prophylaxis or early intervention. Whether comparable effects can be achieved after the onset of established cognitive impairment remains to be determined.

Related evidence was reported by Hamzeh et al. who investigated Lactobacillus casei and *Bifidobacterium breve*, separately and in combination, during eight weeks of D-galactose exposure [4]. Improvements in working memory and selected hippocampal indices of inflammation, oxidative stress, and neuroprotection support further exploration of these strains. The findings should, however, be situated within the context of experimentally induced aging rather than interpreted as direct evidence of efficacy in AD. Concurrent probiotic administration also limits conclusions regarding treatment of established disease. Although the combined preparation performed favorably on several endpoints, the pattern of results does not establish pharmacological synergy.

Clinical findings are less consistent. In a randomized, double-blind trial of 90 patients with mild or moderate AD, Akhgarjand et al. reported improvements in Mini-Mental State Examination scores (MMSE) after 12 weeks of *Lactobacillus rhamnosus* HA-114 or *Bifidobacterium longum* R0175 supplementation relative to placebo [5]. No statistically significant difference was observed between the probiotic groups. By contrast, Agahi et al. found no significant cognitive benefit following a multistrain intervention in a 12-week trial with 48 analyzed participants, most of whom had severe AD [6]. Disease stage may partly account for these divergent findings, although differences in formulation, outcome assessment, and participant characteristics preclude attributing the discrepancy to severity alone.

The trial by Hsu et al. further illustrates the difficulty of interpreting biomarker responses as therapeutic efficacy [7]. Forty patients were randomized to higher-dose or lower-dose formulations of the same five-strain preparation; 32 completed the 12-week intervention. Improvements in serum BDNF and selected inflammatory and antioxidant measures were not accompanied by significant differences in cognitive or functional outcomes. Moreover, the use of an active comparator means that the study examined differences between probiotic doses rather than efficacy relative to an inert placebo. These results support biological activity, but leave the clinical relevance of that activity unresolved. Selected studies are summarized in Table 1.

The interpretation of this literature also depends on the integrity and applicability of the underlying evidence. Findings in cognitively healthy older adults or individuals with mild cognitive impairment cannot be extrapolated directly to patients with established AD. Multiple reports arising from the same trial should be identified to avoid overestimating the extent of independent replication. Publication notices warrant similar scrutiny: the frequently cited trial by Akbari et al. received an editorial expression of concern regarding the validity of participant data [8]. Its findings therefore require explicit qualification when incorporated into narrative syntheses or quantitative estimates of treatment efficacy.

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Greater methodological consistency would help clarify the circumstances under which probiotics might confer benefit. Studies should specify strain identity, viable counts at administration, storage conditions, formulation stability, and adherence. Claims of superiority for multistrain products require direct comparisons with their individual components, while proposed synergistic effects require appropriate interaction analyses. Synbiotic interventions introduce an additional substrate and should be evaluated separately when attributing treatment effects [9]. Diet, antibiotic exposure, bowel function, comorbidities, and concomitant medication also merit documentation. Baseline microbiome profiles and sex may inform prespecified analyses of treatment heterogeneity, provided that such analyses are supported by an adequate sample size.

For clinical translation, adequately powered multicenter trials should recruit well-characterized AD populations and incorporate biomarker confirmation where feasible. Stratification by disease stage would permit a more informative assessment of the therapeutic window. Supplementation should be evaluated alongside stable standard care, using matched placebo controls and sufficiently prolonged follow-up. Prespecified cognitive and functional outcomes should remain central, with caregiver-relevant measures providing complementary information. Safety assessments should document tolerability, discontinuation, and clinically relevant infections, particularly in frail participants. Intention-to-treat analyses, confidence intervals, and appropriate adjustment for multiple comparisons would strengthen interpretation. Longitudinal microbial and metabolomic measurements could then examine whether biological responses precede and mediate clinical improvement, while post-treatment assessments could establish the persistence of any benefit. Such studies should also distinguish symptomatic improvement from disease modification.

Available evidence supports continued investigation of probiotics as adjunctive interventions in AD, but does not yet establish a generalizable therapeutic effect or sustained disease modification [1, 5-7]. The priority is to determine which preparations, if any, benefit a defined patient population and whether the observed effects extend beyond laboratory measures to cognition and everyday functioning. Resolving these questions would provide a firmer basis for clinical use and allow mechanistic observations to inform treatment development without exceeding what the current evidence can substantiate.

Table 1: Selected original studies and their relevance to probiotic therapy in Alzheimer disease

Study	Population and duration	Intervention and comparator	Main finding	Interpretation
Akhgarjand et al. [5]	Mild/moderate AD; 90 randomized; 12 weeks	*L. rhamnosus* HA-114 or *B. longum* R0175 vs placebo	MMSE improved vs placebo; no significant difference between strains	Short-term cognitive signal; durability untested
Agahi et al. [6]	Predominantly severe AD; 48 analyzed; 12 weeks	Six-species probiotic blend vs. placebo	No significant cognitive benefit on TYM	Severity alone cannot explain differences across trials
Hsu et al. [7]	AD; 40 randomized, 32 completed; 12 weeks	Five-strain blend: 10^{10} vs. 5×10^{7} CFU/day	Selected biomarkers improved; cognition/function not significantly different	Active comparator; biological response is not clinical efficacy
Prajapati et al. [3]	APP/PS1 mice; 40 animals; 16 weeks	Ten-strain probiotic cocktail vs. vehicle	Improved learning and selected amyloid, inflammatory and barrier measures	Early prophylactic intervention; animal evidence
Hamzeh et al. [4]	D-galactose aging mice; 40 animals; 8 weeks	*L. casei*, *B. breve*, or both, during D-galactose exposure	Working memory and selected hippocampal measures improved	Indirect aging evidence; no AD-specific efficacy demonstrated

AD, Alzheimer disease; BDNF, brain-derived neurotrophic factor; CFU, colony-forming units; MMSE, Mini-Mental State Examination; TYM, Test Your Memory. Sample sizes describe the full study or analyzed human cohort; animal endpoint subsamples may be smaller. This is a selected evidence summary, not a systematic inventory

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Conflict of Interests

The authors declare no conflict of interest related to this study.

Author's contribution

All authors contributed to the conception and design of the study, data collection, data analysis, interpretation of the results, and preparation and revision of the manuscript. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Ethics statement

None

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