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REVIEW

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The effects of probiotic supplementation on cerebral cognitive function: a systematic review

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Abstract

Background Alzheimer's disease (AD) stands as a formidable challenge within the realm of neurodegenerative disorders, characterized by its inexorable progression and the profound cognitive impairments it engenders. Despite decades of research, the management of AD remains in a conundrum, with currently available treatments offering only modest symptomatic relief and none that can definitively alter the course of the disease.

Objective This investigation seeks to provide a concise overview of the influence of probiotics on the cognitive aspects of AD, drawing upon a compilation of conducted studies.

Methods The study was conducted by means of comprehensive searches in MEDLINE, Pubmed, and Google Scholar databases spanning from January 2015 to December 2020. The composition of this review adhered to the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The evaluation of eligibility criteria was guided by the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework, a methodology that was systematically applied to each identified research entry.

Results Upon the implementation of the search protocol, a total of five articles that satisfied the predetermined inclusion criteria were incorporated into this review. Among these, four encompassed randomized controlled trials (RCTs), while the fifth pertained to an explorative interventional study. AD stands as a progressive neurodegenerative affliction of considerable clinical import. Through the assessment of diverse investigations, compelling evidence has emerged affirming that probiotic microorganisms, acting via the intricate gut–brain axis signaling pathway, harbor the capacity to ameliorate cognitive function in AD. The collective findings across all the studies unequivocally indicate a notable enhancement in cognitive function subsequent to the administration of probiotic supplementation ($p < 0.05$). While not all domains of cognitive function exhibit amelioration in response to probiotic supplementation, the consideration of incorporating probiotics within the therapeutic schema for AD warrants deliberation as a strategy to enhance cognitive performance.

Conclusion Despite the intricate pathophysiology of AD, probiotic supplementation exerts a discernible influence on cognitive well-being. Notably, the symbiotic interplay between the gut and the brain, elucidated through the intricate gut–brain axis, emerges as a conduit through which probiotics could potentially modulate cognitive function.

Keywords Alzheimer's disease, Cognitive function, Probiotic

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Introduction

Alzheimer's disease (AD) represents a progressive neurodegenerative disorder characterized by a profound deterioration in cognitive function and overall quality of life. This ailment stands as one of the most prevalent neurodegenerative conditions globally, encompassing over 80% of dementia cases among the elderly population [1]. The demographic of individuals afflicted by AD, those aged 65 years or older, comprises approximately 5 million individuals. Projections indicate that by the year 2050, a new case of AD will emerge every 33 s, contributing to an anticipated total prevalence of 13.8 million cases [2]. Current therapeutic interventions for AD predominantly focus on symptom delay rather than disease modification. Extensive endeavors have been undertaken to identify disease-altering therapies capable of arresting the progression of clinical manifestations, targeting an array of molecular pathways [1].

Numerous investigations conducted on animal models have underscored the significance of an optimal functioning of the gut–brain axis in influencing behavioral and electrophysiological aspects of cerebral activity [3]. The intricate interplay between gut microbiota and the central nervous system has garnered attention, particularly due to the capacity of gut microorganisms to generate short-chain fatty acids from complex dietary carbohydrates, a process integral to intestinal and blood–brain barrier integrity. Furthermore, these microorganisms contribute to the synthesis of neurotransmitters and precursors, including γ-aminobutyric acid (GABA), noradrenaline, and tryptophan [4]. The gastrointestinal tract, in tandem with its commensal microbiota, has been extensively studied for its regulatory role in inflammatory response and neuromodulation mechanisms, as well as immunity regulation [4]. Intriguingly, the gut microbiota serves as a source of amyloid protein, pivotal for bacterial cell aggregation in the form of biofilms to evade immune factors [5]. Despite dissimilar primary structures, the tertiary structure of gut amyloid parallels that of brain amyloid [5]. Notably, exposure to bacterial amyloid proteins within the gut milieu may prime the immune system, potentially augmenting the immune response to endogenously produced neuronal amyloid in the brain [5].

A multitude of investigations have revealed promising outcomes pertaining to cognitive function enhancement in AD through the supplementation of probiotics. According to the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO) in 2001, probiotics are characterized as live microorganisms that, when administered in adequate quantities, provide a health advantage to the host [6, 7]. In recent times, there has been substantial progress in the domain of probiotics, fueled by worldwide advancements in grasping the function of the human microbiome in health and illness, along with the necessity to devise effective methods for enhancing a healthier microbiome [7]. This review seeks to elaborate the impacts of probiotics on the cognitive function of AD patients, drawing upon the findings evaluated from conducted studies in this field.

Methods

Literature search and criteria screening

A comprehensive literature search was conducted across various databases, including Medline, PubMed Central, and Google Scholar, spanning from January 2015 to December 2020. The search strategy employed the combination of relevant keyword [('Alzheimer Disease') AND (Probiotics) AND (Cognitive Function)]. This inquiry yielded an initial of 8,503 articles. Subsequently, a meticulous procedure was undertaken to eliminate duplicate entries and screen the identified studies for adherence to the predetermined inclusion criteria. As a result of this rigorous process, a total of 8024 articles were excluded from consideration. The PICOS model was systematically applied to evaluate the eligibility of each study across the databases. The compilation of this review adhered to the guidelines outlined by the PRISMA statement. Systematic reviews and meta-analyses were specifically excluded from this review. The inclusion criteria focused solely on English-language publications involving human subjects, including clinical trials such as randomized controlled trials (RCTs) and cohort studies. The inclusion of clinical trials focusing on cognitive function in older adults, rather than specifically on Alzheimer's disease, is justified by the shared manifestation of cognitive decline in both contexts. Due to the limited studies directly addressing probiotics' impact on Alzheimer's, the systematic review broadened its scope to encompass cognitive decline in older adults. This approach aims to gather comprehensive insights into probiotics' potential benefits in mitigating cognitive impairment, including that associated with Alzheimer's disease. The diagrammatic representation of this systematic selection process, in accordance with the PRISMA statement, is depicted in Fig. 1.

Results

Search result and studies selection

Upon the application of the established search methodology, a total of 5 articles that satisfactorily met the predetermined eligibility criteria for this systematic review were included for comprehensive analysis. Among these selected articles, 4 encompass RCTs, while the remaining article represents an explorative interventional study. It is noteworthy that all the RCTs adopted a double-blind methodology, wherein the effect of probiotic

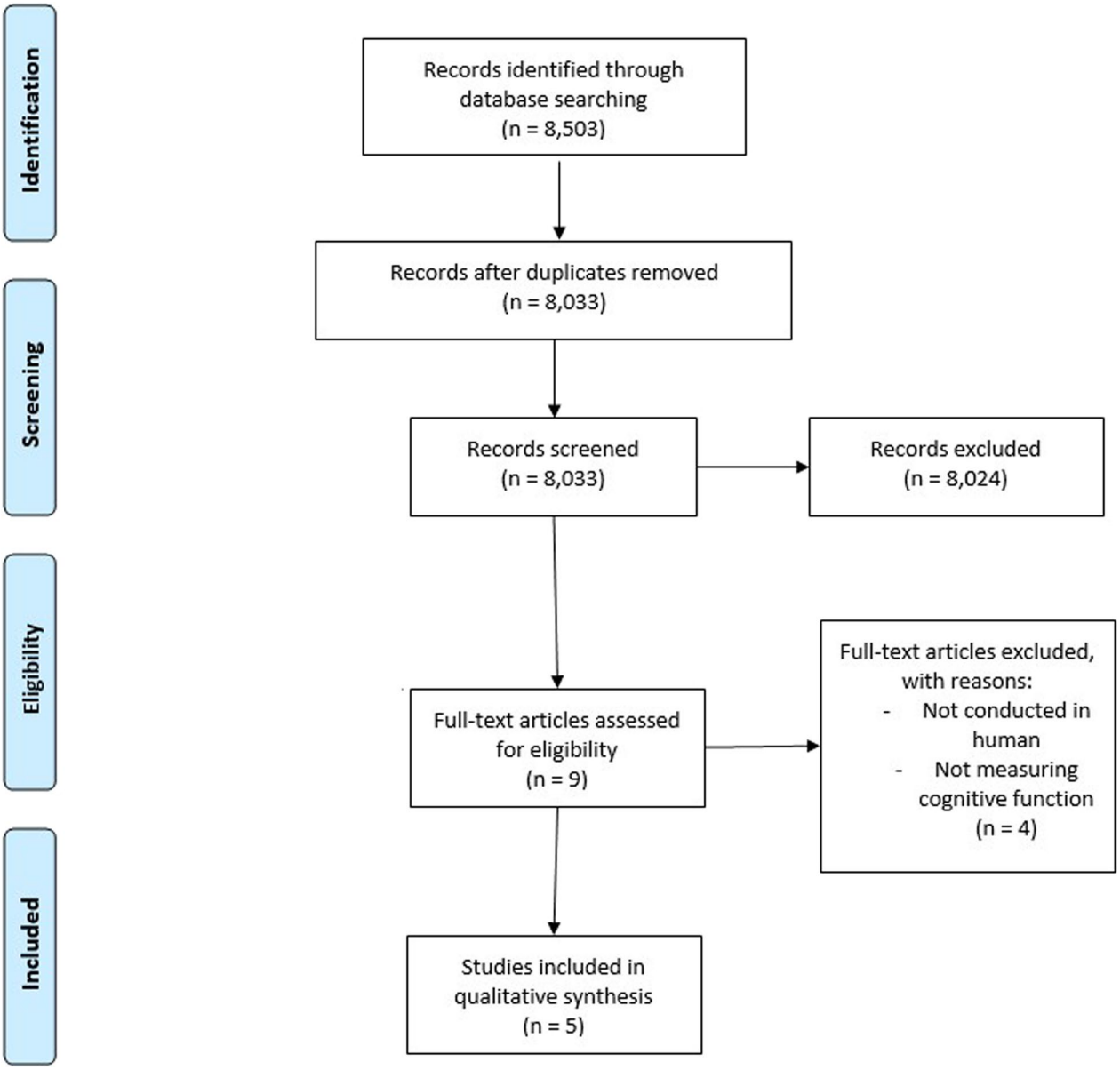

Fig. 1 Flow diagram of the stages of study selection for the systematic review

supplementation was juxtaposed against that of a placebo. In alignment with the primary objective, each of these articles focused on individuals afflicted by AD, investigating the alterations in cognitive function following the administration of probiotic supplementation. Multiple cognitive assessment tools were employed across the examined studies to meticulously gauge the cognitive changes pre- and post-probiotic intervention. The comprehensive compilation of the extracted data from each study is meticulously presented within Table 1. Moreover, in pursuit of enhanced clarity, the outcomes pertaining to the placebo and probiotic groups within each study shall be distinctly represented in separate tables.

Probiotic supplementation effect on cognitive function

According to the information derived from Table 1, the cognitive function evaluation methodologies employed across the five studies exhibited considerable diversity. Specifically, two of the studies employed the Mini-Mental State Examination (MMSE) as the tool of cognitive assessment, whereas the Rivermead Behavioral Memory Test (RBANS), Consortium to Establish a Registry for Alzheimer's Disease-Korean Version (CERAD-K), and

Table 1 Extracted data of each study

Author	Time of study	Study design	Number of patients	Probiotic supplementation method	Probiotic supplementation preparation	Probiotic microbes	Cognitive assessment tool
Akbari et al	December 2015–February 2016	Randomized control trial, double-blind	60 patients	Each group take milk (placebo) or milk containing a mixture of probiotics for 12 weeks	Milk containing a mixture of probiotics	*L. acidophilus* *L. casei* *B. bifidum* *L. fermentum*	Mini-Mental State Examination (MMSE)
Hwang et al	2019	A randomized clinical trial, double-blind, placebo-controlled	100 patients	DW2009 orally intake of 2 capsules once a day for 12 weeks	DW2009 capsule (a combination of fermented soybean powder and *L. plantarum* C29 freeze-dried powder)	*L. plantarum* C29	Verbal Learning Test (VLT); Auditory Continuous Performance Test (ACPT); Digit Span Test (DST)
Leblhuber et al	October 2017–February 2018	An explorative intervention study	20 patients	Aqueous suspension of probiotic administered daily in the morning before breakfast for 28 days	Aqueous suspension of probiotic	*L. acidophilus* W22 *L. casei* W56 *Lactococcus lactis* W19 *L. paracasei* W20 *L. plantarum* W62 *L. salivarius* W24 *B. bifidum* W23 *B. lactis* W51 *B. lactis* W52	Mini-Mental State Examination (MMSE)
Xiao et al	2020	Randomized control trial, double-blind, placebo-controlled	79 patients	2 probiotics or placebo capsules/day for 16 weeks	lyophilized powder of *B. breve* A1 (capsule)	*B. breve* A1	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
Kim et al	March 2018–March 2019	Randomized clinical trial, double-blind, placebo-controlled	63 patients	2 probiotic capsules after meal every morning and evening (4 capsules/day) for 12 weeks (week 0, week 4, week 8, and week 12)	Probiotics capsule	*B. bifidum* BGN4 *B. longum* BORI	Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K)

a computerized neurocognitive function test were each employed in a single study for this purpose. In terms of the mode of probiotic administration, notable heterogeneity was observed. Notably, three out of the five studies, specifically those conducted by Hwang et al., Xiao et al., and Kim et al., employed capsule formulations as the vehicle for probiotic supplementation. In contrast, Akbari et al. opted for a milk-based delivery medium, while Leblhuber et al. chose an aqueous suspension for the administration of probiotics. All five studies underscored the utilization of probiotics sourced from the *Lactobacillus* and *Bifidobacterium* genus; however specific species exhibited variations between the studies.

Kim et al. conducted a comprehensive cognitive evaluation for each participant utilizing the CERAD-K. The CERAD-K serves as a validated cognitive assessment battery that meticulously gauges diverse cognitive domains encompassing language, memory, visuospatial processing, and attention/executive functions, thereby providing a holistic understanding of cognitive performance [8]. In Table 2, the outcomes of this assessment are described, contrasting the discerned results between the control and probiotic groups. Across all cognitive domains, incremental improvements were observed in participants receiving probiotic supplementation relative to their counterparts in the control group. Nevertheless, the degree of significance within these enhancements was not uniformly robust across the various cognitive domains. Notably, mental flexibility emerged as a cognitive facet that exhibited notable improvement upon the completion of the 12-week trial period within the probiotic group, thereby signifying statistical significance in comparison to the control group ($p < 0.05$)[8].

Akbari et al. and Leblhuber et al. evaluated patients' cognitive function by means of MMSE test (Table 3). The discernment of the probiotic group's cognitive function in Akbari et al.'s study revealed a notable and statistically significant enhancement ($p < 0.001$), an improvement that became manifest after a rigorous 12-week intervention period [3]. Corroborating this positive trend, Leblhuber et al. similarly demonstrated a remarkable and statistically significant amelioration in cognitive function within the probiotic cohort, as deduced from the MMSE scores ($p < 0.001$) [4].

Hwang et al. evaluated patients' cognitive function using computerized neurocognitive function tests,

Table 2 CERAD-K score of Kim et al. study. [8]

	Control group (placebo)		*p*-value	Probiotic group		*p*-value
	Baseline	End-of-trial		Baseline	End-of trial	
Language function						
Verbal fluency	14.96	16.88	0.01	14.44	15.41	0.39
Naming	11.69	12.23	0.28	12.15	12.96	0.23
Memory function						
Word list encoding	18.92	22.23	< 0.001	18.26	22.22	0.47
Word list recall	6.38	7.54	0.01	6.19	7.52	0.68
Word list savings	83.83	92.21	0.13	84.68	89.30	0.71
Word list recognition	8.77	9.23	0.09	9.22	9.63	0.88
Visuospatial processing function						
Constructional praxis	10.04	10.27	0.36	10.00	10.52	0.74
Executive Function and Attention						
Trail making A	61.88	47.35	< 0.001	47.33	46.22	0.21
Trail making B	189.69	161.19	0.15	172.59	131.11	0.39
Mental flexibility	2.15	2.52	0.48	2.72	2.08	0.03
Digit span test	13.35	13.65	0.59	13.41	14.59	0.16

Table 3 MMSE score of Akbari et al. and Leblhuber et al. studies. [3, 4]

	Control group		Probiotic group		*p*-value
	Baseline	End-of-trial	Baseline	End-of-trial	
Akbari and colleagues	8.47	8.00	8.67	10.57	< 0.001
Leblhuber and colleagues	No control group		17.9	18.5	< 0.001

which test for working memory, verbal memory function, and attention. The probiotic group exhibited a marked and statistically significant elevation in cognitive performance compared to the control cohort, as evidenced by the end of the trial (Table 4) [9]. The probiotic group showed a more significant improvement in the combined cognitive function in contrast to their control counterparts ($p < 0.02$) [9]. This effect is especially pronounced within the context of the attention composite score change, where the alterations observed with statistical significance ($p < 0.02$), encompassing the entirety of the domain composite scores examined [9].

Table 5 presents the comprehensive neuropsychological assessment outcomes obtained at both the baseline and the culmination of the 16-week trial period, subsequent to the administration of either probiotic supplementation or placebo. The total score showed a significant improvement in cognitive function in the probiotic group compared to the control group ($p < 0.0001$) [10]. Of particular prominence are the domains of immediate memory, visuospatial/constructional abilities, and delayed memory, which exhibit marked improvements subsequent to probiotic supplementation ($p < 0.0001$). Furthermore, while the language and attention domains evince improvements in the RBANS score post-probiotic administration, these advancements, regrettably, do not attain the threshold of statistical significance, as denoted by p-values of 0.085 and 0.67, respectively.

Risk of bias of the studies

The impartiality of scientific publications is inherently susceptible to various forms of bias. In our comprehensive analysis, we conscientiously evaluated the potential sources of bias, encompassing aspects such as selection bias, performance bias, detection bias, attrition bias, reporting bias, and other inherent forms of bias in each included study. This evaluation adhered rigorously to the Cochrane Risk of Bias Assessment Tool, which provides a robust framework for such assessments. To provide a concise overview, the forthcoming Table 6 will summarize the identified sources of bias, offering valuable insights into the limitations and strengths inherent in the studies under review.

Discussion

Based on the findings extracted from this systematic review, it becomes evident that probiotic supplementation emerges as a viable intervention with the capacity to effectively ameliorate cognitive function in AD patients. Among the array of microbial strains harnessed within the five encompassed studies, *Lactobacillus* strains included *L. acidophilus*, *L. casei*, *L. fermentum*, *L. plantarum*, *L. salivarius*, and *L. lactis*. Complementing this, *Bifidobacterium* strains comprised *B. bifidum*, *B. lactis*, *B. breve*, and *B. longum*. The integration of these diverse *Lactobacillus* and *Bifidobacterium* strains in the probiotic interventions underpins the investigation's therapeutic framework. A substantial body of research has

Table 4 Hwang et al. study composite scores of attention, working memory, and verbal memory function measured by the computerized neurocognitive function tests [9]

Domain composite score	Control group (placebo)		Probiotic group (DW2009)		*p*-value
	Baseline	End-of-trial	Baseline	End-of-trial	
Attention/prefrontal function	0.00	0.15	(−0.54)	(−0.09)	0.02
Working memory function	0.00	0.02	0.02	0.11	0.53
Verbal memory function	0.00	0.58	(−0.28)	(0.52	0.21
Combined cognitive function	0.01	0.25	(−0.27)	0.18	0.02

Table 5 Results of RBANS total score of Xiao et al. study [10]

	Control group (placebo)		Probiotic group		95%CI	*p*-value (comparison)
	Baseline	End-of-trial	Baseline	End-of-trial		
Total score	32.4	38.3	30.4	48.0	11.5 (6.9–16.1)	< 0.0001
Immediate memory	36.4	38.7	36.9	48.5	9.5 (5.4–13.6)	< 0.0001
Visuospatial/constructional	34.4	35.8	32.0	46.0	11.3 (6.6–15.9)	< 0.0001
Language	47.3	50.1	49.8	53.9	3.2 (−0.5–6.9)	0.085
Attention	49.2	52.3	45.6	51.1	0.7 (−2.6–4.0)	0.67
Delayed memory	31.1	34.6	31.3	45.9	11.1 (6.6–15.5)	< 0.0001

Table 6 Risk of bias of the studies

Studies	Selection bias		Performance bias (blinding of participants and personnel)	Detection bias (blinding of outcome assessment)	Attrition bias (Incomplete outcome data)	Reporting bias (Selective reporting)	Other bias
	Random sequence generation	Allocation concealment					
Akbari et al.	+	+	+	+	+	+	–
Hwang et al.	+	+	–	–	+	+	?
Leblhuber et al.	–	–	–	–	+	+	?
Xiao et al.	+	+	+	+	–	+	?
Kim et al.	+	+	–	–	+	+	?

+= Low risk of bias– = High risk of bias?= unknown/unclear risk of bias

extensively investigated the profound impact of probiotics, predominantly encompassing strains from the *Lactobacillus* and *Bifidobacterium* groups, on the reinforcement of intestinal barrier integrity. This effect is notably attributed to the augmentation of tight junction proteins' expression, thereby contributing to the preservation of the intestinal barrier's structural integrity [5]. The study conducted by Akbari et al. yielded findings of cognitive function improvements among patients subjected to probiotic intervention. Notably, the improvement in cognitive function was evidenced through the alteration in MMSE scores within the probiotic-treated cohort [3]. Microbiome is known to play an essential role in synaptic transmission [3]. Several studies have shown that gut microbiota could produce neuromodulators and neurotransmitters, including GABA, serotonin, dopamine, norepinephrine, and acetylcholine [3, 5]. GABA, the principal inhibitory neurotransmitter within the central nervous system (CNS), plays a pivotal role in modulating neural activity. Dysregulations in GABAergic signaling have been interlinked with a spectrum of neuropsychiatric implications including anxiety, depression, and cognitive deficits [3]. A study by Leblhuber et al. also showed improvements in cognitive function. Their research reported connections between discrete biomarkers indicative of immune activation and inflammation in individuals afflicted by cognitive impairment, and the intricate compositional makeup of the gut microbiome [4].

Hwang et al. administered DW2009 orally, which has been substantiated to yield enhancements in cognitive capabilities. The probiotic-treated group demonstrated substantial cognitive amelioration, particularly within the domain of attention [9]. Similarly, the study conducted by Xiao et al. unveiled cognitive enhancements as indicated by the RBANS score following a 16-week regimen of probiotic intervention. The findings accentuate the potential of RBANS as a valuable and responsive neuropsychological assessment tool, particularly for evaluating the primary impacts of probiotics on memory functions and the efficacy of specific probiotic strains in enhancing memory-related capacities [10].

A growing body of empirical evidence has underscored the notable impact of probiotics on cerebral functions, largely attributed to their regulatory role within the gut–brain axis, particularly discernible in individuals beset by cognitive impairments such as AD and mild cognitive impairment (MCI) [8]. In this context, the principal focus of this review resides in patients afflicted by AD, a population with inherent vulnerability to a spectrum of complications encompassing augmented oxidative stress, microvascular pathology, insulin resistance, dyslipidemia, and heightened mortality [3]. The discernments drawn from these studies collectively underscore the substantial impact of probiotics on the intricate interplay of the gut–brain axis within individuals afflicted by AD. Central to this phenomenon is the gut–brain axis, a bidirectional conduit facilitating unceasing communication between the central enteric nervous system (ENS), a neural network orchestrating gastrointestinal function, and the CNS. This intricate communication mechanism encompasses an array of processes, including endocrine and metabolic signaling, as well as immune and neural interactions [5]. The ENS holds the capacity to function autonomously or respond to CNS influences through the mediation of sympathetic signaling (via the prevertebral ganglia) and parasympathetic signaling (via the vagal nerve) [5].

Researches have indicated that numerous bacteria within the gut microbiota have the capability to generate substantial quantities of monomeric soluble lipopolysaccharide (LPS) and amyloid beta (Aβ), which could potentially modulate signaling pathways influencing the host immune and nervous systems [11, 12]. Should there be any compromise in intestinal barrier integrity, it could result in the activation of immune cells via the interaction between LPS derived from gut bacteria and the toll-like receptor 4 (TLR4) signaling pathway. Over time, the

soluble form of Aβ may undergo polymerization, forming insoluble fibrous protein aggregates that could contribute to the pathogenic processes of AD [13]. The observed improvements in cognitive performance following probiotic supplementation underscore the multifaceted nature of the gut–brain axis and its role in modulating cognitive processes. Probiotics, through their influence on gut microbial composition and activity, have demonstrated the capacity to impact neurotransmitter systems, attenuate neuroinflammation, and enhance neuroplasticity [14]. Probiotic strains have been shown to produce neurotransmitters or precursor molecules, thereby influencing neurotransmitter synthesis and release within the central nervous system. Previously identified supplements consisting of a multispecies live mixture of *bifidobacterium* and *lactobacillus* were administered to aging rats, resulting in alterations in brain metabolites, specifically GABA and glutamate, within the cortex and hippocampus. These alterations were found to be conducive to enhancing neuronal signaling and memory function [15]. This intricate interplay extends to the modulation of neuroinflammatory pathways, wherein probiotics may serve to mitigate systemic inflammation and attenuate neuroinflammation, both of which are implicated in cognitive decline [16]. From memory consolidation and executive function to attentional processing and mood regulation, probiotics exhibit a broad spectrum of effects on cognitive performance. These effects are likely mediated through various pathways, including direct interactions with neural circuits, modulation of immune responses, and alterations in gut microbial metabolites [17]. The primary myeloid cell in the brain, microglia, is sustained by the host microbiota during normal conditions to prime for the innate immune response in the CNS. It is indicated by evidence that activated microglia form a defensive shield around amyloid deposits, impeding the addition of new Aβ onto established plaques [11]. Minter et al. demonstrated that antibiotic treatment leads to modifications in the composition of the gastrointestinal microbiome, which is associated with a decrease in Aβ deposition [18].

This review is not without limitations, notably in the heterogeneity of cognitive assessment tools employed across the five studies. Specifically, the cognitive evaluation methods encompassed MMSE in two studies, RBANS in one study, a computerized neurocognitive function test in another, and CERAD-K in the remaining study. Despite the diversity in assessment instruments, it is noteworthy that all included investigations arrived at a consistent conclusion, collectively substantiating the substantial potential of probiotics to positively impact cognitive function among individuals afflicted by AD. Another limitation of this review pertains to the inherent heterogeneity observed in the strains of probiotic microorganisms employed across the diverse studies. This variability in strains introduces the potential for divergent outcomes, as distinct strains may confer disparate effects on cognitive function. In the systematic review, four RCTs were included, where participants were randomly assigned to intervention and control groups. Additionally, one interventional study was incorporated, which might have utilized different design methodologies without strict randomization or control groups. This diversity in study design may affect the overall comparability and generalizability of the findings. Ultimately, these efforts stand to unravel the true therapeutic potential of probiotics and contribute to the refinement of treatment strategies for cognitive impairment in AD.

Conclusion

AD represents a formidable challenge within the landscape of neurodegenerative disorders. The evidence evaluated from multiple studies highlights the potential of probiotic microorganisms to enhance cognitive function in the context of this progressive ailment, primarily through their modulation of the intricate gut–brain axis. While the scope of cognitive domains influenced by probiotic supplementation may vary, the significance of this intervention in the therapeutic approach for AD is evident. Incorporating probiotics into treatment regimens holds promise as a strategy to enhance cognitive function, offering a therapy amidst the complex landscape of neurodegeneration. Further research endeavors are warranted to refine our understanding of the specific mechanisms and optimal protocols, thereby highlighting the path towards more effective interventions for individuals afflicted by AD.

Abbreviations

AD	Alzheimer's disease
CERAD-K	Korean version of the Consortium to Establish a Registry for Alzheimer's disease
CNS	Central nervous system
ENS	Enteric nervous system
GABA	γ-Aminobutyric acid
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
PICOS	People, intervention, control, outcome, study design
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized control trial

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Author contributions
The initial concept for this literature review was hatched by AH. The text was written by AH, BGdL, and NLPSWP with guidance from IPEW, AWI, AED, and INS completed, copyedited and revised the manuscript. BGdL was in charge of revising the manuscript. All authors assisted in reviewing, composing the manuscript, creating the figures and reviewing the final manuscript.

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