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Exploring the gut-brain axis in alzheimer's disease treatment via probiotics: evidence from animal studies-a systematic review and meta-analysis

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Abstract

Introduction Alzheimer's disease (AD) is a prevalent neurodegenerative disorder in the elderly, causing cognitive impairment. Its pathogenesis is characterized by amyloid beta deposition, neurofibrillary tangles, and neuroinflammation. Recent research has identified the link between gut dysbiosis, an imbalance of intestinal microorganisms, to this pathogenesis via the gut-brain axis. This study aims to review the probiotics' therapeutic effect, targeting the gut-brain axis, for AD treatment in animals.

Methods The method utilized in this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Three reviewers searched articles through PubMed, Scopus, and Embase using advanced search strategy. Articles published between 2010 and 2023 that met the criteria were included.

Results Of 2,273 articles, 21 animal studies measuring the effects of probiotics genera *Lactobacillus* and/or *Bifidobacterium* on AD via at least one of these four outcomes: AD pathology, cognitive function, neuroinflammation, and gut microbiota composition. The results demonstrated that probiotics could repair gut dysbiosis by decreasing pro-inflammatory bacteria and increasing anti-inflammatory bacteria. Repaired dysbiosis was found to be associated with less neuroinflammation as significant reductions in neuroinflammatory markers related to the pathogenesis of AD such as TNF-α (SMD = -2.08, $P = 0.005$), IL-6 (SMD = -2.98, $P < 0.0005$), and IL-1β (SMD = -2.49, $P = 0.003$) were observed. Reduced amyloid beta deposition (SMD = -1.17, $P = 0.009$) was reported, but reduction in tau hyperphosphorylation was found to be insignificant. For cognitive function, positive results were demonstrated for all three aspects of cognitive function including long-term memory (SMD = 2.55, $P < 0.00001$), short-term memory (SMD = 1.32, $P = 0.003$), and spatial recognition (SMD = -1.13, $P < 0.00001$).

Conclusions Particular formulas of probiotics showed potential effectiveness in AD therapies with demonstrated association with the gut-brain axis. Future studies are required to investigate strain-specific results and optimal dosages and regimens.

Keywords Gut microbiota, Gut-brain axis, Alzheimer's disease, Probiotics

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Introduction

Every five years after turning 65, the number of people with AD doubles. According to the Centers for Disease Control and Prevention, this number will nearly triple by 2060, reaching 14 million, making it one of the significant issues in the future [1]. AD risk increases from the age 65 to 85 by 3% to nearly 30%. AD can develop before 65 (early onset) or after 65 (late onset) [2]. Most of the cases are late onset. Even though there are substantial studies on amyloid beta and tau protein as pathologic features of this disease, it is still challenging to understand the causes of this disease because patient-specific risk factors combination can cause AD via various mechanisms [3].

Since the beginning of the twentieth century, amyloid-beta deposition and tau hyperphosphorylation have been the hallmark of cognitive decline [4]. The hyperphosphorylation of tau causes tau aggregation, leading to paired helical filament-like structures. This is the component of neurofibrillary tangles, which is a hallmark of AD [5]. One of the earliest signs of this disease is memory loss. Short-term memory is mostly impaired in its early stages. However, patients will become more forgetful after the disease progresses or lose long-term memory [6].

Besides short and long-term memory loss, spatial memory impairment can also be found in mild AD patients [7]. Spatial memory is the memory that is used to return to rewarding locations such as home. This memory is found to be crucial in a variety of animals from invertebrates to humans [8]. There is also evidence that certain inflammatory markers, such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and acute phase reactant protein C reactive protein (CRP), act on the brains or the peripheral areas of dementia patients [9].

Although there are several proposed pathogeneses of this disease, there is still a lack of effective treatment for this disease. The recent investigation exposed a gap in our knowledge of AD pathology by claiming the hypothesis that gut microbiota are related to brain development and behavioral functions [10]. Through systems like the immune system, neuroendocrine system, and autonomic nervous system, the gut microbiota communicates in both directions with the central nervous system (CNS). Microbiota creates metabolites and neuroactive substances. These substances can affect immunological reactions, metabolism, brain signaling, and integrity of intestinal barriers [11]. The brain also directly influences the function of the gut by releasing signaling molecules to control the physiological function of the gastrointestinal system in relation to hunger and satiety [12].

Gut dysbiosis is a general term that is used to describe the imbalance of the gut microbiota that can lead to negative consequences [13]. Gut dysbiosis may make it easier for pathogens to enter the blood and brain because it increases permeability and damages the intestinal barrier and blood–brain barrier (BBB), leading to the state of leaky gut and BBB, increasing neuroinflammation and triggering amyloid accumulation, which is a primitive immune response in the brain. Consequently, raised IL-6 levels in the blood are a way that increased intestinal permeability and microbial dysbiosis cause systemic inflammation in the body [14]. It is also suggested that systemic inflammation in AD causes proinflammatory microglial and astrocytic characteristics. These phenotypes promote tau hyperphosphorylation, oligomerization, component activation, and the degradation of neurotransmitters into potentially harmful metabolites [15].

One way to disrupt the pathogenesis of AD is to repair gut dysbiosis or alter the gut microbiota composition by adding beneficial bacteria to the gut lumen. The beneficial bacteria that can improve people's health when consumed are called probiotics. Probiotics can be found in several dietary choices, including yogurt, fermented foods, dietary supplements, and cosmetics products. Some strains can produce vitamins, assist in the breakdown of disease-causing cells, and aid with food digestion [16]. Several bacteria may be present in probiotics. Bacteria from the families *Lactobacillus* and *Bifidobacterium* are the most prevalent. As probiotics, other bacteria and yeasts such as *Saccharomyces boulardii,* may be employed. Different species and strains of probiotics exhibit different properties on human bodies [16].

Several studies have evaluated current evidence on the application of probiotic treatments for the therapeutic purpose of AD and other neurological disorders [17, 18]. However, only a few studies demonstrated the therapeutic effects of probiotics on AD by covering the four important parameters and outcome measurements including AD pathology, cognitive function, neuroinflammation, and gut microbiota composition. Hence, this systematic review and meta-analysis aims to assess the therapeutic potential of probiotics via all of these four main outcome measurements enabling the discussion about potential mechanisms of probiotics on the gut-brain axis which is currently unclear.

Materials and methods

Eligibility criteria

The study inclusion criteria were: (i) controlled trials focusing on probiotics genera *Lactobacillus* and/or *Bifidobacterium* (ii) studies conducted only in animals (iii) studies investigating at least one of the following outcomes: AD pathology, cognitive function, neuroinflammation, and gut microbiota composition (iv) a study published in English (v) a study published in year 2010–2023. While (i) reviews, meta-analyses, case reports, commentaries and patents (ii) studies investigating

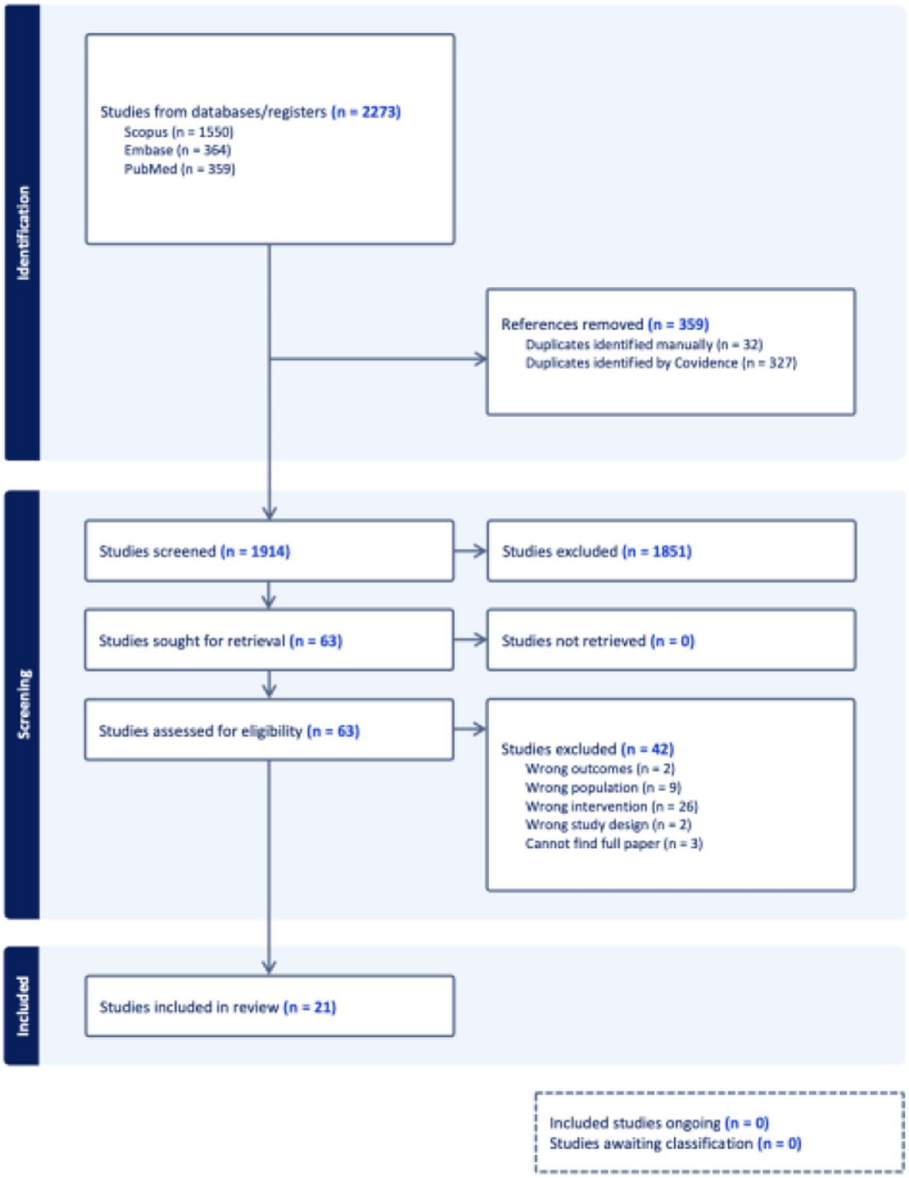

Fig. 1 PRISMA flow chart

probiotics combined with other interventions were excluded.

Search Strategy and Study Selection

The literature was done following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. A systematic search of the literature was conducted in PubMed, Central, Embase, and Scopus using search string (Supplementary material 1): from 2010 to April 2023.

Three reviewers independently screened and included the title, abstracts, and full-text articles that meet the criteria based on the Fig. 1. The initial search yielded 2,273 studies, of which 359 duplicates were removed. A total of 1,851 articles were ruled out as they did not meet the inclusion criteria, which resulted in 63 studies eligible for full-text evaluation. Another 42 articles were excluded due to wrong outcomes, population, intervention, or study design, along with no full-texts available. Consequently, 21 studies were included in this review.

Risk of bias assessment

The risk of bias was assessed using the Systematic Review Center for Laboratory Animal Experimentation

(SYRCLE), based on the Cochrane Collaboration Risk of Bias tool and adapted to be more specific to animal research [20]. Ten domains consist of sequence generation, baseline characteristics, allocation concealment, random housing, blinding (performance bias), random outcome assessment, blinding (detection bias), incomplete outcome data, selective outcome, and other sources of bias. The risk of bias was assessed by answering SYRCLE's signaling questions with "yes" indicating low risk of bias, "no" indicating high risk of bias, and "unclear" indicating an unclear risk of bias. The number of yeses compared to the number of SYRCLE items were calculated as a summary score. Two of three reviewers conducted an assessment, and consensus resolved discrepancies Fig. 2.

Study characteristics (Table 1)

Statistical analysis

The RevMan 5.4 software [41] was used for meta-analysis. The primary outcome of this study was the standardized mean differences (SMDs) of AD pathology, cognitive function, and neuroinflammation between control group and experimental group. A Z statistical test tested the SMDs, and a two-tailed $P<0.05$ was considered statistically significant. A P value of 0.10 is used for the test of heterogeneity. The I^2 statistic, ranging from 0 to 100%, indicates the magnitude of heterogeneity. Greater I^2 indicates more heterogeneity. The I^2 below 40% may suggest no important heterogeneity, while the I^2 over 75% may suggest considerable heterogeneity [42]. For all analyses, SMDs were calculated by a random-effects model.

Results

The research results consist of three animal types: mice, rats, and drosophila. The outcomes from 21 studies were grouped into four categories: AD pathology, cognitive function, neuroinflammation, and gut microbiota composition. The numerical results were reported using SMD with 95% confidence intervals and presented in a forest plot. We used AD animals as models and administered probiotics to the intervention group.

AD pathology

Pooled data from included studies show a significant reduction of amyloid beta deposition in AD induced animals (SMD = −1.17, $P=0.009$) (Fig. 3), however, probiotics treatment did not show a significant reduction in tau hyperphosphorylation (SMD = 0.36, $P=0.35$) (Fig. 4).

Cognitive function

For the next parameter, cognitive function. The included studies' data were grouped into three categories which are short-term memory, long-term memory, and spatial recognition. Short-term memory, using results from the y-maze test to assess the animals' short-term memory. The y-maze test was the method used to assess animals' willingness to explore new environments. The results show a significant improvement in the probiotics treatment group (SMD = 1.32, $P=0.003$) (Fig. 5). For long-term memory, the passive avoidance test was used to evaluate the animals' latency time to avoid an unpleasant stimulus. The results showed a significant improvement in the probiotics treatment group (SMD = 2.55, $P<0.00001$) (Fig. 6). Spatial recognition was measured using the Morris water maze test which is the test that observes animals' ability to find a hidden platform in the water. The results also showed a significant improvement in probiotic treatment group (SMD = −1.13, $P<0.00001$) (Fig. 7).

Neuroinflammation

In this review, the neuroinflammatory markers from all findings were into three groups: inflammatory markers, glial cell markers, and synaptic plasticity markers. TNF-α, IL-1β, and IL-6 from inflammatory markers group, Ionized calcium-binding adaptor molecule 1 (Iba1), Glial fibrillary protein (GFAP) from glial cell markers group, and Brain-derived neurotrophic factor (BDNF) from synaptic plasticity markers group were selected for the study as shown in the figures.

Probiotic-fed groups showed significant decreases in TNF-α (SMD = −2.08, $P=0.005$) (Fig. 8), IL-1 (SMD = −2.49, $P=0.003$) (Fig. 9), and IL-6 (SMD = −2.98, $P=0.0005$) (Fig. 10), Iba1 (SMD = −3.12, $P=0.002$) (Fig. 11). However, no significant change in GFAP level was observed (SMD = −1.87, $P=0.12$) (Fig. 12). Moreover, the experimental groups showed a significant increase in BDNF (SMD = 2.23, $P=0.04$) (Fig. 13).

Gut microbiota composition

Among all included studies, eleven studies measured gut microbiota composition changes in the probiotic-treated group (Table 2). Two aspects of microbiome composition were assessed, diversity and abundance. Six studies investigated the effects of probiotics on gut microbiome diversity. Four studies observed an increase in either or both alpha and beta diversity, while *Webberley* et al. and *Abdelhamid* et al. observed no significant change in alpha diversity and both types of diversity, respectively. All eleven studies measure the changes in abundance of the bacteria. At phylum level, increases in phylum *Verrucomicrobia, Actinobacteria* and *Firmicutes* as well as decreases in phylum *Proteobacteria* and *Bacteroidetes* were observed. At family level, family *Lactobacillaceae, Bifidobacteriaceae, Lachnospiraceae, Oscillospiraceae,*

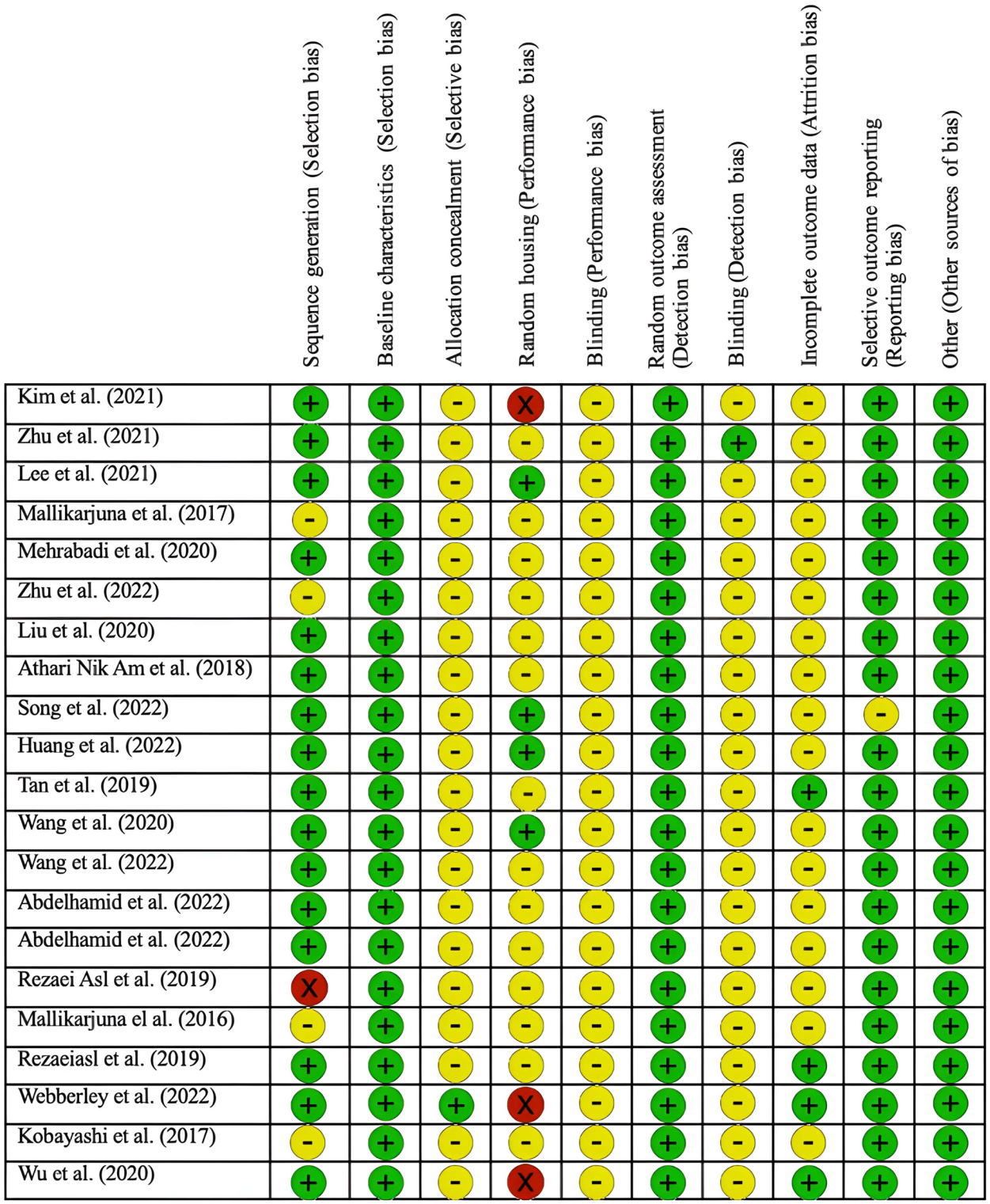

Fig. 2 Table of risk of bias assessment (+ reflects yes, x reflects no, and—reflects unclear)

Table 1 Overview of characteristics of included studies

Study	Animal Model	Probiotics (Pro)	Intervention Characteristics	Methods of Measurement
Hongwon Kim et al. 2021 [21]	Mice: 3-month-old C57Bl/6 (*n*=20) & 5xFAD (*n*=20). Groups: (1) Control (2) Control+Pro (3) AD (4) AD+Pro	*B. bifidum BGN4; B. longum BORI* (freezed dried power)	30 days; 1×10^9 colony-forming unit (CFU) in 0.2 mL sterile water; oral adm.	Behavioral tests (Y-maze test, contextual fear conditioning test, Morris water maze test); western blot analysis; immunofluorescence staining analysis; quantitative RT-PCR analysis; ELISA; mic robiome profiling (16S rRNA gene sequencing, PCR)
Guangsu Zhu et al. 2021 [22]	Mice: 8-week-old ♂ C57BL/6J (*n*=64). Groups: (1) Control (2) AD (3) AD+donepezil (4) AD+NMG (5) AD+MY (6) AD+CCFM1025 (7) AD+XY (8) AD+WX	*B. breve NMG*, *B. breve MY*, *B. breve CCFM1025*, *B. breve XY*, and *B. breve WX*	6 weeks; 200 µL bacteria suspension (3×10^9 CFU/mL cells); oral adm.	Behavioral tests (Y-maze test, Morris water maze test, passive avoidance test); ELISA; SCFAs extraction and analysis; microbiome profiling (16S rRNA gene sequencing, PCR)
Dong-Yun Lee et al. 2021 [23]	Mice: 6-week-old ♂ C57BL/6 (*n*=35). Groups: (1) Control (2) AD (3) AD+NK151 (4) AD+ NK173 (5) AD+Mixed	*L. plantarum NK151*, *B. longum NK173*, Mixed-*L. plantarum NK151*&*B. longum* NK174	5 days (after the final gavage of E. *coli K1*); 1×10^9 CFU/mouse/day (4:1 in mixed group); oral adm., 5 days (after the final injection of LPS); 1×10^9 CFU/mouse/day (4:1 in mixed group); oral adm.	Behavioral test (Y-maze test, novel object recognition test); myeloperoxidase activity assay; ELISA; immunoblotting; immunofluorescence staining analysis; microbiome profiling (16S rRNA gene sequencing); whole genome analysis
Mallikarjuna et al. 2017 [24]	Rats: 3-month-old ♂ Wistar (*n*=48). Groups: (1) Control (2) AD (3) AD+Pro (4) Pro	*L. plantarum MTCC1325*	60 days; 12×10^8 CFU/mL for 10 mL/kg body weight; intraperitoneal injection.	Behavioral tests (Morris water maze test); histopathological test; biochemical test of cholinergic system
Shima Mehrabadi et al. 2020 [25]	Rats: ♂ Wistar (*n*=50). Groups: (1) Control (2) Sham (3) AD (4) AD+Pro (5) AD+rivastigmine	*L. reuteri*, *L. rhamnosus*, *B. infantis*	10 weeks; 2 g. (10^{10} CFU); oral adm.	Behavioral tests (Morris water maze test); histopathological test; malondialdehyde level measurement; superoxide dismutase enzyme activity measurement; ELISA
Guangsu Zhu et al. 2022 [22]	Mice: 8-week-old ♂ C57BL/6J (*n*=24). Groups: (1) Control (2) AD (3) AD+Pro	*B. breve CCFM1025*	6 weeks; 200 µL of bacterial suspension (5×10^9 CFU/mL); oral adm.	Metabolomic analysis (metabolite sample, UPLC-MS analysis)

Table 1 (continued)

Study	Animal Model	Probiotics (Pro)	Intervention Characteristics	Methods of Measurement
G. Liu et al. 2020 [26]	Flies: Oregon-R. Groups: (1) Control (GMR-OreR) (2) AD (transgenic GMR-Aβ42 Drosophila) (3) AD+Pro.	*L. paracasei 0291, L. helveticus 1515, L. reuteri 8513d, L. fermentum 8312, L. sakei Probio65, L. reuteri 30242, L. casei Y*	LAB strains (100 µL) were added at 1×10^{11} CFU/ml to the cooled feed.	External eye surface digital imaging; microbiome profiling (16S rRNA gene sequencing)
Somayeh Athari Nik Am et al. 2018 [27]	Rats: 8-week-old ♂ Wistar (n=60). Groups: (1) Control (2) Control+Pro (3) Sham (PBS) (4) AD (5) AD+Pro	*L. acidophilus*, *L. fermentum*, *B. lactis*, *B. longum*	8 weeks; 500 mg of each with 1×10^{10} CFU/g; oral adm.	Behavioral test (Morris water maze test); histopathological test; malondialdehyde, superoxide dismutase, and catalase enzyme activity measurement; detection of bacteria counts in stool samples
Xinping Song et al. 2022 [28]	Mice: 8-week-old ♂& ♀(n=30). Groups: (1) Control (2) AD (3) AD+Pro	*L. plantarum DP189*	10 weeks; 10 mL/kg body; intraperitoneal injection.	Behavioral tests (Morris water maze test, step-down test); histopathological test; immunohistochemistry; ELISA; western blotting; microbiome profiling (16S rRNA gene sequencing, PCR)
Hei-Jen Huang et al. 2022 [29]	Mice: 6-month-old ♂ C57BL/6 J & 6-month-old 3×Tg-AD. Groups: (1) Control (2) Wild-type+PS128 (3) AD+saline (4) AD+PS128/STZ (5) AD+saline/STZ (6) AD+PS128/STZ	*L. plantarum PS128*	7 days; 100 µL of *PS128* (10^{10} CFU/mL); oral adm.	Behavioral tests (Morris water maze test, open field test, elevated plus maze test); immunohistochemistry; western blotting; SCFAs extraction and analysis
F.H.P. Tan et al. 2019 [30]	Drosophila: Oregon-R wild type (#5), Glass multiple reporter-GAL4 (#1104), YAS-Aβ (#33769). Groups: (1) Control (2) AD (transgenic GMR-Aβ42) (3) AD+Pro	*L. plantarum DR7, L. fermentum DR9, L. casei*	100 µl of each strains were added at within 2 hr. of solidification; $1x10^{11}$ CFU/mL.	External eye surface digital imaging and phenotypic analysis; microbiome profiling (16S rRNA gene sequencing)
Feng Wang et al. 2020 [31]	Mice: 8-week-old ♂ APP/PS1 (n=40). Groups: (1) AD (2) TMC3115 (3) LP45 (4) TMC3115&LP45 Mice: wild-type littermates (n=10). Groups: (1) Control	*B. bifidum TMC3115, L. plantarum LP45*	22 weeks; 0.2 mL of *TMC3115* (1×10^9 CFU), 0.2 mL of LP45 (1×10^9 CFU), mixed 0.1 mL of *TMC3115* (5×10^8 CFU) and 0.1 mL of *LP45* (5×10^8 CFU); oral adm.	Behavioral test (Morris water maze test, open field test, novel object recognition test); microbiome profiling (16S rRNA gene sequencing)

Table 1 (continued)

Study	Animal Model	Probiotics (Pro)	Intervention Characteristics	Methods of Measurement
Yuanwang Wang et al. 2022 [32]	Rats: ♂ Wistar (*n*=40). Groups: (1) Control (2) AD (3) AD+low dose of MA2 (4) AD+high dose of MA2 (5) AD+GV-971 (sodium oligomannate)	*L. plantarum MA2*	12 -13 weeks; low dose of *MA2*, 10^8 CFU/kg/day), high dose of *MA2*, 10^9 CFU/kg/day; oral adm.	Behavioral tests (Morris water maze test, open field test); immunohistochemistry; biochemical analysis, RT-qPCR; microbiome profiling (16S rRNA gene sequencing); metabolomic analysis; isolation and purification of MA2 exopolysaccharide (MA2); Thioflavin T; Atomic force microscopy; MTT assays
Mona Abdelhamid et al. 2022 [33]	Mice: 2 month-old ♂ C57BL/6J (*n*=40). Groups: (1) Control (2) Pro	*B. breve MCC1274*	4 months; 1×10^9 CFU/6.25 mg/200 µL saline/mouse/day (5 times/week); oral adm.	Western blotting; ELISA; immunohistochemistry; immunofluorescence staining analysis
Mona Abdelhamid et al. 2022 [34]	Mice: 3 month-old App knock-in (KI) (*AppNL-G-F*) (*n*=52). Groups: (1) Vehicle (2) Pro	*B. breve MCC1274*	4 months (5 times/week); 1×10^9 CFU/5.56mg/200µL saline/mouse; oral adm.	Behavior test (novel object recognition test); ELISA; western blotting; immunohistochemistry; immunofluorescence staining analysis; staining of Aβ fibril; quantitative RT-PCR analysis; microbiome profiling (16S rRNA gene sequencing)
Zahra Rezaei Asl et al. 2019 [35]	Rats: ♂ Wistar. Groups: (1) Control (2) AD+vehicle (3) AD+Pro (4) Sham (5) Normal+Pro	Mixture of *L. acidophilus*, *B. bifidum*, and *B. longum* (capsulated)	56 days; 500 mg of the bacteria mixture with a total CFU of 15×10^9; intragastric gavage.	Behavioral tests (Morris water maze test, spatial performance test); electrophysiologic test; microbiome profiling; biomarkers measurement; histological test
Nimgampalle Mallikarjuna el al. 2016 [36]	Rats: 3-month-old ♂ Wistar (*n*=24). Groups: (1) Control (2) AD (3) Control+Pro (4) AD+Pro	*L. plantarum MTC1325*	60 days: 10 mL/kg body weight of rat; 12×10^8 CFU/mL; intraperitoneal injection.	Biochemical analysis; total ATPases; Mg^{2+} -ATPases/Ca^{2+}-ATPases activities; inorganic phosphate estimation; protein estimation
Zahra Rezaeiasl et al. 2019 [37]	Rats: ♂ Sprague-Dawley (*n*=40). Groups: (1) Control (2) Sham (3) AD (4) AD+Pro	*L. acidophilus*, *B. bifidum*, *B. longum*	6 weeks before and 2 weeks after Aβ(1–42) injection; 500 mg. Probiotics (15×10^9 CFU); oral adm.	Behavioral tests (Morris water maze test, spatial performance test); electrophysiologic test; biochemical analysis

Table 1 (continued)

Study	Animal Model	Probiotics (Pro)	Intervention Characteristics	Methods of Measurement
Thomas S. Webberley et al. 2022 [38]	Mice: ♂ 3xTg-AD (*n*=20). Groups: (1) AD (2) AD+Pro	Lab4b; *L. salivarius CUL61 (NCIMB 30211), L. paracasei CUL08 (NCIMB 30154), B. bifidum CUL20 (NCIMB 30153),* and *B. animalis* subsp. *lactis-CUL34* (*NCIMB 30172*)	12 weeks; 5×10^8 CFU/mouse/day; oral adm.	Behavioral tests (Novel object recognition test); hippocampal dendritic spines density test; histological test; RT-PCR; plasma lipid and cytokine profiling; ^{1}H NMR spectroscopic analysis of tissue ; microbiome profiling (16S rRNA gene sequencing)
Yodai Kobayashi et al. 2017 [39]	Mice: 10-week-old ♂ ddY. Groups: (1) Control (2) AD+Pro (3) AD+Sodium Acetate	*B. breve A1*	2 days before Aβ injection; 1×10^9 organisms in 0.2 mL; oral adm.	Behavioral tests (Y-maze test, passive avoidance test); physiological analyses; RNA sequencing analysis; microbiome profiling (16S rRNA gene sequencing); SCFAs extraction and analysis
Qiong Wu et al. 2020 [40]	Mice: 10-month-old WT (control) and APP/PS1(AD). Groups: (1) Control (2) Control+Pro (3) AD (4) AD+Pro	*B. longum 1714*	0.2 ml/10 g of body mass (1×10^9 CFU/mL); oral adm.	Immunohistochemistry; immunofluorescence staining analysis; western blotting; PCR; ELISA; quantitative assays for Aβ42

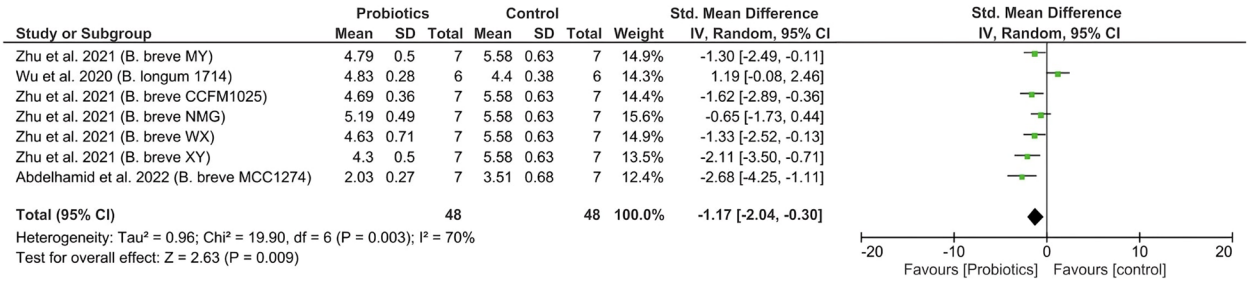

Fig. 3 Forest plot showing the effects of probiotics treatment on amyloid beta deposition in AD induced animals (ng/mL)

and *Ruminococcaceae* were found in increased richness, while family *Rikenellaceae, Christensenellaceae, AC160630_f, Prevotellaceae, Muribaculaceae, Odoribacteraceae* and *Lachnospiraceae* decreased in richness. At genus level, Genus *Bifidobacterium, Akkermansia, Faecalibacterium, Erysipelatoclostridium, Candidatus_Stoquefichus, LLKB_g, PAC001092_g, Stenotrophomonas, Serratia, Corynebacterium_1, Enterococcus, Parabacteroides, Alistipes, Coprobacillus, Aerococcus, Jeotgalicoccus, Prevotella, and Candidatus arthromitus, Pseudomonas, Acetatifactor, and Millionella* increases, while genus *Parvibacter, Incertae_Sedis, Oscillibacter, Coprococcus, Alistipes*, *Helicobacter, Wolbachia,* Desulfovibrio, *Intestinimonas,* and unidentified *Ruminococcaceae* were found in decreased abundance compared to AD group. Some studies showed increases in genus *Lactobacillus* and *Bacteroides*, while some showed decreases in both. At species level, increases in species *Akkermansia muciniphila* and *Lactobacillus reuteri* and a decrease in species *PAC001071_s* were observed. However, *Abdelhamid* et al. reported no significant change in microbiome richness.

Discussion

Potential mechanism of probiotics on the gut-brain axis

Role of the gut-brain axis on the pathogenesis of AD

Several studies mentioned the protective effects of probiotics along the gut-brain axis, which is eventually linked to the pathogenesis of AD. To elucidate the potential mechanism of action of this therapeutic intervention, the pathogenesis of AD that is a result of the alteration of the gut-brain axis should be discussed. One postulated AD pathogenesis mentioned gut dysbiosis as the cause [43]. Gut dysbiosis, characterized by an increase in *Firmicutes/Bacteroidetes* ratio, leads to a decrease in the releases of protective microbial metabolites and an increase in the release of harmful microbial metabolites such as Trimethylamine-N-oxide (TMAO), which has been claimed to deteriorate the cognitive functions during the aging process in mice models [44]. Short-chain fatty acids (SCFA), protective microbial metabolites, exhibit protective effects on AD via the disruption of toxic soluble Aβ aggregates formation [45]. These alterations in microbial metabolites lead to the state of a leaky intestinal barrier and blood–brain barrier, activating peripheral immune responses and central oxidative stress levels. This eventually leads to neuroinflammation and amyloid plaque deposition [43].

Gut dysbiosis as AD therapeutic target of probiotics

According to the results from four outcome measurements, probiotics as therapeutic interventions for AD may reduce the pathogeneses via treating gut dysbiosis. The findings from the included studies supported this hypothesis as a partial restoration of both alpha and beta diversity, as well as a decrease in *Firmicutes/Bacteroidetes* ratio in the probiotic-treated AD group, were reported [22, 23, 38]. Changes in the abundance of particular bacteria were also investigated. Probiotics increase the "good" bacteria, which exhibit anti-inflammatory effects on the gut while decrease the "bad" bacteria, which exhibit pro-inflammatory effects on the gut. Phylum Proteobacteria, claimed as a microbial signature of gut dysbiosis, was found in a decreased abundance [23]. At the genus level, significant changes in some particular groups of bacteria were mentioned: increases in genus *Akkermansia, Acetobacter, Strenotrophomonas,* and *Lactobacillus* and a decrease in genus *Wolbachia*. These changes in abundance may result in altered metabolites and oxidative stress leading to less neuroinflammation, neuronal damage and amyloid plaque deposition. For instance, *Lactobacillus* spp. was found to have anti-oxidative potential in the aging process in animal models [46].

Effects of probiotics on neuroinflammatory responses and AD pathology

Aβ plaque deposition is strongly supported by scientific evidence to be the hallmark of AD. From the findings of the studies measuring this parameter, probiotics can significantly reduce Aβ deposition in AD animal models.

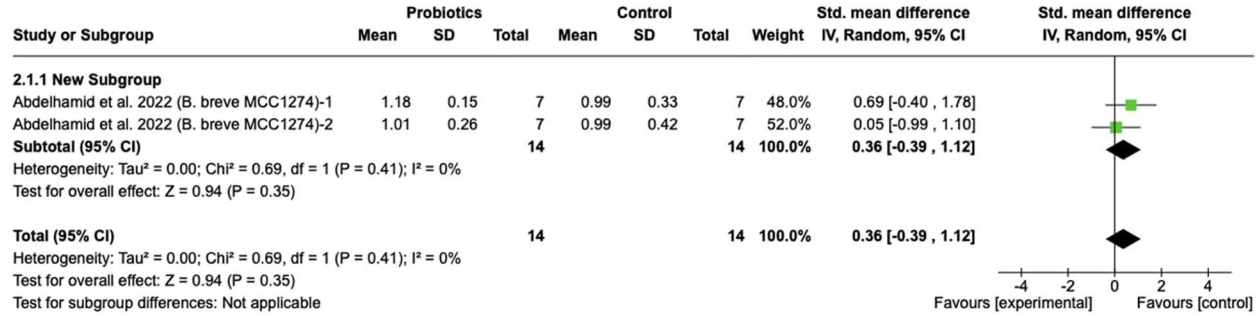

Fig. 4 Forest plot showing the effects of probiotics treatment on tau hyperphosphorylation in AD induced animals (relative value)

Another distinctive feature of AD patients' brains is tau hyperphosphorylation. However, the findings of the effects of probiotics on tau hyperphosphorylation were insignificant, indicating that cognitive function improvements are not associated with this mechanism. Another hypothesis that may be associated with the negative findings of tau hyperphosphorylation is host genetic variation which was not included in the inclusion or exclusion criteria of this study. While gut microbiota composition may strongly be influenced by various environmental factors such as diet, lifestyle, host genetic factor is also considered a strong regulator of the host microbiome [47, 48]. A recent study has investigated the interrelationships between gut microbiota, neuroinflammation, and tau-mediated neurodegeneration using genetically engineered mouse model of taupathy with human ApoE isoforms expression. The results showed that gut microbiota alteration reduced gliosis, tau pathology, and neugeneration. However, these manipulations occur in a sex- and ApoE isoform-dependent manner [48–50]. This implies that the relationship between gut microbiota alteration and reduced tau hyperphosphorylation may not show positive correlation in animal models without ApoE expression.

Neuroinflammatory responses were measured in some included studies to monitor the progression of AD. Neuroinflammation, inflammation within the central nervous system, leads to an activated state of astrocytes and microglia which eventually promotes amyloid beta plaque deposition [51]. However, a piece of scientific evidence mentioned that neuroinflammation itself may also possibly be the direct etiology of AD since treatments that can effectively reduce Aβ plaque deposition cannot delay or thwart the progression of AD in some studies [52]. Hence, neuronal damage in AD may directly or indirectly come from neuroinflammation.

In this study, probiotic-treated AD groups demonstrated significantly lower levels of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. The findings in most studies that measured both neuroinflammatory cytokines and gut microbiota profile support the hypothesis that altered gut microbiota profile may influence neuroinflammatory processes. Interestingly, *Abdelhamid* et al. observed no significant change in gut microbiota profile, but a significant decrease of IL-6 and IL-1β in the hippocampus and cortex were reported in the probiotic-treated AD group, suggesting that other possible mechanisms of probiotics without treating dysbiosis may also exist [33, 34].

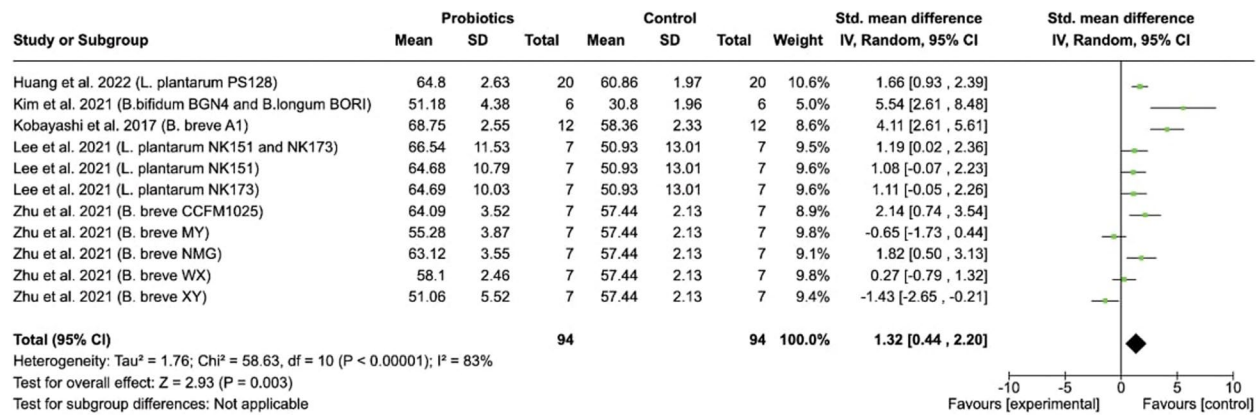

Fig. 5 Forest plot showing the effects of probiotics treatment on short term memory of AD-induced animals (percent of alteration)

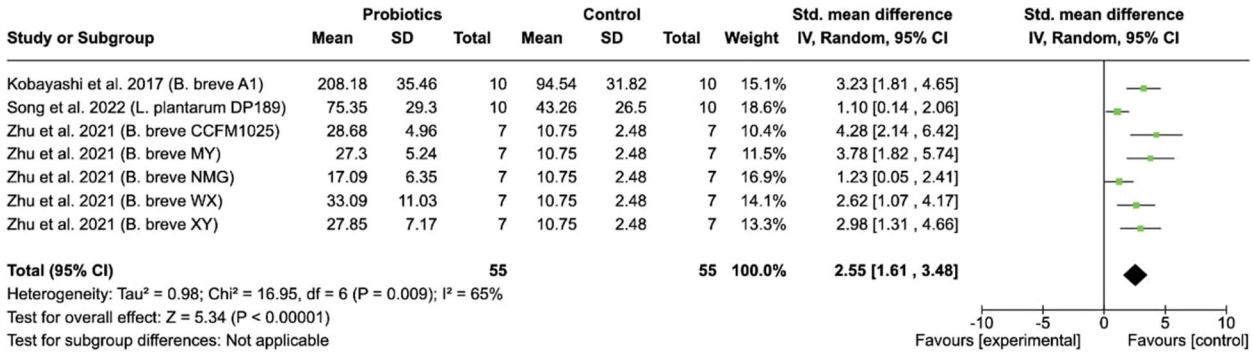

Fig. 6 Forest plot showing the effects of probiotics treatment on long term memory of AD-induced animals using the unit latency time (second)

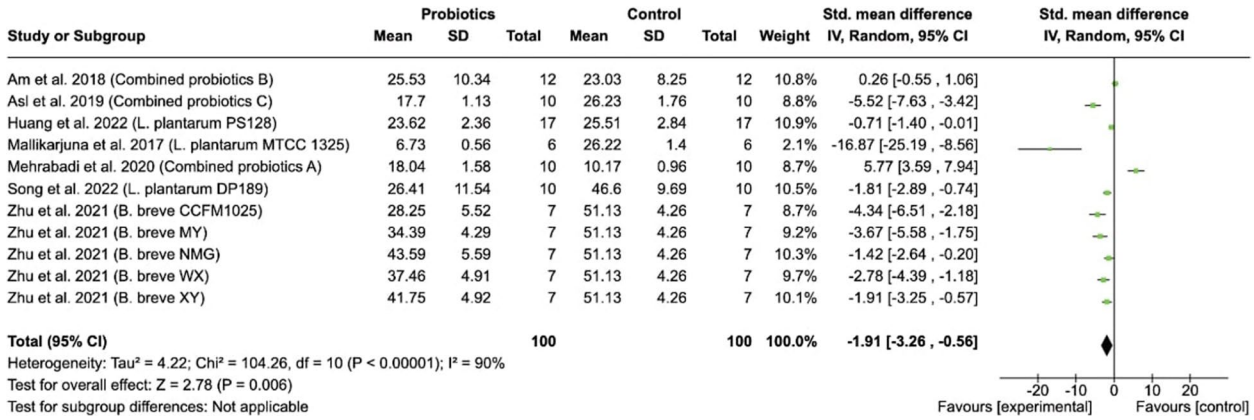

Fig. 7 Forest plot showing the effects of probiotics treatment on spatial recognition of AD induced animals using the unit latency time (second). Combined probiotics A = L. reuteri, L. rhamnosus, and B. infantis. Combined probiotics B = L. acidophilus, L. fermentum, B. lactis, and B. longum. Combined probiotics C = L. acidophilus, B. bifidum and B. longum in capsulated form

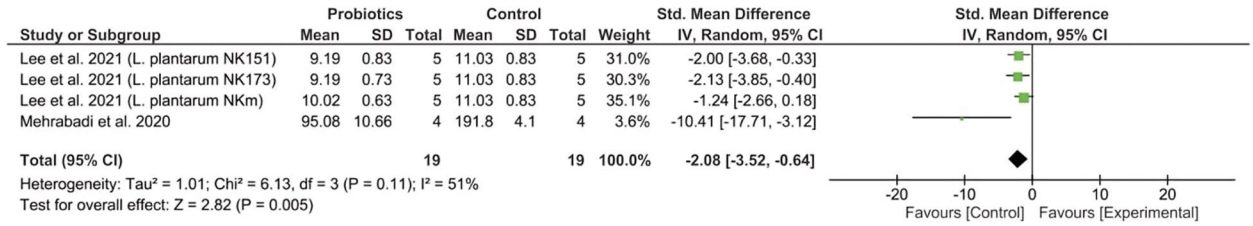

Fig. 8 Forest plot showing the effects of probiotics treatment on TNF-α level (pg/mg)

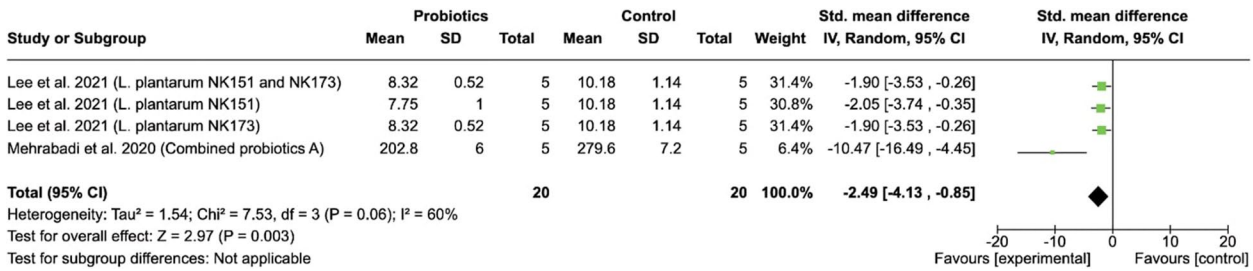

Fig. 9 Forest plot showing the effects of probiotics treatment on IL-1β level (pg/mg)

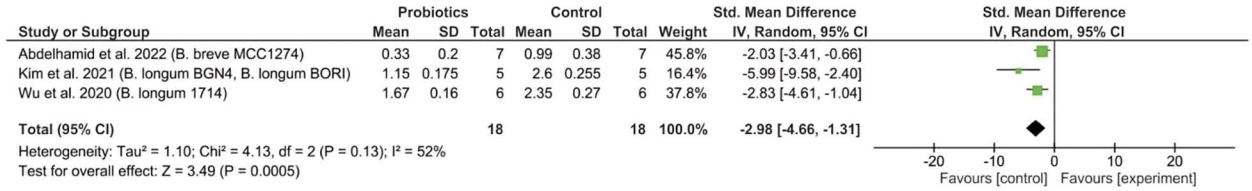

Fig. 10 Forest plot showing the effects of probiotics treatment on IL-6 level (relative value)

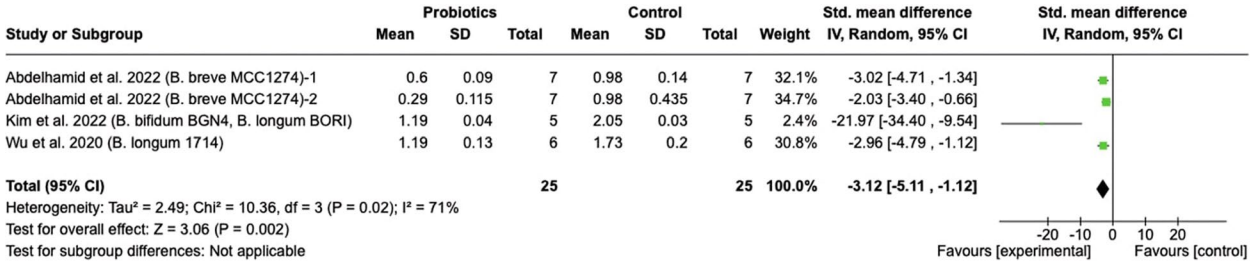

Fig. 11 Forest plot showing the effects of probiotics treatment on Iba1 level (relative value)

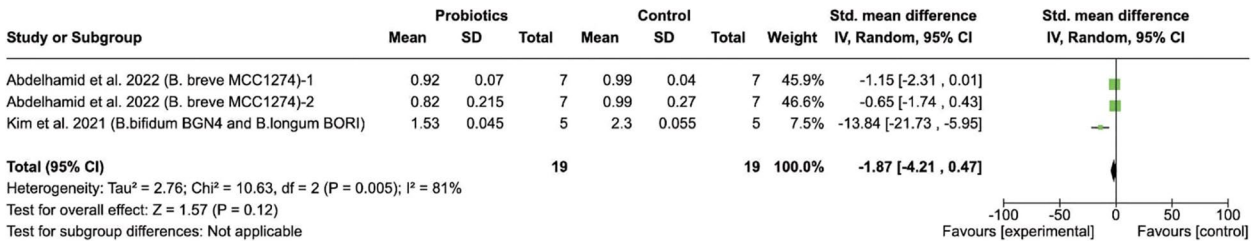

Fig. 12 Forest plot showing the effects of probiotics treatment on GFAP level (relative value)

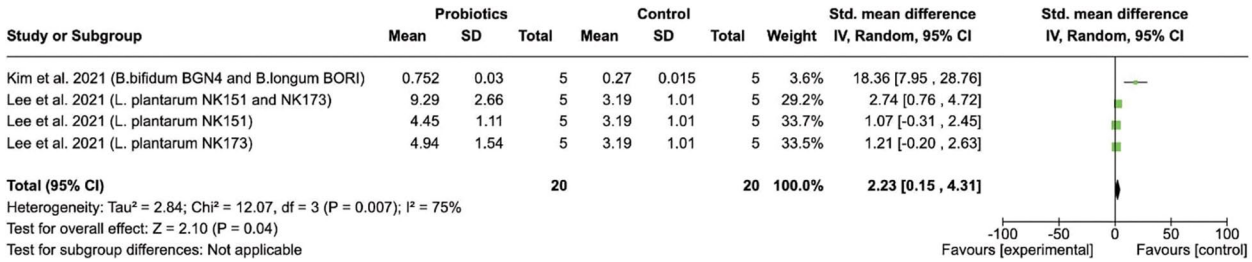

Fig. 13 Forest plot showing the effects of probiotics treatment on BDNF level (relative value)

Glial hyperactivation was also measured via two biomarkers, Iba1 and GFAP levels, respectively. Oral supplementation of probiotics significantly decreases the level of Iba1 protein, while there are no significant alterations in GFAP, an astrocytic marker, in the probiotic-treated AD group. This suggests that probiotic supplementation may be associated with the attenuation of microglial activation.

BDNF, as a synaptic plasticity marker, controls the metabolism of glucose and energy and shows preventive properties towards the exhaustion of beta cells. A decrease in BDNF level is associated with neurodegenerative diseases with neuronal loss [53]. The findings in this study demonstrated the therapeutic effects of probiotics on synaptic plasticity as BDNF levels were restored after the probiotic supplementation.

Effects of probiotics on cognitive functions

Cognitive functions in animal models were assessed in three different aspects: spatial recognition using the

Table 2 Results of gut microbiota composition in terms of richness and diversity in AD animals that were treated with probiotics compared with AD animals without probiotic supplementation

Study	Strains	Changes in gut microbiota		Alpha Diversity	Beta Diversity
		Increase	Decrease		
Kim et al. [21]	*B. bifidum BGN4* & *B. longum BORI*	Genus *Bifidobacterium* Genus *Akkermansia* Genus *Faecalibacterium* Genus *Erysipelatoclostridium* Genus *Candidatus_Stoquefichus*	Genus *Parvibacter* Genus *Incertae_Sedis* Genus *Oscillibacter*	-	-
Zhu et al. [22]	*B. breve NMG*	-	-	increase	-
	B. breve MY	-	-		
	B. breve CCFM1025	Genus *Bifidobacterium* Species *L.reuteri*	-		
	B. breve XY	Genus *Akkermansia* Genus *Bifidobacterium* Species *B.adolescentis* Species *L.reuteri* Species *A.muciniphila*	Genus *Coprococcus*		
	B. breve WX	Genus *Akkermansia* Species *A.muciniphila*	Genus *Coprococcus*		
Lee at al [23].	*L. plantarum NK151* *B. longum NK173* *NKm (NK151 & NK173* [4:1] mixture)	Phylum *Verrucomicrobia* Phylum *Firmicutes* Family *Lactobacillaceae* Family *Bifidobacteriaceae* Genus *Lactobacillus* Genus *LLKB_g,* Genus *PAC001092_g* Species *Lactobacillus reuteri*	Phylum *Proteobacteria* Family *Rikenellaceae* Family *Christensenellaceae* Family *AC160630_f* Genus *Alistipes* Genus *Helicobacter* *Species PAC001071_s*	increase	increase
Liu et al. [26]	*L. paracasei 0291*	Genus *Acetobacter* Genus *Lactobacillus* Genus *Stenotrophomonas* Genus *Serratia* Genus *Corynebacterium_1* Genus *Enterococcus*	Genus *Wolbachia*	-	-
	L. helveticus 1515	-	-	-	-
	L. reuteri 30242	-	-	-	-
	L. reuteri 8513d	-	-	-	-
	L. fermentum 8312	-	-	-	-
	L. casei Y	-	-	-	-
	L. sakei Probio65	Genus *Acetobacter* Genus *Lactobacillus* Genus *Stenotrophomonas* Genus *Serratia* Genus *Corynebacterium_1* Genus *Enterococcus*	Genus *Wolbachia*	increase	-
Song et al. [28]	*L. plantarum DP189*	Phylum *Firmicutes* Genus *Parabacteroides* Genus *Alistipes* Genus *Bacteroides* Genus *Coprobacillus* Genus *Aerococcus* Genus *Jeotgalicoccus* Genus *Prevotella* Genus *Candidatus arthromitus*	Phylum *Bacteroidetes*	-	-

Table 2 (continued)

Study	Strains	Changes in gut microbiota		Alpha Diversity	Beta Diversity
		Increase	Decrease		
Tan et al. [30]	*L. casei* isolated from Yakult	Genus *Strenotrophomonas* Genus *Lactobacillus* Genus *Corynebacterium_1*	Genus *Wolbachia*	-	-
	L. plantarum DR7	Genus *Acetobacter* Genus *Strenotrophomonas* Genus *Pseudomonas*	Genus *Wolbachia* Genus *Lactobacillus*	-	-
	L. fermentum DR9	Genus *Acetobacter*	-	-	-
Wang et al. 2020 [31]	*B. bifidum TMC3115* and *L. plantarum 45*	Genus *Parabacteroides* Genus *Acetatifactor* Genus *Millionella*	Genus *Bacteroides* Genus *Desulfovibrio*	-	-
	B. bifidum TMC3115		Genus *Desulfovibrio* Genus *Intestinimonas*	-	-
	L. plantarum 45		Genus unidentified *Ruminococcaceae* Genus *Desulfovibrio* Genus *Intestinimonas*	-	-
Wang et al. 2022 [32]	*L. plantarum MA2*	*Firmicutes/Bacteroidetes* ratio (nearly same level as control) Family *Lactobacillaceae* Family *Ruminococcaceae*	Family *Prevotellaceae* Family *Muribaculaceae*	increase	increase
Abdelhamid et al. [33]	*B. breve MCC1274*	no change			
Webberley et al. [38]	Lab4b: *L. salivarius CUL61 (NCIMB 30211)*, *L. paracasei CUL08 (NCIMB 30154)*, *B. bifidum CUL20 (NCIMB 30153)*, and *B. animalis* subsp. *lactis CUL34 (NCIMB 30172)*	Genus *Ligilactobacillus* Genus *Bacteroides* Genus *Enterococcus* Family *Lachnospiraceae* Family *Oscillospiraceae*	*Firmicutes/Bacteroidetes* ratio Genus *lactobacillus* Family *Enterobacteriaceae*	no change	-
Kobayashi et al. [39]	*B. breve A1*	Phylum *Actinobacteria* Family *Bifidobacteriaceae*	Family *Odoribacteraceae* Family *Lachnospiraceae*	-	-

Morris water maze test, short-term memory using the Y-maze test, and long-term memory using the passive avoidance test. Probiotics can significantly improve spatial recognition, long-term memory and short-term memory as shown in Figs. 5, 6, 7. In some studies, AD Mice treated with *B. breve XY* from *Zhu* et al. did not show obvious improvement in behavioral tests in spite of the reduction in Aβ plaque deposition [22]. This suggests that further application should consider clinical significance in accordance with measured pathology.

Dosages & feasibility in delivering therapeutic doses in human

Dosages of probiotic administration are among the biggest concerns in clinical application As dosages in certain animal studies that showed positive results may not be able to be administered in human. Hence, human equivalent dose (HED) should be considered. Conversion to HED of probiotics was performed (except included studies with drosophila models due to no available data for dosage conversion and those with inadequate information) using the method from *Nair* et al. that is based on body surface area [54]. The extrapolated HED was presented in Supplementary material 2 which is adjusted to the dosage per day for 60 kg in weight for human. The dosage ranges from a minimum of 9.72×10^{8} CFU/day to a maximum of 8.75×10^{14} CFU/day. Compared with the doses in commercial yogurts, the doses range from 4.8×10^{9} to 9.5×10^{10} CFU per a single 100 mL serving [55]. Moreover, probiotic dosages that were used in human studies about obesity-related microbiota dysbiosis range from 1×10^{8} CFU/day to 1.35×10^{15} CFU/day [56]. Therefore, the doses in the included studies can be delivered in human. Although this extrapolation may show feasibility in the admistration of probiotic in clinical setting, higher CFU counts may not reflect improvement in therapeutic effects [57]. This would suggest further studies in human to investigate optimal dosages for clinical use.

Limitations, strengths and suggestions for further studies

There are some limitations of this study to be considered. The first limitation is the variations in outcome measurements. As the inclusion criteria for outcomes measured in included studies were set to measure at least one out of four outcomes, including AD pathology, cognitive function, neuroinflammation, and gut microbiota composition, a direct comparison of a single outcome among all included studies could not be made. Moreover, one outcome may be measured via different methods. For instance, the measurements of amyloid beta plaque deposition were done in different manners, such as histological examination and quantification of amyloid beta plaque, which resulted in different units of measurement. Different aspects of cognitive function assessment in each study, such as short-term memory and spatial recognition, also make it difficult for the conclusions to be drawn. The second limitation includes the variations in strains and dosages of probiotics treatment, species of animal models, and intervention time. There are three species of animal models included in this study: mice, rats, and drosophila. The lifespans of each species vary. Along with the differences in the intervention time, variations in the percentage of intervention time per lifespan may disrupt the conclusion of long-term results of probiotics on AD which are the effect that lasts long even after a certain period of time of the intervention cessation. Most studies did not continue to observe these effects such as the progression of AD pathology, cognitive function. For instance, the gut microbiota composition was not continuously detected to find the duration of the probiotic action or the duration when the pathology may return after the cessation of probiotic administration. The third limitation is AD pathological conditions created in animal models. Different substances were used to simulate the pathological condition of AD. Most studies injected intrahippocampal amyloid beta into animal models, which may not be able to fully represent the actual pathological conditions of AD in humans.

The strengths of this study are the demonstration of the therapeutic effects of probiotics on AD via several parameters and outcome measurements, which enables the discussion about potential mechanisms of probiotics on the gut-brain axis. Despite the variations in probiotic strains and animal species, probiotics still reveal promising therapeutic results in most outcomes.

Further studies are suggested to focus on strain-specific results of probiotics in clinical settings. It should be noted that different species respond differently to the same interventions. Hence, more clinical trials should be done to elucidate clearer mechanisms of each strain of probiotics on AD, optimal dosages, and possible side effects. Moreover, the effects of long-term use of probiotics on memory impairment and cognitive function should be assessed. Importantly, the safety of each strain or formula is the primary concern. Probiotics are claimed as Generally Recognized as Safe (GRAS) by the American Food and Drug Administration (FDA) [58]. Some widely-mentioned strains for treating AD include *L. acidophilus, L. casei, B. bifidum, L. fermentum* [58]. However, probiotics should be used with caution in some situations, including immunodeficient patients, premature babies, patients with a catheter inserted into large veins, and patients in severe clinical conditions [58].

Conclusion

This study demonstrates the effects of probiotic administration in animal models on multiple outcomes including gut microbiota profile, AD pathology, neuroinflammation, and cognitive function. The results showed significant reductions in Aβ plaque deposition, decreased neuroinflammation, and improved cognitive function along with the alterations in gut microbiota profile in both diversity and richness. Future studies are suggested to further elucidate the strain-specific results and optimal dosages and regimens before clinical application.

Abbreviations

AD	Alzheimer's disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Iba1	Ionized calcium-binding adaptor molecule, also called allograft inflammatory factor 1, is a well-established marker for microglia/macrophages
BDNF	Brain-derived neurotrophic factor (BDNF) plays an important role in neuronal survival and growth, serves as a neurotransmitter modulator, and participates in neuronal plasticity, which is essential for learning and memory. It is widely expressed in the CNS, gut and other tissues

Glossary

IL-1β	is used as a biological response modifier to boost the immune system in cancer therapy. Interleukin-1-beta is a type of cytokine. Also called IL-1-beta and IL-1B
IL-6	is a soluble mediator with a pleiotropic effect on inflammation, immune response, and hematopoiesis
TNF-α	Tumour Necrosis Factor alpha is an inflammatory cytokine produced by macrophages / monocytes during acute inflammation and is responsible for a diverse range of signalling events within cells, leading to necrosis or apoptosis
GFAP	Glial fibrillary acidic protein is an intermediate filament (IF) III protein uniquely found in astrocytes in the CNS, non-myelinating Schwann cells in the peripheral nervous system (PNS), and enteric glial cells

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
YS: project administration, conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing original draft (results, discussion, conclusion), writing-review and editing. OC: data curation, formal analysis, investigation, methodology, visualization, writing original draft (introduction, results), writing-review and editing. TA: data curation, formal analysis, investigation, methodology, visualization, writing original draft (methodology, results), writing-review and editing. AS: funding acquisition, supervision, validation. All authors have approved the final version of this manuscript and contributed to the process of making arguments within the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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