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REVIEW

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Gut microbiome-targeted therapies for Alzheimer's disease

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ABSTRACT

The advent of high-throughput 'omics' technologies has improved our knowledge of gut microbiome in human health and disease, including Alzheimer's disease (AD), a neurodegenerative disorder. Frequent bidirectional communications and mutual regulation exist between the gastrointestinal tract and the central nervous system through the gut-brain axis. A large body of research has reported a close association between the gut microbiota and AD development, and restoring a healthy gut microbiota may curb or even improve AD symptoms and progression. Thus, modulation of the gut microbiota has become a novel paradigm for clinical management of AD, and emerging effort has focused on developing potential novel strategies for preventing and/or treating the disease. In this review, we provide an overview of the connection and causal relationship between gut dysbiosis and AD, the mechanisms of gut microbiota in driving AD progression, and the successes and challenges of implementing available gut microbiome-targeted therapies (including probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation) in preventive and/or therapeutic preclinical and clinical intervention studies of AD. Finally, we discuss the future directions in this field.

Box 1 Glossary

Gut microbiota: The collection of microbes that inhabit the gut[13].

Gut microbiome: The collection of all genomes of microbes that reside in the gut[14].

Probiotic: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host"[15].

Prebiotic: "A substrate that is selectively utilized by host microorganisms conferring a health benefit"[16].

Synbiotic: "A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host"[17].

Postbiotic: "Preparation of inanimate microorganisms and/or their components that confers a health benefit on the host"[18].

Fecal microbiota transplantation: Transfer of feces from a healthy donor to a recipient patient to attempt to treat a specific disease associated with the gut microbiota[19].

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Introduction

Alzheimer's disease (AD) is one of the most common forms of dementia that can range in severity from cognitive impairment to incapacitation. It is a neurological disorder characterized by the accumulation of β-amyloid-containing extracellular plaques and tau-containing intracellular neurofibrillary tangles.[1] Around 6.07 million people aged 65 and older in the United States experienced AD in 2020, which is predicted to climb to 13.85 million in 2060.[2] The mortality of AD is 121,499 individuals in 2019, making it the sixth-leading cause of death in the United States.[3] The short life expectancy, low quality of life, and high health-care costs incurred by the AD have triggered a heavy social burden.[3] Although the pathogenesis of AD remains incompletely understood, multiple confounding factors that contribute to disease progression have been determined.[4] Age,

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genetics, and family history are the well-established risk factors for AD. Individuals of 65 y of age and older exhibit greater susceptibility to AD than younger people.[5] A recent genome-wide association study has identified 38 susceptibility loci regulating AD risk, acting via immune dysregulation and protein catabolism,[6] of which the apolipoprotein E (*APOE*) alleles have the strongest association with the disease, especially *APOE4* allele.[7] Parental history of dementia has also been linked to an increased risk of dementia.[8] Modifiable risk factors (air pollution, lack of education, hearing loss, smoking, etc.) for AD in addition to the aforementioned events also deserve emphasis.[9] Although the major strides in the pathophysiology of AD have been made, no 'magic bullet' therapies are available. Of note, aducanumab, a monoclonal antibody targeting amyloid β (Aβ), has been granted accelerated approval by the United Food and Drug Administration for treating AD in 2021.[10] The divergence related to real-world effectiveness and safety over this first-in-class drug, however, causes anxiety for clinicians and patients.[11] Thus, concerted effort to expand the limited treatment options would tremendously aid clinical management of AD.

Although the clinical manifestations of gastrointestinal dysfunction associated with the pathogenesis of Parkinson's disease,[12] another clinicopathological entity of neurodegenerative diseases, are not established in patients with AD, accumulating evidence suggests that the gut microbiota (see Box 1 for definitions)[13–19] plays an important role in the onset and progression of AD.[20] Alterations in the gut microbiome composition and functionality have been observed both in animal and human studies,[21] and the results of fecal microbiota transplantation (FMT) intervention studies conducted in both germ-free (GF) mice and antibiotic-treated pseudo-GF mice further suggested that the gut microbiome is a key driver of AD development.[22] The establishment of a causality relationship between alterations in gut microbiota and the progress of AD forms the basis for designing novel therapeutic strategies targeting the gut microbiome, such as probiotics, prebiotics, synbiotics, postbiotics, and FMT.

This review summarizes the current knowledge of the mechanistic role of the gut microbiome in the development of AD and potential gut microbiome-targeting therapies in managing the disease. Finally, we discuss future directions of translating the gut microbiome research into clinical practice.

The gut microbiome and AD

Aberrant gut microbiota in AD patients

Nineteen next-generation sequencing technology-based observational studies have reported the observation of an altered gut microbiota in patients diagnosed with AD compared with healthy controls (Supplementary Table S1). At least 11 phyla, 15 classes, 14 orders, 38 families, 137 genera, and 51 species were regarded as significantly differential bacterial taxa between healthy and diseased individuals, though only a low proportion (26/266, 9.77%) of them altered in one study showed consistent changes in another study (Supplementary Table S2). The most frequently reported differentially abundant families and genera are: the families *Enterococcaceae* (four studies), *Lachnospiraceae* (four studies), and *Ruminococcaceae* (four studies); the genera *Bifidobacterium* (seven studies), *Bacteroides* (six studies), *Blautia* (six studies), *Dorea* (four studies), *Eubacterium* (four studies), and *Parabacteroides* (four studies). However, for most reported differentially abundant taxa, contradictory results are seen between studies. For example, five studies detected more gene sequences representing *Bifidobacterium* in the gut microbiota of patients with AD, while two studies found an opposite trend of difference. Only few families and genera exhibit a consistent trend of difference between patients with AD and healthy subjects (Supplementary Table S2), including: an increase representation in the families *Enterobacteriaceae* (two studies), *Erysipelotrichaceae* (two studies), and *Gemellaceae* (two studies), but a decrease representation in the family *Lachnospiraceae* (four studies) and *Clostridiaceae* (two studies) in the gut microbiota of patients with AD; an increase representation in the genera *Akkermansia* (three studies), *Anaerotruncus* (three studies), *Collinsella* (three studies), *Bilophila* (two studies), *Escherichia-Shigella* (two studies), *Flavobacterium* (two studies), *Gemella* (two studies), *Lactobacillus* (two studies), and *Solobacterium* (two studies), but a decrease representation in the genera *Roseburia*

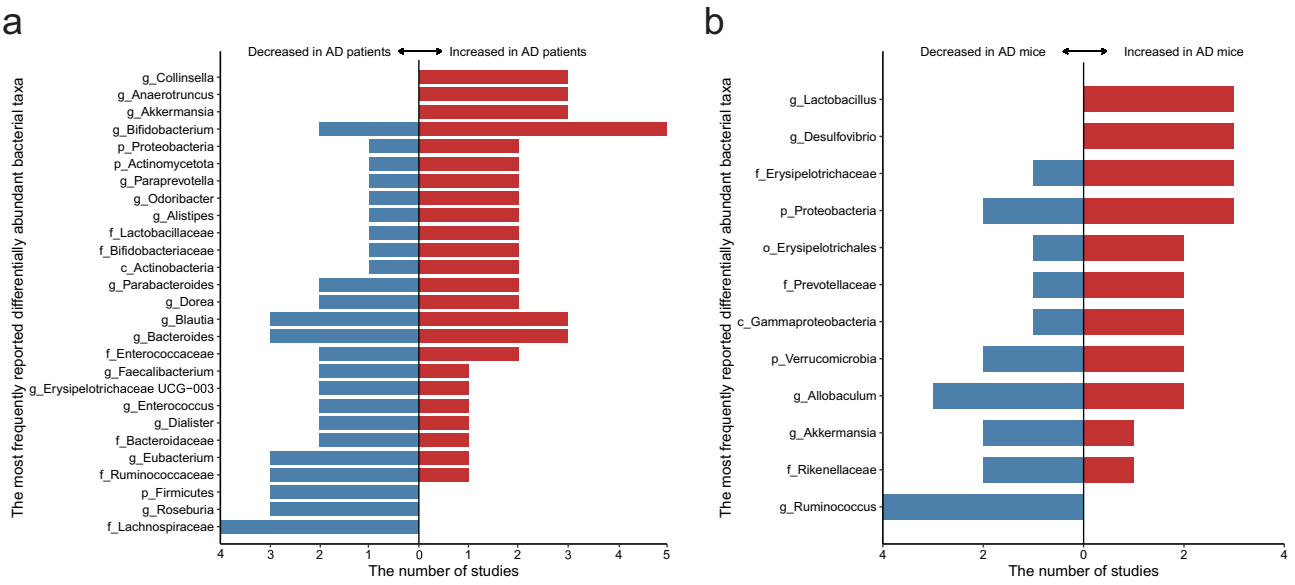

Figure 1. An overview of the most frequently reported differentially abundant gut taxa (reported in at least three studies) of Alzheimer's disease (AD) in (a) humans and (b) animals. Red represents a stronger enrichment in the gut microbiota of subjects with AD, while blue represents a stronger enrichment in the gut microbiota of healthy controls. The prefix code in the taxon name represents taxonomic level; p = phylum; c = class; o = order; f = family; g = genus.

(three studies), *Anaerostipes* (two studies), *Butyricicoccus* (two studies), *Coprococcus* (two studies), *Lachnoclostridium* (two studies), *Lachnospira* (two studies), *Megamonas* (two studies), *Parasutterella* (two studies), and *Ruminococcus* (two studies) in the gut microbiota of patients with AD.

Although the gut microbiota profile in patients with AD represents substantial heterogeneity, patients with AD seem to have a distinct intestinal microbial landscape from healthy individuals, and the role of the differential abundant taxa in the development and pathogenesis in AD are still obscure, which warrants further confirmation and investigation.

Dysregulated gut microbiota in animal models of AD

Similarly, alterations in the gut microbiota composition have been reported in animal models of AD (Supplementary Table S3). One hundred and forty-three bacterial taxa were reported to show statistical significance between the gut microbiota of healthy and AD model mice in 11 observational studies, including seven phyla, four classes, eight orders, 35 families, 69 genera, and 20 species (Supplementary Table S4). At least 14 of these 143 bacterial taxa showed consistent results between at least two independent studies, particularly, the genus *Ruminococcus* was concordantly reported to be decreased in AD model mice in four unrelated studies. In addition, the genera *Desulfovibrio* and *Lactobacillus* were concordantly reported to be increased in AD model mice in three unrelated studies. Notably, the phyla Proteobacteria (five studies) and Verrucomicrobia (four studies), the family *Erysipelotrichaceae* (four studies), the genus *Allobaculum* (five studies) and *Ruminococcus* (four studies) were most frequently reported differentially abundant bacterial taxa in the selected studies. Altogether, these data suggested that the gut microbiota in AD model mice is distinct from those of the healthy controls, and some common differential bacterial taxa have been captured across studies.

It is worth mentioning that the AD differential microbial taxa identified in clinical and preclinical studies are largely non-overlapping (Figure 1). Such finding represents an enormous challenge of translational gut microbiome research, which is likely due to the substantial intrinsic difference between the mouse and human gut microbiome configurations.[23] In addition, 77.8% (21/27) and 75% (9/12) of the most frequently reported differentially abundant bacterial taxa (reported in at least

three studies) showed inconsistent results in human and animal observational studies, respectively, suggesting that there are intrinsic differences both among humans and among animals, not just the differences between humans and animals. The variability of the human and animal microbiota results may be attributed to differences in methodology applied (such as fecal sample preservation, sequencing methods and bioinformatic analyses). Furthermore, factors that influence the gut microbiome should not be ignored, especially diet and lifestyle, as they are crucial determinants of overall gut microbial composition and function.[24] Together, these various confounders affecting the heterogeneity between studies should be taken into account in future studies, which will greatly facilitate the repeatability and reproducibility of data between laboratories.

Relationship between the gut microbiome and AD

An overwhelming amount of observational data from animal and human studies have consistently pointed to a close association between the gut microbiota and AD development, and, in recent years, the field of gut microbiome research in AD has started to move rapidly from correlation to causation.

The first generation of studies that disentangle the causality of gut microbiome in AD is mainly achieved by depleting the indigenous gut microbiota in transgenic (Tg) mouse models with AD phenotypes via implementing broad-spectrum combination antibiotics. For example, both short- and long-term antibiotic treatment-induced perturbations in the gut microbiota could lead to decreased Aβ plaque deposition and attenuated plaque-localized glial reactivity in male APP/PS1 mice.[25,26] However, the latter effect was not obvious in female APP/PS1 mice,[26] suggesting that the gut microbiome played a sex-specific role in brain Aβ amyloidosis and microglial homeostasis.[27] Yet it is worth noting that disrupting the gut microbiota by individual antibiotics (rather than a wide-spectrum antibiotic cocktail) was insufficient to reproduce these desired outcomes.[28]

The second generation of studies dissecting the causal relationship of the gut microbiota in AD development and AD pathology are conducted mainly through FMT experiments, which will be discussed later in the FMT section. Results obtained from the emerging explanatory research have started to present compelling and converging evidence supporting that the gut microbiome is a major determinant driving AD pathology.

Mechanisms of action of gut microbiota in driving AD progression

There is growing evidence that close connections and bidirectional communications exist between the brain and the gut through the gut-brain axis via the immune, endocrine/systemic, and neuronal pathways.[29] The following sections discuss new insights into the mechanisms by which the gut microbiota contributes to AD (Figure 2).

Gut microbiota-microglia connections

Microglia are the resident macrophages of the central nervous system (CNS)[30]. They are of paramount importance to ensure a healthy brain development and homeostasis under normal conditions. In AD, dynamic changes in microglial activation can affect disease progression[31,32], playing a central role for promoting disease pathogenesis.

It is known that microglia can be orchestrated by gut microbiota. This notion is supported by a groundbreaking animal study, which reported the observations of global defects in microglia in GF mice and severely changed microglia properties in antibiotic-treated specific pathogen-free (SPF) mice and the defective phenotype could be, at least in part, reversed by a co-housing experiment.[33] Intriguingly, two other studies further substantiated that the impact of gut microbiota on microglia,[34,35] meanwhile reporting that such effect was temporal- and sex-specific.[35] Furthermore, the increased gut barrier permeability driven by the gut microbiota during aging results in increased translocation of gut-derived N^6-carboxymethyllysine into the brain, consequently triggering oxidative stress and mitochondrial dysfunction in the microglia.[36] In fact, it has also been shown that microglia were required in the process of gut microbiota-driven brain Aβ plaque deposition in a mouse model of AD.[37,38]

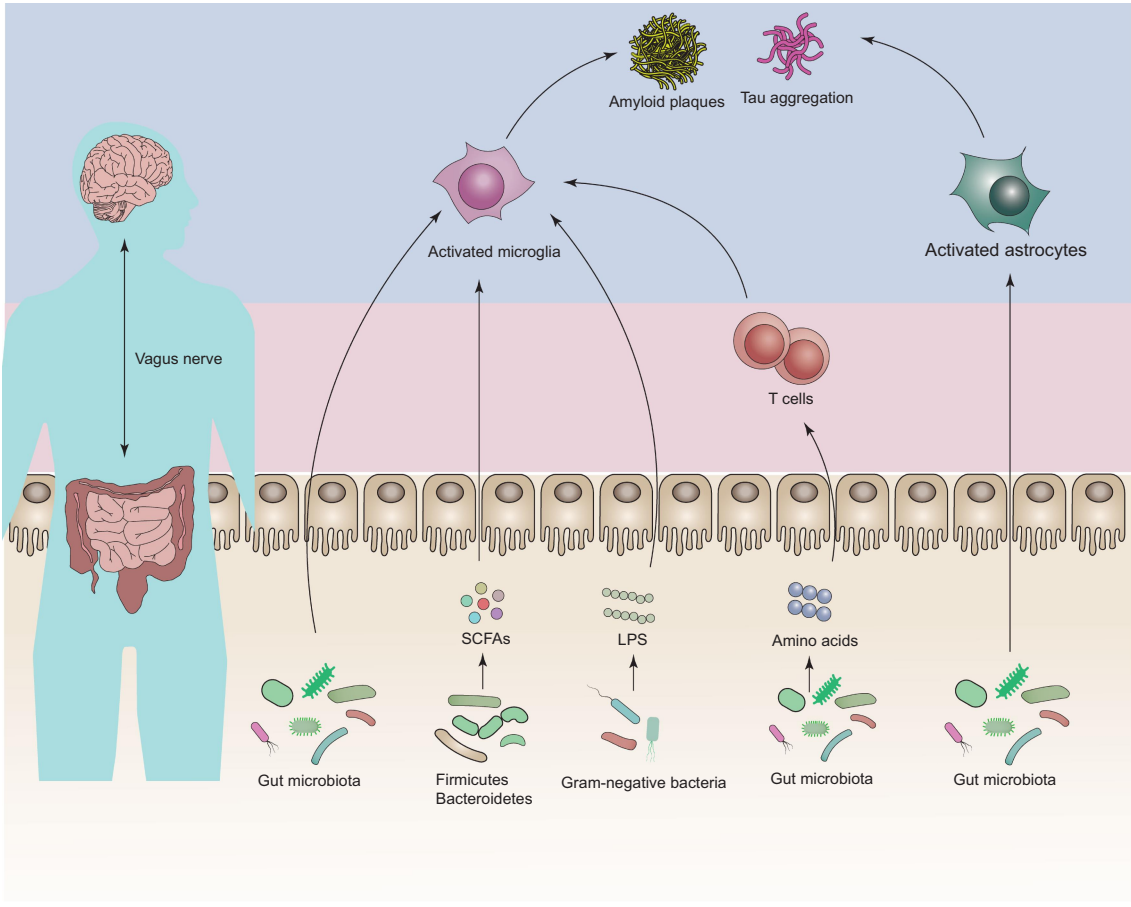

Figure 2. Mechanistic insights of gut microbiota in Alzheimer's disease (AD) development. In AD, the intestinal barrier is compromised, which allows gut microbes and molecules to cross the intestinal epithelium.[202] Gut microbiota can directly impact microglia.[33–36] Importantly, microglia are required in the process of gut microbiota-driven brain amyloid β (Aβ) plaque deposition.[37] Short-chain fatty acids (SCFAs) produced by gut Firmicutes and Bacteroidetes can cross the intestinal barrier into the circulation, leading to Aβ plaque deposition through modulating plaque-associated microglial functions.[60,61] Lipopolysaccharides (LPS), pro-inflammatory compounds produced by Gram-negative bacterial membranes, can also enter the circulation, leading to amyloid and tau pathology.[66,67] Likewise, astrocyte activation can be regulated by gut microbiota, leading to Aβ deposition.[45] T cells also play an important role in AD.[203] The peripheral accumulation of phenylalanine and isoleucine caused by gut microbiota can stimulate the differentiation and proliferation of pro-inflammatory T helper 1 cells which crosstalk with M1 microglial cells in the brain, resulting in AD-associated neuroinflammation and cognitive impairment.[53] The role of T cells and other immune cells in the development of AD through the control of the gut microbiota requires further investigation. Whether these mechanisms occur individually or in combination to promote AD requires further investigation.

Additionally, single-nucleus RNA-sequencing of brain cells of GF, SPF, and colonized-GF mice revealed that the absence of gut microbiota could lead to cell-specific transcriptomic changes, preferentially in microglia; and such cellular alterations were associated with AD and could be effectively reversed by microbial colonization.[39] Another study conducted by Seo et al. (2023) found that GF or antibiotic-treated genetically engineered mice of tauopathy expressing human *APOE* isoforms exhibited reduced gliosis, tau pathology, and neurodegeneration in a sex- and *APOE* isoform-dependent manner, providing direct evidence of the role of the gut microbiota in interactive regulation of neuroinflammation and tau-mediated neurodegeneration.[40]

Gut microbiota-astrocytes connections

Astrocytes are the predominant type of glial cells in the CNS, which is known to play a part in the cellular phase of AD.[41] Although several recent studies have further reinforced the essential role of astrocytes in AD pathogenesis,[42–44] the

connections between astrocytes and intestinal microbiota are less explored compared with microglia.

One previous work found that transferring the feces from 16-month-old APP/PS1 mice to antibiotic-pretreated 3-month-old APP/PS1 mice for 7 d could lead to increased Aβ deposition, presumably through inhibiting the activation of astrocytes around Aβ plaques.[45] In a mouse model of multiple sclerosis, another nervous system disease, the combined application of microbial metabolites of tryptophan and type I interferons could activate aryl hydrocarbon receptor signaling in astrocytes and suppress CNS inflammation.[46] In an experimental autoimmune encephalomyelitis model, it was found that gut microbiome-driven production of interferon-γ by meningeal natural killer cells could upregulate the expression of the tumor necrosis factor-related apoptosis inducing ligand in astrocytes, thereby limiting CNS inflammation through inducing T cell apoptosis.[47] Together, these limited data suggest that the gut microbiota has the capacity to modulate astrocyte function, and whether and how these astrocyte-based anti-inflammatory mechanisms affect AD remains to be further investigated.

Gut microbiota-T cell connections

The gut microbiota can manipulate immune cells to influence disease manifestation, such as stroke[48] and multiple sclerosis.[47] Thus, apart from the CNS immune cells, such as microglia and astrocytes, brain-infiltrated peripheral immune cells may also play a part in AD neuropathogenesis.[49–52]

A previous study found that, the shift in the gut microbiota during AD progression led to the peripheral accumulation of phenylalanine and isoleucine, stimulating the differentiation and proliferation of pro-inflammatory T helper 1 (Th1) cells. Pro-inflammatory Th1 cells were associated with the M1 microglia activation, contributing to AD-associated neuroinflammation and cognitive impairment. Moreover, healthy control mice exhibited an increase in Th1 cell infiltration and M1 microglia activation when exposed to fecal bacteria of AD mice by co-housing or FMT, and FMT of WT mice feces into AD mice could reduce Th1 cells of the recipient mice.[53] The study supported that gut dysbiosis is a driver for AD progression. Given the interconnectedness of the gut microbiota and immune system in neurodegenerative diseases, continual efforts should be made to decipher the precise role of T cells and other immune cells in the development of AD through the control of the gut microbiota.[54]

In addition, it is noteworthy that gut-derived metabolites are integral to AD development.[55] Although changes in metabolite profile with respect to AD have been identified with the help of metabolomics, including but not limited to short-chain fatty acids (SCFAs),[56] lipopolysaccharides (LPS),[56] bile acids,[57] trimethylamine-N-oxide[58] and amino acids,[59] few studies have investigated the causative links between these bioactive compounds and AD progression. Two distinct mouse models of AD have provided elegant examples of cause- and- effect relationships between the SCFAs and the disease progress. In these studies, it was shown that supplementing SCFAs to either GF APP/PS1 or 5×FAD mice could lead to increased Aβ plaque deposition through modulating plaque-associated microglial functions, compared to their SPF.[60,61] Akin to the notion that SCFA supplementation could modulate microglia and worsen disease progression in a mouse model of Parkinson's disease.[62] These converging studies suggest a detrimental effect of SCFAs on neurodegenerative diseases. Conversely, SCFAs have also been shown to be beneficial for AD in vitro and in vivo.[63–65] In addition, LPS, pro-inflammatory compounds produced by Gram-negative bacterial membranes, could also lead to amyloid and tau pathology in animal models.[66,67] The role of other metabolites in AD needs to be further validated and tested in mechanistic models.

Collectively, studies dissecting the potential mechanisms by which the gut microbiota and their metabolites influence AD remain in its infancy, and additional research is needed to explore whether other action pipelines exist.

Gut microbiome-targeted therapies

Given that the tight connection between the gut microbiota and AD, and the mounting evidence supporting that microbial dysbiosis is a driver of the onset and progression of AD, attempts to circumvent AD through microbiome modification

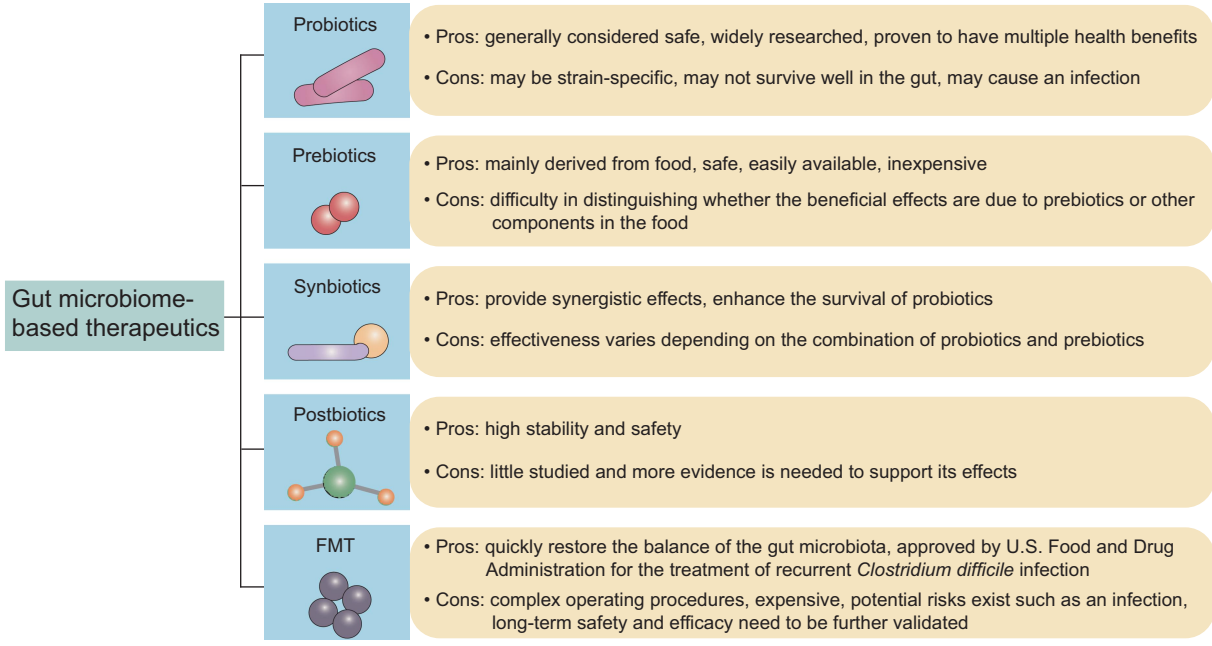

Figure 3. Microbiome-based therapeutics in Alzheimer's disease (AD). Microbiome-based therapeutics for AD including probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT). The beneficial effects of these intervention approaches on AD remain to be tested, and the exact mechanism of AD improvement through regulating the intestinal microbiota needs to be also explored.

that restores gut homeostasis hold great promise. In the following sections, we summarize available strategies that target the gut microbiota, including probiotics, prebiotics, synbiotics, postbiotics, and FMT (Figure 3), and current challenges.

Probiotics

The excellent ability of probiotics to modulate the gut microbiota has motivated their widespread use in various disease management, ranging from intestinal diseases to extraintestinal diseases, including AD.

Preclinical evidence

While experimental animal models of AD might not accurately recapitulate clinical scenarios, they are essential for us to understand AD pathophysiology and related drug development. Animal models of AD include Tg and non-Tg models, of which Tg mouse models are most commonly used.[68] Probiotic intervention studies in AD Tg rodent models are summarized in Table 1.[69–95]

The pioneering work of Bonfili et al. (2017) provided evidence supporting the improvement effect of SLAB51 probiotic formulation in reducing cognitive decline, Aβ plaque and brain damages through restoring the gut microbial homeostasis in 3×Tg AD mice, providing a paradigm for managing AD with probiotic-based therapeutics.[69] Over the ensuing years, the neuroprotective effects of a multitude of probiotics on AD were investigated, including not only well-known probiotic species belonging to the genera *Lactobacillus* and *Bifidobacterium*, such as *Lactobacillus plantarum*, [71,80,85] *Bifidobacterium longum*, [72,81] *Lactobacillus lactis* subsp. *cremoris*, [74] *Bifidobacterium lactis*, [82] and *Bifidobacterium breve*, [89,91,95] but also less conventional probiotic species including *Akkermansia muciniphila*, [77] *Clostridium butyricum*, [78] *Agathobaculum butyriciproducens*, [83] and *Saccharomyces boulardii*. [93] Besides single-strain probiotics, some intervention trials evaluated the beneficial effects of multi-strain probiotics in AD.[69,70,73,75,76,79,84,87,88,90,92,94]

Most of these animal-based probiotic intervention trials have observed some extent of beneficial or even therapeutic effects on AD after the intervention with only few exceptions, although different study parameters were used, including probiotic strain used, probiotic dose, treatment duration, and the animal model. For example,

Table 1. Comprehensive summary of probiotic intervention studies of Alzheimer's disease (AD) using transgenic rodent models.

Study	Probiotic product or strain	Probiotic dose	Duration of probiotic intervention	Information of transgenic rodent model	Main observations
Bonfili et al. (2017)[69]	SLAB51 probiotic formulation	2×10^{11} bacteria/kg/day	4 months	8-week-old male 3×Tg-AD mice	• Reduced cognitive decline, amyloid load and brain damage • Increased gut hormone concentration • Changed the gut microbiota composition
Bonfili et al. (2018)[70]	SLAB51 probiotic formulation	2×10^{11} bacteria/kg/day	4 months	8-week-old male 3×Tg-AD mice	• Reduced oxidative stress in the brain of AD mice by activating sirtuin 1-dependent mechanisms
Lee et al. (2018)[71]	*Lactobacillus plantarum* C29	1×10^{9} CFU	2 months	6-month-old male 5×FAD mice	• Slowed down the progression of memory impairment • Suppressed amyloid β (Aβ) plaque formation and expression of β-/γ-secretases and caspase-3 • Suppressed blood and fecal lipopolysaccharide levels • Increased brain-derived neurotrophic factor expression and inhibited nuclear factor kappa-B activation • Restored the disturbed gut microbial community • Improved gut membrane permeability
Lee et al. (2019)[72]	*Bifidobacterium longum* NK46	1×10^{11} CFU	2 months	6-month-old male 5×FAD mice	• Attenuated cognitive decline • Shifted the gut microbiota composition • Suppressed gut inflammatory markers, such as myeloperoxidase, interleukin (IL)-6, and tumor necrosis factor-alpha (TNF-α)
Bonfili et al. (2020)[73]	SLAB51 probiotic formulation	2×10^{11} bacteria/kg	14 months	8-week-old male 3×Tg-AD mice	• Influenced glucose uptake • Decreased phosphorylated tau level • Attenuated the increase in glycated hemoglobin
Cecarini et al. (2020)[74]	*Lactobacillus lactis* subsp. *cremoris* MG1363	1×10^{9} CFU	2 months	8-week-old male 3×Tg-AD mice	• No difference in cognitive function • Reduced brain amyloid load • Modulated the ubiquitin-proteasome system and autophagy • Diminished neuronal oxidative and inflammatory processes
Kaur et al. (2020)[75]	VSL#3	$.32 \times 10^{9}$ CFU/25 g mice	2 months	6–8-month-old female APP^{NL-G-F} mice	• Altered the gut microbiota composition • Increased short-chain fatty acid concentrations, including serum acetate, butyrate, isobutyrate, lactate, and propionate levels; brain acetate and lactate levels • No effect on Aβ accumulation and gliosis
Kaur et al. (2020)[76]	VSL#3	$.32 \times 10^{9}$ CFU/25 g mice	2 months	6–8-month-old female APP^{NL-G-F} mice	• Regulated the gut microbiota composition • Attenuated gut permeability and intestinal inflammation • Regulated the level of some eicosanoids, such as prostaglandin E2, F2α, and 6-keto-prostaglandin F1α in serum; arachidonic acid in brain • No effect on most bile acids in serum and brain • No effect on Aβ accumulation, cytokines, gliosis, and memory function
Ou et al. (2020)[77]	*Akkermansia muciniphila* GP01	5×10^{9} CFU	6 months	3-month-old male APP/PS1 mice	• Ameliorated glucose homeostasis and restored intestinal barrier function • Reduced Aβ plaque deposits and Aβ levels • Ameliorated lipid metabolism disorder • Relieved cognitive impairment and anxiety-related behaviors
Sun et al. (2020)[78]	*Clostridium butyricum* CGMCC 9831	2×10^{8} CFU	1 month	6-month-old APP/PS1 mice	• Ameliorated cognitive deficits • Reduced Aβ deposition • Suppressed microglial activation and proinflammatory cytokine levels, such as IL-1β and TNF-α • Regulated abnormal gut microbiota and metabolites, such as butyrate
Wang et al. (2020)[79]	*Bifidobacterium bifidum* TMC3115 and *Lactobacillus plantarum* 45	1×10^{9} CFU	3.5 months	8-week-old male APP/PS1 mice	• Significant improvement only seen in Morris water maze test but not open field test and novel object recognition test • Elevated alpha and beta microbial diversity • Reversed gut dysbiosis by suppressing *Bacteroides* and enhancing *Acetatifactor* and *Millionella*

(*Continued*)

Table 1. (Continued).

Study	Probiotic product or strain	Probiotic dose	Duration of probiotic intervention	Information of transgenic rodent model	Main observations
Wang et al. (2020)[80]	*Lactobacillus plantarum* ATCC 8014	1×10^9 CFU/mL	3 months	6-month-old male APP/PS1 mice	• No differences in cognitive impairment • Reduced Aβ plaques • Slightly effected hippocampal neuron and plasticity • Reduced plasma trimethylamine and trimethylamine-N-oxide levels • Reduced proinflammatory cytokines (IL-2, IL-17 and TNF-α) in the hippocampus
Wu et al. (2020)[81]	*Bifidobacterium longum* 1714	1×10^9 CFU/mL	6 months	4-month-old APP/PS1 mice	• Reduced Aβ deposition • Inhibited microglia activation • Decreased neural pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-4, IL-6, and interferon-γ
Cao et al. (2021)[82]	*Bifidobacterium lactis* Probio-M8	1×10^9 CFU/mL	1.5 months	4-month-old APP/PS1 mice	• Reduced Aβ plaques • Protected against gut microbiota dysbiosis • Attenuated cognitive impairment
Go et al. (2021)[83]	*Agathobaculum butyriciproducens* SR79	2×10^8 CFU	2 to 2.25 months	APP/PS1 mice	• Improved cognitive impairment • Reduced Aβ plaque deposition and microglial activation in the parietal cortex and hippocampus • Decreased expression of IL-1β and C1QB; increased expression of insulin-like growth factor-1
Guilherme et al. (2021)[84]	OptiBac for those on antibiotics	1×10^9 CFU/mL	3.5 months	4-week-old male 5×FAD mice	• No differences in Nesting score, Aβ deposition, body weight, and blood glucose
Huang et al. (2021)[85]	*Lactobacillus plantarum* PS128	1×10^9 CFU	33 d	6-month-old male 3×Tg-AD mice	• No differences in cognitive dysfunction • No differences in Aβ deposition- and tau protein-related protein levels • No differences in fecal short-chain fatty acid levels, such as propionic acid, acetic acid, and butyric acid • Reduced the activation of microglia but not astrocytes • No differences in the synaptic plasticity and cognition-related neuronal loss
Kaur et al. (2021)[86]	VSL#3	4×10^9 CFU/25 g mice	2 months	2–3-month-old male and female APP^{NL-G-F} mice	• Decreased Aβ plaques, microgliosis, and brain TNF-α level • Memory improvement observed only in female APP^{NL-G-F} mice
Kim et al. (2021)[87]	*Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI	1×10^9 CFU	1 month	3-month-old 5×FAD mice	• Attenuated cognitive impairment • Reduced hippocampal neuronal death • Suppressed amyloidosis and apoptotic processes • Improved synaptic plasticity • Altered the gut microbiome
Sun et al. (2021)[88]	BIOCG	1×10^9 CFU/kg	3 months	6-month-old male 3×Tg-AD mice	• Alleviated learning and memory impairment • Reduced Aβ burden • Alleviated brain inflammation • Reduced intracellular Aβ accumulation
Abdelhamid et al. (2022)[89]	*Bifidobacterium breve* A1	1×10^9 CFU	4 months	3-month-old APP^{NL-G-F} mice	• Prevented memory impairment • Reduced Aβ production, deposition, and fibril formation in the hippocampus • Enhanced the hippocampal levels of a disintegrin and metalloproteinase 10 • Attenuated microglial activation • No change in tau phosphorylation • Increased hippocampal synaptic protein levels
Bonfili et al. (2022)[90]	SLAB51 probiotic formulation	2×10^{11} bacteria/kg/day	14 months	8-week-old male 3×Tg-AD mice	• No difference in genus-level gut microbiota composition • Ameliorated blood lipid profile and modified plasma fatty acid composition • Influenced cholesterol biosynthesis and metabolism • Reduced 27-hydroxycholesterol in plasma and brain

(*Continued*)

Table 1. (Continued).

Study	Probiotic product or strain	Probiotic dose	Duration of probiotic intervention	Information of transgenic rodent model	Main observations
Ohno et al. (2022)[91]	*Bifidobacterium breve* A1	1×10^9 CFU	4 months	3-month-old APP^{NL-G-F} mice	• Increased genistein, 2-oxoglutaric acid, succinic acid, and glutathione divalent
Webberley et al. (2022)[92]	Lab4b	5×10^8 CFU	3 months	3-month-old male 3×Tg-AD mice	• Slowed down cognitive decline • Minimized the loss of thin neuronal spines in the hippocampus • Altered plasma levels of IL-10, keratinocyte chemoattractant/growth regulated oncogene, and TNF-α • Influenced the liver metabolic profile • Altered the gut microbiota composition
Ye et al. (2022)[93]	*Saccharomyces boulardii* HANSEN CBS 5926	1×10^8 CFU	1 month	6-month-old male APP/PS1 mice	• Attenuated cognitive impairment • Reduced Aβ deposition and tau hyperphosphorylation • Improved the synaptic plasticity • Attenuated microglia-induced neuroinflammation • Regulated toll-like receptor signaling pathway • Improved intestinal barrier integrity • Regulated fungal microbiota homeostasis
Webberley et al. (2023)[94]	Lab4P	5×10^8 CFU	6 months	6-month-old male 3×Tg-AD mice	• Prevented disease-associated deteriorations in novel object recognition, hippocampal neuron spine density, and hippocampal mRNA expression of inflammation-associated genes
Zhu et al. (2023)[95]	*Bifidobacterium breve* HNXY26M4	1×10^9 CFU	3 months	4-month-old male APP/PS1 mice	• Alleviated amyloid deposition and cognitive impairment • Ameliorated brain inflammation, oxidative damage, and synaptic impairment • Upregulated claudin-5 expression and promotes intestinal barrier function • Restored gut microbiota composition and short-chain fatty acid levels.

SLAB51 probiotic formulation comprises *Streptococcus thermophilus* DSM 32,245, *Bifidobacterium lactis* DSM 32,246, *Bifidobacterium lactis* DSM 32,247, *Lactobacillus acidophilus* DSM 32,241, *Lactobacillus helveticus* DSM 32,242, *Lactobacillus paracasei* DSM 32,243, *Lactobacillus plantarum* DSM 32,244, and *Lactobacillus brevis* DSM 27,961.

VSL#3 comprises *Lactobacillus plantarum*, *Lactobacillus delbrueckii* subsp. *Bulgaricus*, *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, and *Streptococcus salivarius* subsp. *thermophilus*.

OptiBac for those on antibiotics is composed of *Lactobacillus rhamnosus* Rosell-11 and *Lactobacillus acidophilus/helveticus* Rosell-52.

BIOCG contains *Lactobacillus plantarum* Lp3a, *Bifidobacterium animalis* subsp. *lactis* Bla019, and *Bifidobacterium longum* BL5b.

The Lab4P probiotic consortium is composed of *Lactobacillus acidophilus* CUL21 (NCIMB 30,156), *Lactobacillus acidophilus* CUL60 (NCIMB 30,157), *Lactobacillus plantarum* CUL66 (NCIMB 30,280), *Bifidobacterium bifidum* CUL20 (NCIMB 30,153) and *Bifidobacterium animalis* subsp. *lactis* CUL34 (NCIMB 30,172).

The Lab4b probiotic comprises *Lactobacillus salivarius* CUL61 (NCIMB 30,211), *Lactobacillus paracasei* CUL08 (NCIMB 30,154), *Bifidobacterium bifidum* CUL20 (NCIMB 30,153), and *Bifidobacterium animalis* subsp. *lactis* CUL34 (NCIMB 30,172).

orally administered *Saccharomyces boulardii* HANSEN CBS 5926 had the potential to attenuate cognitive impairment of APP/PS1 mice by regulation of the fungal microbiota-gut-brain axis.[93] Conversely, administering *Lactobacillus plantarum* PS128 did not significantly change the cognitive dysfunction, levels of Aβ- and tau-related proteins, astrocyte activation state, synaptic plasticity, and cognition-related neuronal loss in 3×Tg AD mice.[85]

Strain specificity is one of the most influential factors contributing to the observed heterogeneity in therapeutic effects across studies. A previous study investigated how the physiological characteristics of different *Lactobacillus plantarum* were related to their ulcerative colitis-alleviating function, and, after extensive experimentation, it was discovered that conjugated linoleic acid synthesizing capacity could be a determining factor associating with ulcerative colitis alleviation.[96] Beck et al. (2022) reported that probiotic strain-specificity is an important driver of gut microbiome development in preterm infants, influencing the host-microbe interaction in human gut in the very early stage of life.[97] The implementation of genetically engineered probiotics that express a specific functional molecule against AD, such as p62 protein, a multifunctional signaling protein involved in regulating protein turnover via the ubiquitin-proteasome system and autophagy, cell proliferation and death, oxidative stress, inflammation and immune response has been demonstrated to be a safe, non-pathogenic, and noninvasive approach to deliver therapeutics to mice with AD.[74] Genetically designed AD-targeting therapeutic probiotics may represent a novel paradigm for realistic therapeutic management in AD compared to traditional natural probiotics.

Furthermore, animal models also seem to be a vital determinant of discordant results, as there were minimal to no preclinical benefits from *Lactobacillus plantarum* PS128 consumption in 3×Tg mice, whereas these preclinical benefits were reversed when mice were injected intracerebroventricularly with streptozotocin, a chemical that is extensively applied in constructing diabetic animal models.[85]

Sexual dimorphism appears to be a characteristic in AD, contributing to a divergent therapeutic effect between male and female subjects. For instance, VSL#3 supplementation was correlated with reduced Aβ plaque load, improved memory, and decreased microgliosis in female $App^{NL\text{-}G\text{-}F}$ but not male mice, pointing to a sex-dependent probiotic effect.[86] This interesting finding not only explains part of the discrepant probiotic therapeutic effects observed between studies but also provides an important insight into setting specific guidelines in designing clinical studies addressing the therapeutic efficacy of treatments in a sex-dependent manner.

Finally, whether other study design parameters, such as probiotic dose and treatment duration, would influence the clinical outcomes of probiotic application should be systematically investigated.

Clinical evidence

Akbari et al. (2016) conducted a randomized, double-blind, and controlled clinical trial (n = 60) to evaluate the effects of a multispecies probiotic milk (containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum*) and found that a 12-week probiotic consumption could improve the cognitive function (measured by mini-mental state examination score) and affect the metabolic statuses of patients with AD.[98] This early study has provided a rationale for the clinical practice of probiotic-assisted therapy in AD management, and, shortly thereafter, a number of other probiotic intervention studies were published, in which the beneficial effects of administering a variety of probiotic strains in AD were tested (Table 2), including *Lactobacillus plantarum* (n = 100),[101] *Bifidobacterium breve* (n = 27, 121, 80, 80, 130),[102,103,105,106,108] *Bifidobacterium longum* (n = 90),[107] *Lactobacillus rhamnosus* (n = 90),[107] and some probiotic consortia (n = 60, 60, 20, 90).[98–100,104] As in the probiotic intervention trials conducted in animals, the therapeutic effects of probiotics in AD seen in human subjects are promising. Although these studies applied a considerably wide range of probiotic doses (from as low as 3×10^9 to as much as

Table 2. Comprehensive summary of human probiotic intervention studies of Alzheimer's disease (AD).

Study	Country/ Region of trial	Study design	Disease stage	Sample size	Probiotic strain(s)	Probiotic dose	Duration of probiotic intervention (months)	Key findings
Akbari et al. (2016)[98]	Iran	Randomized, double-blind, and controlled clinical trial	AD	60	*Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum*	8×10^9 CFU/g	3	• Improved MMSE score • Increased triglyceride, VLDL, and QUICKI levels • Reduced MDA, hs-CRP, HOMA-IR and HOMA-B levels
Agahi et al. (2018)[99]	Iran	Randomized, double-blind, and placebo-controlled clinical trial	AD	60	*Lactobacillus fermentum*, *Lactobacillus plantarum*, and *Bifidobacterium lactis*; or *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*	3×10^9 CFU	3	• No difference in cognitive tests • No difference in serum TNF-α, IL-10, TAC, GSH, NO, MDA, and 8-OHdG levels
Leblhuber et al. (2018)[100]	Austria	Explorative intervention study	AD	20	*Lactobacillus casei* W56, *Lactococcus lactis* W19, *Lactobacillus acidophilus* W22, *Bifidobacterium lactis* W52, *Lactobacillus paracasei* W20, *Lactobacillus plantarum* W62, *Bifidobacterium lactis* W51, *Bifidobacterium bifidum* W23, and *Lactobacillus salivarius* W24	7.5×10^9 CFU	1	• Increased serum kynurenine level • Increased RNA representing *Faecalibacterium prausnitzii* • Reduced zonulin concentration
Hwang et al. (2019)[101]	Korea	Multi-center, randomized, double-blind, placebo-controlled clinical trial	MCI	100	*Lactobacillus plantarum* C29	$>1.25 \times 10^{10}$ CFU/g	3	• Enhanced cognitive function • Increased serum BDNF level
Kobayashi et al. (2019)[102]	Japan	Open-label, single-arm study	MCI	27	*Bifidobacterium breve* A1	2×10^{10} CFU	6	• Increased MMSE, POMS2, and GSRS scores
Kobayashi et al. (2019)[103]	Japan	Randomized, double-blind, placebo-controlled trial	Subjective memory complains	121	*Bifidobacterium breve* A1	2×10^{10} CFU	3	• Improved cognitive function • No significant differences in blood parameters

(*Continued*)

Table 2. (Continued).

Study	Country/ Region of trial	Study design	Disease stage	Sample size	Probiotic strain(s)	Probiotic dose	Duration of probiotic intervention (months)	Key findings
Tamtaji et al. (2019)[104]	Iran	Randomized, double-blind, controlled clinical trial	AD	90	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*	6×10^9 CFU	3	• Increased MMSE score • Increased TAC, GSH, and QUICKI levels • Reduced hs-CRP, insulin, HOMA-IR, triglycerides, VLDL-cholesterol, LDL-cholesterol, and total-/HDL-cholesterol levels
Xiao et al. (2020)[105]	Japan	Randomized, double-blind, placebo-controlled trial	Suspected MCI	80	*Bifidobacterium breve* A1	2×10^{10} CFU	4	• Improved the total score of RBANS • Improved domain scores of immediate memory, visuospatial/constructional and delayed memory·
Bernier et al. (2021)[106]	Japan	Randomized, double-blind, placebo-controlled trial	Suspected MCI	80	*Bifidobacterium breve* A1	2×10^{10} CFU	4	• Inverse correlation between HbA1c serum concentration and RBANS total score
Akhgarjand et al. (2022)[107]	Iran	Randomized, double-blind, placebo-controlled trial	Mild and moderate AD	90	*Lactobacillus rhamnosus* HA-114 or *Bifidobacterium longum* R0175	1×10^{15} CFU	3	• Improved MMSE score • No effects on activities of daily living
Asaoka et al. (2022)[108]	Japan	Randomized, double-blind, placebo-controlled trial	Suspected MCI	130	*Bifidobacterium breve* A1	2×10^{10} CFU	6	• Improved ADAS-Jcog subscale "orientation"; and MMSE subscales "orientation in time" and "writing" • No changes in the overall gut microbiota composition

Abbreviations: 8-OHdG = 8-hydroxy-2′-deoxyguanosine; AD = Alzheimer's disease; ADAS-Jcog = Japanese version of Alzheimer's Disease Assessment Scale; BDNF = brain-derived neurotrophic factor; CFU = colony-forming units; GSH = glutathione; GSRS = Gastrointestinal Symptom Rating Scale; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; HOMA-B = homeostasis model of assessment-estimated B cell function; HOMA-IR = homeostasis model of assessment-estimated insulin resistance; hs-CRP = high-sensitivity C-reactive protein; IL-10 = interleukin-10; LDL = low density lipoprotein; MCI = mild cognitive impairment; MDA = malondialdehyde; MMSE = Mini-Mental State Examination; NO = nitric oxide; POMS2 = Profile of Mood States 2nd Edition; QUICKI = quantitative insulin sensitivity check index; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; RNA = ribonucleic acid; TAC = total antioxidant capacity; TNF-α = tumor necrosis factor-alpha; VLDL = very low density lipoprotein.

1×10^{15} colony-forming units) and treatment durations (lasting between 1 and 6 months), most studies (nine out of 10) consistently reported significant clinical effects on improving cognitive impairment after probiotic administration. However, it is worth noting that the randomized, double-blind, and placebo-controlled clinical trial ($n = 60$) conducted by Agahi et al. (2018) found that the cognitive (Test Your Memory score) and biochemical (oxidant/antioxidant and inflammatory/anti-inflammatory biomarkers) functions in patients with severe AD were insensitive to the probiotic supplementation.[99] Thus, the disease stage of AD should be taken in consideration when designing treatment regimen.

Despite the excitement around health benefits from probiotics in AD clinical trials, these studies have several bottlenecks. First, the sample size of some studies was small, decreasing the statistical power and effect size.[100,102] Second, the design of some of the clinical trials did not adhere to the general principles of control, randomization, or blinding.[98,100,102] Third, it would be more conclusive to include key clinical indicators of diagnostic and therapeutic implication, fulling the primary neuropathologic criteria for AD, such as the presence/level of extracellular Aβ deposition and intracellular accumulation of hyperphosphorylated tau in the brain.[109] However, only a paucity of studies have focused on these definitive pathological parameters.

In short, in both human and animal intervention trials, probiotic administration has shown consistent and promising symptom alleviation effects in AD, opening a new paradigm for probiotic-assisted therapy in managing AD. Yet, a lot more well-planned and large-scale intervention studies would be needed to layout guidelines for testing the therapeutic effects and optimal clinical use of probiotics in AD.

Prebiotics

Prebiotics are "substrates that are selectively utilized by host microorganisms conferring a health benefit".[16] Initially, the concept of prebiotics mainly refers to carbohydrate substances such as oligosaccharides and human milk oligosaccharides, which is later extended to non-carbohydrate substances, mainly including polyunsaturated fatty acids (PUFAs), phenolics, and phytochemicals. Among these prebiotics, PUFAs are of particular relevance to AD. The study of Kalmijn et al. (1997) found an inversely relationship between PUFA-rich fish consumption and risk of AD,[110] and such finding has catalyzed investigations into the effects of prebiotics on AD in both animals (Table 3) and humans (Table 4).

Preclinical evidence

Docosahexaenoic acid (DHA) is a PUFA that has been explored extensively as a potential therapeutic option for AD in preclinical studies,[111–127,132,134,136–138] but its clinical efficacy varied largely between studies. The AD alleviation effect of carbohydrate-based prebiotics, including but not limited to inulin,[128,130] fructooligosaccharide,[129,133] xylooligosaccharide,[131] and mannanoligosaccharide,[135] have also been tested, showing satisfactory results.

A closer examination of many of the studies has revealed pitfalls in the experimental design, rendering their conclusions ineffective. For example, a common experimental design is to compare the therapeutic effects of the control and intervention groups, in which a standard diet and a so-called prebiotic-enriched diet are provided, respectively.[114–116,121] Such experimental design assumes that prebiotics are only given to the intervention but not the control group; however, in many studies, the diet of both groups contain carbohydrate- and/or lipid-based prebiotics as part of the basic feed components.[114–116,121] Thus, the observed clinical outcome differences between groups do not really reflect the effects of prebiotic intake on AD development or improvement of the subjects. To obviate such limitation, additional supplement with and without prebiotics between treatment and control groups on the basis of a normal equivalent diet would be a more effective approach. Finally, phenolics and phytochemicals have been shown to reduce the risk of AD in both animal and human studies, reviewed by EI Gaamouch et al. (2022).[167]

Table 3. Summary of common prebiotic intervention studies of Alzheimer's disease (AD) using transgenic rodent models.

Study	Prebiotic used	Prebiotic dose	Duration of prebiotic intervention	Information of transgenic rodent model	Main observations
Calon et al. (2004)[111]	Docosahexaenoic acid (DHA)	.6% (w/w) in the diet	98–108 d	17-month-old male and female Tg2576 mice	• Protected against cognitive deficits and massive loss of postsynaptic proteins, developmentally regulated brain proteins, and postsynaptic density-95
Calon et al. (2005)[112]	DHA	.6% (w/w) in the diet	3–5 months	17-month-old male and female Tg2576 mice	• Protected against N-methyl-d-aspartate receptor subunit loss • Decreased fodrin and gelsolin fragment accumulation
Lim et al. (2005)[113]	DHA	.6% (w/w) in the diet	98–108 d	17–19 months old male and female Tg2576 mice	• Protected against amyloid β (Aβ) production, accumulation, and potential downstream toxicity
Oksman et al. (2006)[114]	DHA	.5% (w/w) in the diet	4 months	6-month-old male APP/PS1 mice	• Lowered Aβ40 and Aβ42 levels • No difference in the average plaque load
Arendash et al. (2007)[115]	DHA and eicosapentaenoic acid	13% (w/w) in the diet	7 months	2-month-old APP/PS1 mice	• No effects on cognitive function, brain fatty acid levels, or hippocampal Aβ levels
Green et al. (2007)[116]	DHA	1.3% (w/w) in the diet	3, 6 or 9 months	3-month-old male and female 3×Tg mice	• Reduced the levels of soluble Aβ and somatodendritic accumulation of tau • No effects on amyloid precursor protein processing and Aβ degradation • Reduced presenilin 1 steady-state levels
Hooijmans et al. (2007)[117]	DHA	.5% (w/w) in the diet	12 months	6-month-old male APP/PS1 mice	• Decreased Aβ deposition in the vasculature of the cingulate gyrus
Ma et al. (2007)[118]	DHA	.6% (w/w) in the diet	98–108 d	17-month-old male and female Tg2576	• Increased the neuronal sorting protein LR11
Hooijmans et al. (2009)[119]	DHA	.4% (w/w) in the diet	6 or 13 months	2-month-old male APP/PS1 mice	• Improved spatial memory, decreased Aβ deposition, and slightly increased relative cerebral blood volume
Perez et al. (2010)[120]	DHA	.6% (w/w) in the diet	3 months	3-month-old male and female APP/PS1 mice	• Reduced Aβ load in the cortex, ventral hippocampus, and striatum of female APP/PS1 mice • No differences in LR11 protein levels in the cortex, hippocampus or striatum • Increased drebrin levels in the hippocampus
Arsenault et al. (2011)[121]	DHA	9.5 μmole/g	8–10 months	4-month-old 3×Tg mice	• Increased DHA and decreased arachidonic acid concentrations in the cortex • No effects on Aβ • Improved mnesic performance deficit • Prevented dysfunction of entorhinal cortex neurons
Fiol-deRoque et al. (2013)[122]	2-hydroxy DHA	15 mg/kg	4 months	3-month-old male 5×FAD mice	• Improved performance in the radial arm maze test • Restored cell proliferation in the dentate gyrus • No changes in Aβ
Ma et al. (2014)[123]	DHA	.6% (w/w) in the diet	5 months	14–15-month-old tau knock-out mice	• Protected against hyperphosphorylation • Improved Morris water maze deficits
Torres et al. (2014)[124]	2-hydroxy DHA	15 mg/kg	4 months	3-month-old male 5×FAD mice	• Induced some of membrane lipid composition in the brain • Diminished the Aβ brain pathology and tau hyperphosphorylation
Hosono et al. (2015)[125]	Arachidonic acid (ARA) or DHA	4% ARA or 4% DHA (w/w) in the diet	4 months	9-month-old female Tg2576 mice	• Reduced Aβ42/Aβ40 ratio
Teng et al. (2015)[126]	DHA	.6% (w/w) in the diet	4 months	13–14-month-old male APP/PS1 rat	• Reduced Aβ plaque density • Improved behavioral testing
Raefsky et al. (2018)[127]	Isotope-reinforced polyunsaturated fatty acid	1% (w/w) in the diet	5 months	4–7-month-old male APP/PS1 mice	• No effects on behavior defect • Reduced brain lipid peroxidation and hippocampal amyloid β-peptide levels
Hoffman et al. (2019)[128]	Inulin	8% (w/w) in the diet	4 months	3-month-old E4FAD mice	• No differences in cognitive dysfunction and Aβ load • Altered gut microbiome diversity • Enhanced systemic metabolism in cecum, blood, and hippocampus • Decreased brain inflammation

(*Continued*)

Table 3. (Continued).

Study	Prebiotic used	Prebiotic dose	Duration of prebiotic intervention	Information of transgenic rodent model	Main observations
Sun et al. (2019)[129]	Fructooligosaccharide	2% (w/w) in the diet	1.5 months	6-month-old male APP/PS1 mice	• Improved cognitive impairment • Decreased Aβ deposition • Increased levels of synaptic plasticity related proteins of postsynaptic density-95 and synapsin I • Reversed the altered intestinal microbial composition • Increased the levels of glucagon-like peptide-1 in the gut and glucagon-like peptide-1 receptor in the brain
Chang et al. (2020)[130]	Inulin	Information not provided	4 months	3-month-old asymptomatic APOE3 (E3FAD) and APOE4 (E4FAD) mice	• Inulin-induced systemic metabolism and gut microbiome changes were *APOE* genotype-dependent
Han et al. (2020)[131]	Xylooligosaccharide	10% (w/v) in phosphate buffered saline	5 weeks	6-month-old male APP/PS1 mice	• No effects on spatial memory dysfunction • No differences in the intestinal microbiota composition, intestinal inflammation, gut barrier integrity • No differences in the neuroinflammatory response
Park et al. (2020)[132]	DHA	200 mg/kg	2 weeks	3-month-old male 5×FAD mice	• Attenuated AD-associated pathologies, such as mitochondrial impairment, Aβ accumulation, neuroinflammation, neuronal loss, and impairment of adult hippocampal neurogenesis
Wu et al. (2020)[133]	Fructooligosaccharide	5% (w/w) in the diet	6 months	5-month-old male or female APP/PS1 mice	• Ameliorated cognitive dysfunction • Alleviated the increase of Aβ plaques in the cerebral cortex • Protected against the decrease in neprilysin expression • Inhibited the increase in histone deacetylase 2 expression
Bie et al. (2021)[134]	DHA	400 mg/kg	2 months	5-month-old female APP/PS1 mice	• Reduced neuronal damage and improved cognitive dysfunction • Inhibited Aβ plaques and tau protein neurofibrillary tangles probably by β-site APP cleavage enzyme 2 expression
Liu et al. (2021)[135]	Mannanoligosaccharide	.12% (w/v) in the drinking water	2 months	6-month-old male 5×FAD mice	• Improved the cognitive and spatial memory loss, but not the working memory impairment • Attenuated anxiety-like behavioral disorders • Improved neuronal morphology and reduced Aβ accumulation • Alleviated neuroinflammation and oxidative damage • Increased short-chain fatty acids generation and related-microbes • Protected the gut barrier integrity
Badesso et al. (2022)[136]	DHA	450 mg/kg	5 weeks	18–20-month-old female Tg2576 mice	• Ameliorated freezing memory deficits, but was not sufficient to restore spatial memory and retention deficits • Increased synapse formation • No effect on Aβ deposition
Xiao et al. (2022)[137]	DHA	50 or 300 mg/kg	4 months	3-month-old APP/PS1 mice	• Improved cognitive decline and depression/anxiety behaviors • No effect on Aβ deposition • No effect on liver functions, kidney functions, and blood lipid levels • Had little effects on brain inositol, glycine, and taurine levels
Zussy et al. (2022)[138]	Nanovectorized DHA	.2181 mg	1 month	3-month-old female J20 mice	• Counteracted tau hyperphosphorylation and cognitive loss

Abbreviations: Aβ = amyloid β; AD = Alzheimer's disease; ARA = arachidonic acid; DHA = docosahexaenoic acid.

Table 4. Comprehensive summary of human prebiotic intervention studies of Alzheimer's disease (AD).

Study	Country/ Region of study	Study design	Disease stage	Number of enrolled subjects (subjects completed the trial)	Prebiotic(s) and placebo materials	Prebiotic dose (g/d)	Duration of prebiotic intervention (months)	Key findings
Freund-Levi et al. (2006)[139]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	204 (174)	Omega-3 fatty acids (docosahexaenoic acid, DHA and eicosapentaenoic acid, EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	12	• Improved cognitive decline only in very mild but not mild to moderate AD patients
Kotani et al. (2006)[140]	Japan	Information not provided	MCI and AD	29 (29)	Arachidonic acid and DHA Placebo group (240 mg/d of olive oil)	0.48	3	• Improved the immediate memory and attention score in MCI but not AD patients
Chiu et al. (2008)[141]	China	Randomized, double-blind placebo-controlled study	Mild or moderate AD and MCI	46 (29)	Omega-3 fatty acids (DHA and EPA) Placebo group (1.8 g/d of olive oil)	1.8	6	• Improved general clinical but not cognitive function
Freund-Levi et al. (2008)[142]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	204 (174)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• No influences on psychiatric, behavior or functional ability
Vedin et al. (2008)[143]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	25 (23)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Increased plasma DHA and EPA levels • Lowered interleukin (IL)-6, IL-1β, and granulocyte colony-stimulating factor
Freund-Levi et al. (2009)[144]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	35 (35)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• No effects on inflammatory and AD biomarkers in cerebrospinal fluid or on inflammatory markers in plasma
Irving et al. (2009)[145]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	204 (174)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	12	• Affected weight and appetite
Quinn et al. (2010)[146]	USA	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	402 (295)	DHA Placebo group: corn or soy oil capsules	2	18	• No effect on slowing cognitive and functional decline
Vedin et al. (2010)[147]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	25 (23)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Reduced prostaglandin F2alpha release from blood mononuclear leukocytes
Sinn et al. (2012)[148]	Australia	Randomized, double-blind, controlled trial	MCI	50 (39)	Omega-3 fatty acids (DHA and EPA) Placebo group (safflower oil, 2.2 g linoleic acid)	1.83–1.95	6	• Improved geriatric depression scale scores both in EPA and DHA groups, and verbal fluency in DHA group • No treatment effects on other cognitive or quality of life parameters
Vedin et al. (2012)[149]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	20 (19)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Affected gene expression in blood mononuclear leukocytes
Faxén-Irving et al. (2013)[150]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	204 (174)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	12	• Increased plasma but not cerebrospinal fluid transthyretin level
Lee et al. (2013)[151]	Malaysia	Randomized, double-blind, placebo-controlled trial	MCI	36 (35)	Omega-3 fatty acids (DHA and EPA) Placebo group (.6 g linoleic acid)	1.74	12	• Improved short-term and working memory, immediate verbal memory, and delayed recall capability
Freund-Levi et al. (2014)[152]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	40 (39)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Increased DHA and EPA levels in the cerebrospinal fluid

(*Continued*)

Table 4. (Continued).

Study	Country/ Region of study	Study design	Disease stage	Number of enrolled subjects (subjects completed the trial)	Prebiotic(s) and placebo materials	Prebiotic dose (g/d)	Duration of prebiotic intervention (months)	Key findings
Freund-Levi et al. (2014)[153]	Sweden	Randomized, double-blind, placebo-controlled trial	Moderate AD	41 (40)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• No effects on oxidative stress and inflammation
Mahmoudi et al. (2014)[154]	Iran	Randomized, double-blind, placebo-controlled trial	Normal or mild to MCI	199 (186)	Omega-3 fatty acids (DHA and EPA) Placebo group (medium chain triglycerides)	.3	6	• No beneficial effects on improving cognition or prevention of cognitive decline
Shinto et al. (2014)[155]	USA	Randomized, double-blind, placebo-controlled trial	AD	39 (34)	Omega-3 fatty acids (DHA and EPA) Placebo group (soybean oil)	1.65	12	• No differences in peripheral F2-isoprostane levels, ADAS-cog and ADL • Decreased IADL
Eriksdotter et al. (2015)[156]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	174 (165)	Omega-3 fatty acids (DHA and EPA) Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	12	• Had dose-response relationships between plasma omega-3 fatty acid levels and cognition preservation
Fiala et al. (2015)[157]	USA	Open study	MCI and AD	29 (29)	DHA + EPA No placebo group	2	17	• Increased amyloid β (Aβ) phagocytosis and resolvin D1 in MCI patients
Phillips et al. (2015)[158]	UK	Randomized, double-blind, placebo-controlled trial	AD	76 (76)	Omega-3 fatty acids (DHA and EPA) Placebo (olive oil)	1.225	4	• No effects on cognition and mood
Wang et al. (2015)[159]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	17 (15)	Omega-3 fatty acids Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Prevented the reduction in specialized pro-resolving mediators released from peripheral blood mononuclear cells
Karimi et al. (2017)[160]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	63 (63)	Omega-3 fatty acids Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Decreased DNA methylation in blood leukocytes
Zhang et al. (2017)[161]	China	Randomized, double-blind, placebo-controlled trial	MCI	240 (219)	DHA Placebo group (corn oil)	2	12	• Increased the scores of full-scale intelligence quotient (FSIQ), information, and digit span • Increased the volumes of left hippocampus, right hippocampus, total hippocampus, and global cerebrum
Schwarz et al. (2018)[162]	Germany	Randomized, double-blind, placebo-controlled trial	MCI	49 (13)	Omega-3 fatty acids (DHA and EPA) Placebo group (sunflower oil)	2.2	6.5	• Elevated cerebral blood flow and cerebral blood volume
Zhang et al. (2018)[163]	China	Randomized, double-blind, placebo-controlled trial	MCI	240 (217)	DHA Placebo group (corn oil without DHA)	2	24	• Increased the scores of FSIQ, verbal intelligence quotient and subdomains of information and digit span • Decreased the blood Aβ42 level and mRNA expression of Aβ protein precursor • Increased Beclin-1 and LC3-II levels and LC3-II mRNA expression
Jernerén et al. (2019)[164]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	171 (171)	Omega-3 fatty acids Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Plasma total homocysteine modified the effects of omega-3 fatty acids supplementation
Tofiq et al. (2021)[165]	Sweden	Randomized, double-blind, placebo-controlled trial	Mild to moderate AD	33 (33)	Omega-3 fatty acids Placebo group (1 g of corn oil, including .6 g of linoleic acid)	2.32	6	• Increased neurofilament light and chitinase-3-like protein 1 in the cerebrospinal fluid
Lin et al. (2022)[166]	China	Randomized, double-blind, placebo-controlled trial	MCI or AD	163 (131)	DHA or EPA or DHA and EPA Placebo group (soybean oil)	.7 or 1.6 or 1.15	24	• No differences in cognitive, functional, mood status scores, biochemical profiles, and inflammatory cytokines levels

Abbreviations: Aβ = amyloid β; AD = Alzheimer's disease; ADAS-cog = Alzheimer Disease Assessment Scale-cognitive subscale; ADL = Activities of Daily Living; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FSIQ = full-scale intelligence quotient; IADL = Instrumental Activities of Daily Living; IL = interleukin; MCI = mild cognitive impairment.

Clinical evidence

A number of clinical studies have evaluated the effects of prebiotics on mitigating AD, particularly the functional effect of PUFAs.

The first effort to interrogate the function of prebiotics in AD patients came from the OmegAD trial conducted in 2006, which is a randomized, double-blind, placebo-controlled trial ($n = 204$). The study preliminarily observed that dietary consumption of omega-3 fatty acids was linked to improved cognitive functions in very mild but not mild to moderate AD patients.[139] Subsequently, the OmegAD trial data were reassessed based on patient stratification, focusing on neuropsychiatric symptoms ($n = 204$),[142] release of cytokines ($n = 25$),[143] inflammatory markers ($n = 35$),[144] weight and appetite ($n = 204$),[145] release of prostaglandin F2alpha ($n = 25$),[147] expression of genes ($n = 20$),[149] transthyretin levels ($n = 204$),[150] PUFA levels ($n = 40$),[152] oxidative stress and inflammation ($n = 41$),[153] plasma fatty acid profiles in relation to cognition and gender ($n = 174$),[156] release of specialized pro-resolving mediators ($n = 17$),[159] DNA methylation ($n = 63$),[160] plasma total homocysteine level ($n = 171$),[164] and cerebrospinal fluid biomarkers ($n = 33$).[165] Aside from the well-known OmegAD study conducted in Sweden, other interventional studies involving prebiotics were conducted in eight countries, including Japan ($n = 29$),[140] China ($n = 46, 240, 240, 163$),[141,161,163,166] USA ($n = 402, 39, 29$),[146,155,157] Australia ($n = 50$),[148] Malaysia ($n = 36$),[151] Iran ($n = 199$),[154] UK ($n = 76$),[158] and Germany ($n = 49$).[162] While most of these studies found significant improvement in patient clinical outcomes after prebiotic use, a few studies reported no apparent beneficial effects on AD, in the aspects of neuropsychiatric symptoms,[142] inflammatory markers,[144] cognitive dysfunction,[146,154,158,166] and oxidative stress and inflammation.[153]

An interesting Cardiovascular Health Cognition Study compared the effects of lean fish versus fatty fish (tuna or other fish) intake on patients with AD, vascular dementia, and other types of dementia (Parkinson's disease and Lewy body dementia), and in relation to *APOE4* status, they found that consumption of fatty fish reduced the risk of AD, Parkinson's disease and Lewy body dementia, especially in patients without *APOE4* allele.[168] Transgenic mice expressing the human *APOE4* isoform had a lower brain uptake of DHA than those expressing the *APOE2* isoform due to limited biodistribution and transport of DHA in cerebral tissues.[169] The inter-individual distribution of the *APOE4* allele is thus a possible factor contributing the heterogeneous response of PUFA intervention in AD, and such genetic risk factor should be considered when implementing prebiotic therapy, especially PUFAs, in future studies and in patients with AD.

Finally, while most prebiotic intervention studies investigated the beneficial effects of PUFAs on AD, few of them explored the functions of carbohydrate-based prebiotics, such as inulin, fructooligosaccharide, xylooligosaccharide, and mannanoligosaccharide. Given the gut microbiota modulation capacity of carbohydrate-based prebiotics, particularly enriching the SCFA-producers and gut microbes synthesizing beneficial bioactive molecules, it merits further attention.

Synbiotics

While an enormous amount of knowledge has been generated from experimental and clinical studies of probiotic and prebiotic intervention in AD, fewer studies have looked into the beneficial effects of synbiotics. By definition, synbiotics are classified into two subsets: a complementary synbiotic that is a mixture of a probiotic plus a prebiotic, and a synergistic synbiotic that is a synbiotic in which the substrate is designed to be selectively utilized by the co-administered microorganism(s).[17]

Data on the use of synbiotics in Tg AD rodent models are limited to few preclinical studies. Deng et al. (2022) found that the application of a complementary synbiotic, comprising inulin and a multispecies probiotic preparation (containing *Bacillus natto*, *Bacillus coagulans*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Bifidobacterium breve*), but not inulin alone, could ameliorate cognitive impairment, decrease Aβ42 and induce neurogenesis, and reduce the inflammatory response, suggesting that synbiotic but not prebiotic supplementation could delay AD progression via regulating the gut-brain axis.[170] Another interesting study conducted in transgenic humanized *Drosophila melanogaster* of AD demonstrated that administering the

synbiotic formulation (containing three metabolically active probiotics, including *Lactobacillus plantarum* NCIMB 8826, *Lactobacillus fermentum* NCIMB 5221, and *Bifidobacteria longum* spp. *infantis*, and a novel polyphenol-rich prebiotic, namely triphala powder) could increase the survivability, motility, and rescued Aβ deposition and acetylcholinesterase activity of the fruit flies. The observed beneficial effects were likely achieved through gut-brain-axis signaling and regulation of metabolic stability, immune signaling, oxidative, and mitochondrial stress.[171]

Collectively, limited available evidence is available to demonstrate the beneficial effects of synbiotics in curbing AD progression. It merits more effort to uncover the beneficial synergistic AD remission effect unleashed by synbiotics than administering probiotics or prebiotics alone, particularly by animal and human intervention trials focusing on elucidating the specific synergistic mechanisms of action.

Postbiotics

Albeit extremely rare, probiotic therapy has some safety concerns, such as the spread of antibiotic resistance genes, the presence of potential virulence factors, and the development of bacteremia or fungemia. Thus, functional research of postbiotics has emerged.[172] Some of the biggest advantages of postbiotics are their good stability and ease of storage.[18] Moreover, increasing evidence shows that postbiotics offer comparable health effects to probiotics, although the available studies are mostly limited to the health-promoting effects of postbiotics in gastrointestinal disorders.[172,173] The safety-stability-health claims triangle from postbiotic intervention has unsurprisingly attracted considerable attention.[174] Thus, high-quality, well-designed animal models and human studies are still needed to fill the gaps in the realm of AD.

FMT

Historical accounts linking FMT and disease date back to the 4th century BC in China when human fecal suspension was used to treat patients with food poisoning, diarrhea, and those with fever and imminent dying.[175] In 1958, the application of FMT in treating *Clostridioides difficile* infection (CDI)-associated pseudomembranous enterocolitis has opened a new era of modern medical research of FMT.[176] The resurgence of FMT in the past decade was due to the efficacy of up to 90% in treating recurrent CDI in a landmark clinical study published in 2013.[177] Contemporaneously, a plethora of FMT-related studies have been conducted to explore other potential therapeutic indications associated with an altered gut microbiome, such as inflammatory bowel disease, with the goals of restoring of the gut microbiota to a premorbid state.[178] In 2022, the first fecal microbiota product, Rebyota, was approved by the United States Food and Drug Administration for the prevention of recurrence of CDI in individuals 18 y of age and older who have completed antibiotic treatment for recurrent CDI.[179] This optimism heralds the emergence of FMT therapy as part of clinical practice. The great progress of FMT in managing gastrointestinal diseases has invigorated its application extending beyond the intestine, including AD (Table 5).[22,27,45,180–193] However, as seen in Table 5, most current FMT-related studies pertaining to AD are animal trials with only very few human clinical studies, and most of these studies demonstrated promising results of FMT therapy in AD, which warrants further evaluation of FMT in both preclinical and clinical research.

A few problems have been identified in some of the current FMT intervention trials, and, in future interventional research, robust experimental designs are of paramount importance for conducting reliable, valid, and safe studies. For instance, the eradication of indigenous microbial communities of recipient animals via broad-spectrum antibiotics prior to FMT appears to be incomplete, and it is not easy to assess the effect of residual microbiota in the experimental process; thus, it would be vital to use GF animals to conduct studies aiming to elucidate the clinical efficacy of FMT. Furthermore, there is a lack of consensual protocol for FMT implementation in the preclinical research included in this review, ranging from 1 time to 24 times of application. Experimental parameters like the method and frequency of FMT application is particularly important for transitioning from preclinical to clinical translation research, ensure reproducibility between and validity of studies. Finally, despite patients' safety is the prime concern

Table 5. Comprehensive summary of studies of fecal microbiota transplantation (FMT) in Alzheimer's disease (AD) transgenic rodent models and patients with AD.

Study	FMT donor	FMT recipient	FMT treatment	Main observations
Animal studies				
Harach et al. (2017)[180]	12-month-old APP/PS1 mice	4-month-old germ-free APP/PS1 mice	Oral gavage of 200 µL of cecal solution once daily for 2 times (3-day intervals)	• Increased cerebral amyloid-β (Aβ) pathology
Dodiya et al. (2019)[27]	APPPS1–21 male mice	Antibiotic-pretreated APP/PS1–21 male mice	Oral gavage of 200 µL of fresh fecal slurry supernatant once daily for 24 d	• Restored fecal microbiome profile • Restored Aβ amyloidosis and microglia morphology
Sun et al. (2019)[181]	6-month-old C57BL/6 male mice	6-month-old antibiotic-pretreated APP/PS1 male mice	Oral administration of 200 µL of fresh fecal solution once daily for 4 weeks	• Improved cognitive deficits • Reduced the brain deposition of Aβ, phosphorylation of tau protein, the levels of Aβ40 and Aβ42, cyclooxygenase-2, and CD11b levels • Increased postsynaptic density protein 95 and synapsin I expressionIncreased postsynaptic density protein 95 and synapsin I expression • Reversed the changes of gut microbiota and short-chain fatty acids
Kim et al. (2020)[22]	C57BL/6 mice	AD-like pathology with amyloid and neurofibrillary tangles (ADLPAPT) mice or antibiotic-pretreated ADLPAPT mice	4 or 16 weeks	• Ameliorated the formation of Aβ plaques and neurofibrillary tangles, glial reactivity and cognitive impairment • Reversed abnormalities in colonic expression of genes related to intestinal macrophage activity and circulating blood inflammatory monocytes
Shen et al. (2020)[182]	AD patients	APP/PS1 mice	Information not provided	• Promoted intestinal NLRP3 inflammasome activation • Up-regulated the expression of inflammatory factors, such as IL-1β, IL-18 and TNF-α both in peripheral blood and hippocampus • Increased cognitive impairment and activated microglia in the central hippocampus
Kim et al. (2021)[183]	9-month-old male 5×FAD mice	Antibiotic-pretreated 9-month-old male C57BL/6 mice	Oral administration of 200 µL of fecal supernatant once daily for 5 d	• Led to memory dysfunction, decreased neurogenesis and increased neuroinflammation in the brain, and colonic inflammation
Valeri et al. (2021)[184]	4-week-old or 12-month-old C57BL/6 mice	Antibiotic-pretreated 5×FAD mice	A single oral gavage of cecum suspension	• Elevated cultivatable fecal *Enterobacteriaceae* and *Lactobacillaceae* representative bacteria and decreased Firmicutes amount • Increased serum lipopolysaccharide binding protein levels • Increased plaque load
Wang et al. (2021)[45]	16 months old male APP/PS1 mice	Antibiotic-pretreated male APP/PS1 mice	Oral gavage of 10^8 cells once daily for 7 d	• Increased Aβ deposition • Altered the morphology of astrocytes but did not impact microglia
Bi et al. (2022)[185]	8-week-old female APP/PS1 mice	8-week-old tumor-bearing female APP/PS1 mice	Oral gavage of 150 µL of fecal supernatant three times a week for 5 weeks	• Increased tumor size
Elangovan et al. (2022)[186]	4–6, 10–12, or 30–32-week-old B6.SJL mice	8–10, or 30–32-week-old 5×FAD mice	Oral gavage of 200 µL of fecal supernatant daily for 7 d	• Improved cognitive function, such as novel object recognition and forced alternation y-maze, and Aβ plaques burden in 32-week-old 5×FAD mice receiving FMT from 10–12-week-old wildtype donors
Hang et al. (2022)[187]	6-month-old female tumor-bearing C57BL/6 mice	6-month-old female APP/PS1 mice	Oral gavage of 200 µL of fresh fecal solution three times a week for one month	• Improved short-term memory and cognitive ability • Decreased Aβ plaque burden in the hippocampus and cortex • Reversed the increased Firmicutes and *Prevotella*; and the decreased Bacteroidetes, *Bacteroides*, and *Sutterella*
Kim et al. (2022)[188]	9–10 months old Tg2576 mice	Antibiotic-pretreated 8-week-old ICR mice	Oral gavage of 200 µL of fecal suspension daily for 3 d, following once every two d for 10 d	• Decreased stool parameters, including weight, water content, and morphology • Lowered the distribution of myenteric neurons and the interstitial cells of Cajal, as well as the enteric nervous system function
Soriano et al. (2022)[189]	18 to 24 months old 3×Tg female mice	9 to 12 weeks old C57BL/6 mice with traumatic brain injury	Oral gavage of a single 200 µL of fecal supernatant	• Aggravated the lesion size and impaired motor ability • Increased activated microglia/macrophages • Increased *Muribaculum* and decreased *Lactobacillus johnsonii*

(*Continued*)

Table 5. (Continued).

Study	FMT donor	FMT recipient	FMT treatment	Main observations
Wang et al. (2022)[190]	APP/PS1 mice or AD patients	Antibiotic-pretreated 6-week-old male C57BL/6J mice	Oral gavage of 200 µL of bacterial supernatant three times a week for 2 weeks	• Induced endoplasmic reticulum stress in the cerebral cortex of wild-type recipient mice • Elevated the serum trimethylamine-N-oxide level
Human studies				
Fujii et al. (2019)[191]	An 82-year-old male with AD	4-week-old germ-free C57BL/6N male mice	Oral gavage of 150 µL of non-settling material	• Colonized and reproduced the bacterial diversity • Triggered cognitive decline
Hazan et al. (2020)[192]	An 85-year-old woman (the patient's wife)	An 82-year-old man with AD and recurrent Clostridioides difficile infection	A single 300 mL fecal infusion	• Improved cognitive function
Park et al. (2021)[193]	A 27-year-old man with no gastrointestinal or other health problems, not using drugs and antibiotics	A 90-year-old woman with AD and severe Clostridioides difficile infection	Stool suspension (60 g) was applied during a colonoscopy for 2 times (3-month intervals)	• Improved cognitive function • Changed the microbiota composition and short-chain fatty acid level

Abbreviations: Aβ = amyloid β; AD = Alzheimer's disease; FMT = fecal microbiota transplantation; IL-18 = interleukin-18; IL-1β = interleukin-1β; TNF-α = tumor necrosis factor-alpha.

for implementing any medical treatment, particularly novel therapies like FMT, this is often omitted. Short-term and long-term safety assessment of FMT should be carefully conducted, recorded, and reported.

Future directions

Despite in its infancy, there is a remarkable leap in our understanding of the gut microbiome in AD in the past 5 y. Mounting information has been generated from both descriptive studies that detail the gut microbiome in AD and explanatory studies aiming to interrogate the causal relationship between the gut microbiome and AD. While increasing evidence supports that gut dysbiosis is a driver for AD, it merits more effort to further verify the causal relationship between the two and to dissect the definitive mechanisms for driving the progress of AD. Future development of the field will require more well-designed, large-scale, and precise observational and mechanistic studies. Multi-omics, such as metagenomics, metabolomics, metaproteomics, and metatranscriptomics, are powerful tools that can help answer some fundamental questions regarding the role of gut microbiome in the initiation, maintenance, and progression of AD.

Successful implementation of the described gut microbiota-targeting strategies in AD improvement remains a formidable challenge. One important reason is that the beneficial effects on AD do not solely depend on the regimen but also on the native host gut microbiota. Our previous study found that the inter-individual endogenous gut microbiota composition was an important factor relating to the heterogenous beneficial effects seen across study subjects.[194] Similarly, the success of FMT in treating recurrent CDI was principally associated with the gut microbiota composition in the recipients.[195] Thus, to maximize treatment benefits, both the specificity of the gut microbiota-modifying products and the host indigenous intestinal microbiome should be taken into account in future studies. Another obvious challenge in applying preclinical data in translational research is the tremendous variability between the rodent and human gut microbiome. Thus, attempts to establish animal models that mimic the characteristics of human intestinal microbiome, e.g., by developing humanized gnotobiotic animal models, will greatly facilitate cross-validation between animal and human studies and, ultimately, promote clinical practice.

Considering that diet and lifestyle are closely related to us and that they are the most influential in shaping gut microbial communities,[24,196] they play a pivotal role in AD management.[197] For example, the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets were linked to a reduced risk of AD,[198] while the Western diet showed an opposite trend.[199] A prospective cohort study conducted in USA and published in 2022 analyzed the impact of lifestyle factors on life expectancy lived with and without Alzheimer's dementia; it was found that they lived a larger proportion of their remaining years without Alzheimer's dementia.[200] However, a very recent study suggested that the MIND diet could not improve brain health, cognitive function, and brain imaging outcomes compared with those who followed a control diet with mild caloric restriction.[201] Despite some unexpected research results, optimism is growing that multidimensional interventions, including dietary patterns and lifestyle, might prevent, or even halt AD development.

Conclusions

A raft of recent observational and mechanistic studies consistently demonstrated that the gut microbiome is a key player in modulating the disease state of AD, opening a new paradigm for intervening or even curbing the progress of AD. Gut microbiome-targeting strategies, such as probiotics, prebiotics, synbiotics, postbiotics, and FMT, hold great promise in the treatment and prophylaxis of AD in the years to come. Yet, concerted effort is still needed to provide answers to unresolved fundamental questions in regards to the role and mechanism of gut microbiota in AD, establish standard protocols for gut microbiome research, and generate high-quality data from preclinical and clinical studies, ultimately translating gut microbiome research into clinical practice.

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Authors' contributions

T.Z. and G.G. designed the outline of the review. T.Z. wrote the manuscript. L.K. and Z.S. critically revised the manuscript and provided advice. All authors read and approved the final manuscript.

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