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REVIEW ARTICLE

Microbiota–gut–brain axis: Modulation of gut microbiota in the management of Alzheimer's disease

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Abstract

Insights into the role of the gut microbiota are advancing our understanding of Alzheimer's disease (AD), which is the most common cause of dementia and a condition characterized by progressive cognitive decline and pathological hallmarks such as amyloid beta (Aβ) plaques and neurofibrillary tangles. The gut microbiota, composed of diverse microorganisms, influences brain health through the microbiota–gut–brain axis. This review outlines how alterations in gut microbial composition and metabolites occur across different stages of cognitive decline. The microbiota–gut–brain axis mediates interactions between the gut and brain, influencing neuroinflammation, Aβ accumulation, tau pathology, and oxidative stress. Therapeutic strategies targeting gut microbiota, including diet modulation, probiotics, prebiotics, synbiotics, microbial metabolites, and fecal microbiota transplantation, have shown potential in improving cognitive function in clinical and animal studies. Despite these advances, challenges remain in addressing individual variability, standardization, and long-term safety. Personalized microbiota-based interventions may provide promising tools for the diagnosis, prevention, and treatment of AD.

Keywords: Alzheimer's disease; Gut microbiota; Microbiota–gut–brain axis; Therapeutic strategies

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1. Introduction

With the global population aging, dementia has become a major public health concern.[1] Dementia is a clinical syndrome characterized by progressive cognitive and memory decline that interferes with daily activities.[2,3] It has various underlying causes, depending on the brain changes involved, with major subtypes[2,3] including Alzheimer's disease (AD) dementia, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and Parkinson's disease dementia (Figure 1). AD is the most common subtype, accounting for about 60–80% of dementia cases in people over 65.[4] In the United States alone, more than 7 million people live with AD, imposing an estimated economic burden

of 384 billion USD in 2024.[4] Mild cognitive impairment (MCI), a transitional stage before dementia, affects 8–11% of older adults.[5] These figures underscore the urgency of identifying modifiable factors, such as the gut microbiota, to develop novel strategies for delaying or preventing cognitive decline.

Amid the growing burden of AD, increasing attention has focused on the gut microbiota's role in human health.[6,7] The human gastrointestinal tract is densely populated by a diverse community of microorganisms, including bacteria, archaea, viruses, and fungi, collectively known as the gut microbiota. These microbes maintain gut barrier integrity, support immune defenses, and protect against pathogens. Beyond local effects, the gut microbiota communicates bidirectionally with the central nervous system (CNS) via the microbiota–gut–brain axis, influencing brain development, mood, and cognition. Recent studies demonstrate its significant impact on nervous system function, with growing evidence linking it to cognition and AD mechanisms.[8] Dysbiosis, involving changes in gut microbiota composition and function, is associated with systemic inflammation[9] and blood–brain barrier (BBB) disruption,[10] which may worsen neurodegeneration. In addition, microbial metabolites, such as short-chain fatty acids (SCFAs) and neurotransmitters, modulate immune responses and neuronal activity, affecting cognition through the microbiota–gut–brain axis.[11] These interactions present therapeutic potential in targeting gut microbiota to restore balance and slow cognitive decline in AD.

Although associations between gut dysbiosis and AD have been reported, most studies to date demonstrate correlations rather than direct causation, and the possibility of reverse causality or shared confounding factors (e.g., age, diet, and comorbidities) cannot be excluded. Nevertheless, understanding the mechanisms by which gut microbiota influence neuroinflammation and neurodegeneration remains essential. Building on this context, this review aims to deepen our insight into the alterations in gut microbial composition across different stages of cognitive decline and the roles of microbial metabolites. In addition, we explore emerging therapeutic strategies targeting the

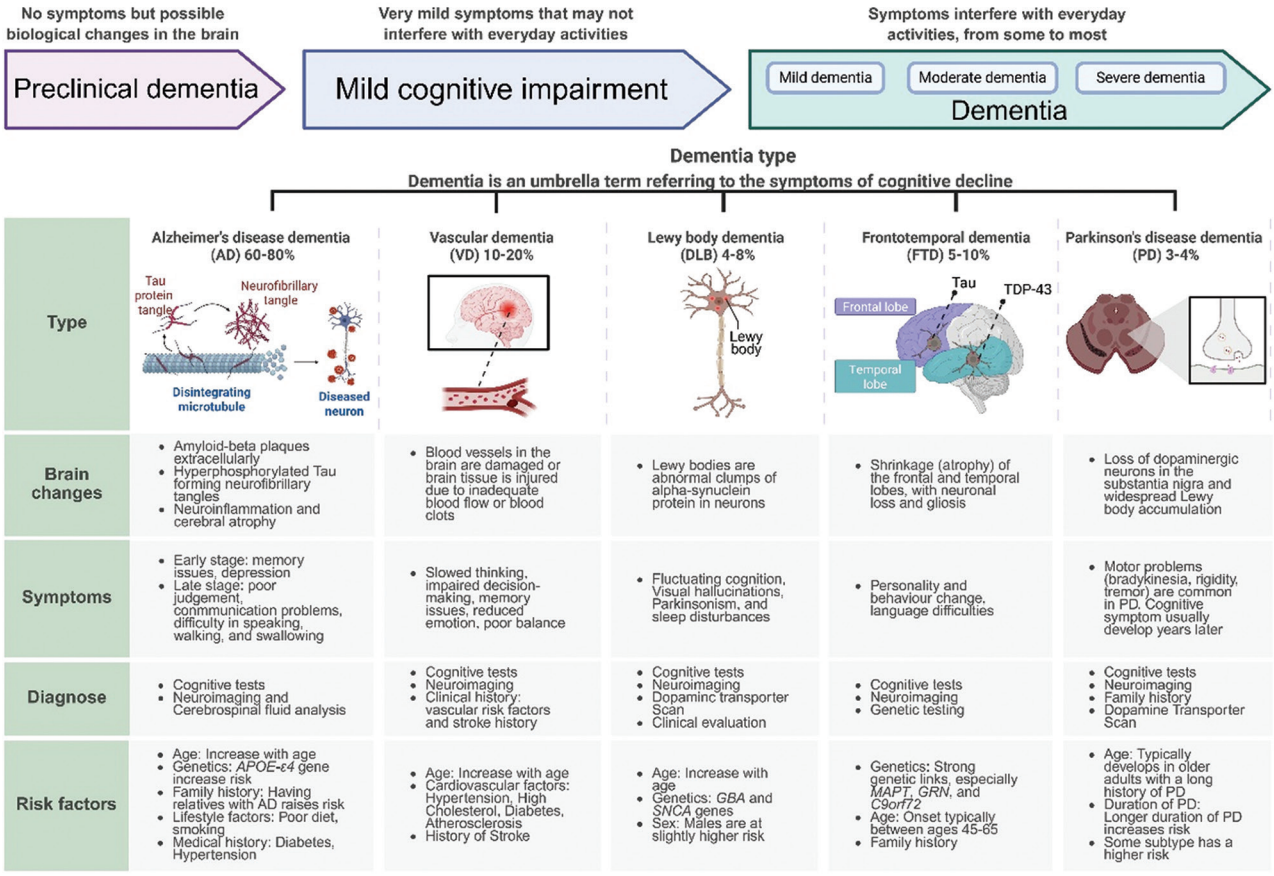

Figure 1. Overview of the dementia continuum and different types of dementia. Created with BioRender.com. JIANG, H. (2025) https://BioRender.com/dw03crz.

gut microbiota, including probiotics, prebiotics, synbiotics, dietary modifications, and fecal microbiota transplantation (FMT), highlighting their potential to slow or prevent cognitive decline.

2. Gut microbiota alterations in AD

Clinical studies have increasingly shown that individuals with AD have altered gut microbiota, with reduced diversity and shifts in specific bacterial taxa (Table 1).[12-32] For instance, a study of 97 individuals, comprising patients with AD, MCI, and healthy controls (HC), revealed notable differences in gut microbiota profiles. AD patients showed reduced microbial diversity compared to MCI and HC. Compositionally, the population of Firmicutes was markedly decreased, while Proteobacteria was enriched in AD patients. These changes extended to higher taxonomic levels, with Gammaproteobacteria, Enterobacteriales, and Enterobacteriaceae progressively increasing from HC to MCI to AD. Functional analysis based on Kyoto Encyclopedia of Genes and Genomes pathways revealed increased modules related to glycan biosynthesis and metabolism in both MCI and AD groups, while immune-related pathways were decreased in AD. Importantly, discriminative models based on predominant microbiota effectively distinguished MCI and AD from HC (area under the curve [AUC] = 0.890 and 0.940, respectively), and also separated AD from MCI (AUC = 0.925).[17] Emerging evidence also suggests that gut microbiota alterations may appear during the early and even preclinical stages of AD. In one study of 164 cognitively normal individuals, which included 49 with early AD biomarkers, distinct microbial patterns were found in those with preclinical AD. These differences were linked to amyloid beta (Aβ) and tau pathology, as well as a reduced Firmicutes/Bacteroidetes ratio. When combined with clinical features, these microbial profiles improved the accuracy of machine learning models in predicting preclinical AD.[29] Another study proposed that gut microbiota, when combined with plasma Aβ, could serve as a non-invasive, cost-effective tool for early AD screening, with an accuracy of 87%.[27] With the advancement of next-generation sequencing technologies, especially shotgun metagenomics, more comprehensive microbial profiling has become possible. Most notably, a recent large-scale metagenomic study involving 476 Chinese participants across five AD stages provided the most detailed characterization to date.[31] The study identified over 70 microbial species with stage-dependent alterations. Notably, *Faecalibacterium* spp., known for producing SCFAs, were elevated in early AD, potentially modulating neuroinflammation and neurodegeneration. In contrast, *Alistipes*, *Bacteroides*, and *Prevotella* spp., associated with inflammation and neurotransmitter disruption, increased in MCI and AD stages. Reductions were also found in lactate-producing *Streptococcus*, possibly weakening anti-inflammatory effects. Functionally, over 10% of microbial gene families were altered, especially those involved in metabolism. These microbial signatures showed strong diagnostic value (AUC = 0.80 cross-validation; 0.75 external validation). Moreover, enrichment of certain opportunistic pathogens, such as *Erysipelatoclostridium ramosum* (formerly *Clostridium ramosum*), has been associated with poorer cognitive function,[33] suggesting a potential pathogenic role in cognitive decline. In addition, microbial metabolites also exhibit alterations in AD and hold promise as potential biomarkers. For example, levels of trimethylamine N-oxide (TMAO), a gut-derived metabolite, are elevated in the cerebrospinal fluid (CSF) of AD patients and correlate with CSF markers of amyloid, tau pathology, and neurodegeneration.[34] Lipopolysaccharides (LPS) and amyloid-like microbial proteins have also been implicated in AD pathogenesis.[35] Moreover, SCFAs, including propionate, butyrate, acetate, valerate, and hexanoate, may influence disease progression by modulating immune-inflammatory responses through prostaglandin and T cell pathways.[36] Altogether, these findings underscore the intricate relationship between gut microbiota and brain health in AD, enabling the advancement of novel diagnostic and treatment strategies directed toward the microbiota–gut–brain axis. Given the strong influence of geography, diet, and ethnicity on gut microbiota composition, cross-population comparisons are essential to identify universal versus population-specific microbial biomarkers for AD. Most existing studies focus on single ethnic groups, such as Chinese or Western cohorts, limiting generalizability. Dietary habits and environmental exposures shape microbial profiles differently, which may affect the reliability of microbiota-based diagnostics across populations. Therefore, multi-ethnic studies are crucial for validating consistent microbial signatures and enhancing the global applicability of gut microbiota in AD prediction and intervention.

Comparable results have also been observed in animal models of AD, which generally show reduced microbial diversity and shifts toward proinflammatory taxa, alongside a decline in beneficial bacteria, such as *Faecalibacterium*, *Bifidobacterium*, and *Lactobacillus* (Table 2).[37-46] In the study by Gu *et al.*,[45] a significant increase in the relative abundance of Firmicutes was observed in amyloid precursor protein (APP)/presenilin-1 (PS1) mice (41% compared to 35% in wild type [WT]), while the Bacteroidetes was reduced (54% compared to 60% in WT). These consistent findings across animal models and human studies strengthen the evidence that gut microbiota dysbiosis is an early event in

Table 1. Overview of human gut microbiota alterations associated with healthy controls, mild cognitive impairment, and Alzheimer's disease

Author	Year	Subjects	Method	Main findings
Cattaneo *et al.*[12]	2017	$A\beta^+$ CI (*n*=40) $A\beta^-$ CI (*n*=40) HC (*n*=10)	Quantitative polymerase chain reaction	Lower *Eubacterium rectale* and higher *Escherichia/Shigella* in $A\beta^+$ CI subjects compared with HC and $A\beta^-$ CI groups.
Vogt *et al.*[13]	2017	AD (*n*=25) HC (*n*=10)	16S rRNA sequencing	Lower Firmicutes and *Bifidobacterium* and higher Bacteroidetes in AD patients.
Zhuang *et al.*[14]	2018	AD (*n*=43) HC (*n*=43)	16S rRNA sequencing	Lower Bacteroidetes and higher Actinobacteria in AD patients.
Haran *et al.*[15]	2019	AD (*n*=24) HC (*n*=51)	Metagenomics sequencing	Higher Bacteroides, Alistipes, Odoribacter, and Barnesiella, and lower Lachnoclostridium in AD patients.
Li *et al.*[16]	2019	AD (*n*=30) MCI (*n*=30) HC (*n*=30)	16S rRNA sequencing	Similar changes in gut bacterial populations in MCI and AD; AD and MCI subjects exhibited higher *Escherichia* in fecal and blood samples.
Liu *et al.*[17]	2019	AD (*n*=33) aMCI (*n*=32) HC (*n*=32)	16S rRNA sequencing	Lower Firmicutes and higher Proteobacteria in AD patients compared with HC controls.
Saji *et al.*[18]	2019	MCI (*n*=61) HC (*n*=21)	16S rRNA sequencing	Higher *Bacteroides* in MCI individuals.
Ling *et al.*[19]	2020	AD (*n*=100) HC (*n*=71)	16S rRNA sequencing	Lower *Faecalibacterium* and higher Bifidobacterium in AD patients.
Zhou *et al.*[20]	2021	AD (*n*=60) HC (*n*=32)	16S rRNA sequencing	Higher Bifidobacterium, Sphingomonas, Lactobacillus, and Blautia, and lower Odoribacter, Anaerobacterium, and Papillibacter in AD patients.
Zhang *et al.*[21]	2021	MCI (*n*=75) HC (*n*=52)	16S rRNA sequencing	Lower microbial diversity and reduced Faecalibacterium, Ruminococcaceae, and *Alistipes* in MCI individuals.
Guo *et al.*[22]	2021	AD (*n*=18) MCI (*n*=20) HC (*n*=18)	16S rRNA sequencing	Lower *Bacteroides*, *Lachnospira*, and *Ruminiclostridium_9* and higher *Prevotella* in AD patients compared with HC controls; *Lachnospira* was also reduced in MCI individuals relative to HC controls.
Pan *et al.*[23]	2021	MCI (*n*=22) HC (*n*=26)	16S rRNA sequencing	Lower Bacteroidetes and higher Fusobacteria in MCI individuals.
Liu *et al.*[24]	2021	aMCI (*n*=20) HC (*n*=22)	16S rRNA sequencing	Higher Bacteroidetes in aMCI individuals.
Jung *et al.*[25]	2022	$A\beta^+$ CN (*n*=18) $A\beta^-$ CN (*n*=60)	16S rRNA sequencing	Higher Megamonas, Serratia, Leptotrichia, and Clostridium, and lower CF231, Victivallis, Enterococcus, and Mitsuokella in $A\beta^+$ CN individuals.
Zhu *et al.*[26]	2022	AD (*n*=83) MCI (*n*=125) HC (*n*=94)	16S rRNA sequencing	Higher Erysipelatoclostridiaceae, Erysipelotrichales, Patescibacteria, Saccharimonadales, and Saccharimonadia in AD and MCI subjects.
Sheng *et al.*[27]	2022	AD (*n*=11) MCI (*n*=11) CN^+ (*n*=32) CN^- (*n*=34)	16S rRNA sequencing	Higher Bacteroidetes and lower Firmicutes and Deltaproteobacteria in CN^+individuals compared with CN^- individuals.
Kaiyrlykyzy *et al.*[28]	2022	AD (*n*=41) HC (*n*=43)	16S rRNA sequencing	Higher Acidobacteriota, Verrucomicrobiota, Planctomycetota, Synergistota, *Prevotella*, *Akkermansia*, and *Ruminococcus*, and lower *Bifidobacterium*, *Roseburia*, Lactobacillaceae, and *Faecalibacterium* in AD patients.
Ferreiro *et al.*[29]	2023	Preclinical AD (*n*=49) HC (*n*=115)	Metagenomic sequencing	Dorea formicigenerans, *Faecalibacterium prausnitzii*, Coprococcus catus, and Anaerostipes hadrus were most strongly related to preclinical AD individuals.

(Cont'd)

Table 1. ***(Continued)***

Author	Year	Subjects	Method	Main findings
He *et al.*[30]	2023	CI (*n*=30) SCD (*n*=62) HC (*n*=35)	16S rRNA sequencing	Lower Lachnospiraceae, *Fusicatenibacter*, *Lachnospiracea_incertae_sedis*, and *Anaerobutyricum* with decreasing cognitive ability; higher Rikenellaceae, *Alistipes*, and Odoribacteraceae in the CI individuals.
Jia *et al.*[31]	2025	NC (*n*=63) SCS (*n*=82) SCD (*n*=90) MCI (*n*=119) AD (*n*=122)	Metagenomic sequencing	Higher *Faecalibacterium* spp. in early-stage AD; increased *Alistipes*, *Bacteroides*, and *Prevotella* spp. in MCI and AD with more severe cognitive impairment.
Fan *et al.*[32]	2025	HC (*n*=320) MCI (*n*=119)	Metagenomic sequencing	A total of 59 microbial taxa were related to AD and MCI biomarkers; species from the same genus, such as *Bacteroides* and *Ruminococcus*, had contrasting effects; *Akkermansia muciniphila* was associated with lower amyloid burden.

Abbreviations: AD: Alzheimer's disease; aMCI: Amnestic mild cognitive impairment; Aβ: Amyloid beta; CI: Cognitive impairment; CN: Cognitive normal; HC: Healthy control; MCI: Mild cognitive impairment; SCD: Subjective cognitive decline; SCS: Subjective cognitive symptoms.

Table 2. Overview of gut microbiota dysbiosis in Alzheimer's disease animal models

Author	Year	Animals	Method	Main findings
Shen *et al.*[37]	2017	APP/PS1 mice WT mice	16S rRNA sequencing	Higher Helicobacteraceae and Desulfovibrionaceae (family level) and *Odoribacter* and *Helicobacter* (genus level) in APP/PS1 mice; *Prevotella* was higher in WT mice.
Zhang *et al.*[38]	2017	APP/PS1 mice WT mice	16S rRNA sequencing	Higher Proteobacteria and Verrucomicrobia in APP/PS1 mice.
Carolin *et al.*[39]	2017	5×FAD mice WT mice	16S rRNA sequencing	Higher Firmicutes and *Clostridium leptum* group and lower Bacteroidetes in 5×FAD mice.
Bäuerl *et al.*[40]	2018	APP/PS1 mice WT mice	16S rRNA sequencing	Higher Proteobacteria and Erysipelotrichaceae in APP/PS1 mice.
Sun *et al.*[41]	2019	P301L mice WT mice	16S rRNA sequencing	Higher Bacteroidetes and lower Firmicutes at the phylum level in P301L mice compared with WT mice after 3 months of age.
Wang *et al.*[42]	2019	5×FAD mice WT mice	16S rRNA sequencing	Higher Bacillota/Bacteroidota ratio in 5×FAD mice.
Chen *et al.*[43]	2020	APP/PS1 mice WT mice	16S rRNA sequencing	Higher Proteobacteriaceae, Verrucomicrobiaceae, Bifidobacteriaceae, Erysipelotrichaceae, and Prevotellaceae, and lower Bacteroidaceae and Rikenellaceae in APP/PS1 mice.
Tan *et al.*[44]	2020	Drosophila melanogaster WT controls	Gut microbiota composition analysis	Higher *Wolbachia* and lower gut microbiota diversity in AD flies.
Gu *et al.*[45]	2021	APP/PS1 mice WT mice	16S rRNA sequencing	Lower SCFA-producer bacteria (*Parasutterella* and *Blautia*) and higher Bacillota/Bacteroidota ratio in APP/PS1 mice.
Medina *et al.*[46]	2021	3×Tg-AD mice WT mice	16S rRNA sequencing	Lower Actinobacteria in 3×Tg-AD mice at 3 months of age.

Abbreviations: AD: Alzheimer's disease; APP: Amyloid precursor protein; PS1: Presenilin-1; WT: Wild-type.

AD development and may actively contribute to disease progression. It is critical to interpret these findings with caution, as the majority of evidence, both across human studies and preclinical models, demonstrates observational associations and correlations rather than definitive causation. The temporal link between alterations in gut microbiota and the emergence of AD is complex, and the potential for reverse causality (e.g., AD-related pathological and lifestyle changes influencing the microbiome) or confounding by factors, such as diet, medication, and comorbidities, cannot be excluded. Despite consensus, both clinical and preclinical studies have shown conflicting trends. For instance, some studies have noted a reduction in Bacteroidetes abundance in AD patients,[14,22] while others have observed an increase.[15,24] These inconsistencies likely stem from differences in population characteristics,

diet, environmental conditions, and sequencing methods, highlighting the need for standardized, multicenter studies. Moreover, while reduced microbial diversity is generally linked to poor health, this is not always the case. Studies have found that individuals with major depressive disorder and autism may exhibit greater gut microbial diversity than HC,[47] indicating that diversity alone may not reflect health status. Instead, specific microbial taxa or functional profiles may play a more decisive role in influencing brain health and AD risk. In view of this, research should perhaps focus less on the overall diversity of the gut microbiota and more on the key microbial signatures that might be protective or harmful. As evidenced by the growing body of research summarized in Table 1, multiple microbial taxa have demonstrated consistent associations with AD across various studies. For instance, genera such as *Bacteroides* (often increased) and *Faecalibacterium* (often decreased) are frequently reported. With the advancement of metagenomic sequencing, species-level signatures are increasingly being identified. However, it is worth noting that the establishment of universal microbial biomarkers remains challenging. The lack of a single consistently replicated signature across all cohorts chiefly stems from substantial heterogeneity in study populations (e.g., genetics, diet, and geography), the functional redundancy of the gut ecosystem, and methodological differences in sequencing and bioinformatic analysis. Therefore, large-scale, multicenter prospective studies with standardized methodologies are urgently needed to overcome these limitations, to definitively elucidate which bacterial species or community structures are causally linked to cognitive trajectories, and to translate these findings into targeted preventive or therapeutic strategies.

3. Microbiota–gut–brain axis and its dysregulation in AD

3.1. Microbiota–gut–brain axis and bidirectional communication

The microbiota–gut–brain axis enables complex bidirectional communication between the gut microbiota, enteric nervous system, and CNS, involving three interconnected routes: local neuronal modulation, systemic circulation, and multiple host-microbe interactions. Locally, microbial signals, such as gamma-aminobutyric acid (GABA), primarily produced by *Lactobacillus*, could modulate the vagus nerve or act directly on enteric neurons to influence brain function and cognition.[48] At the systemic level, microbiota-derived metabolites (e.g., SCFAs and tryptophan derivatives) and host molecules (e.g., cytokines and hormones) might enter the bloodstream and reach the brain via the BBB.[49] Indole derivatives, such as indolepropionic acid and kynurenines, have neuroactive and antioxidative properties, modulating neuronal function and inflammation.[50] At the interface level, microbiota interact with gut enteroendocrine cells, enterochromaffin cells, and mucosal immune cells to influence the release of neuromodulators, such as serotonin (5-HT), which activate receptors on neurons and immune cells, ultimately affecting brain activity via the autonomic nervous system and the hypothalamic–pituitary–adrenal axis.[51] Together, the local, systemic, and immune–endocrine pathways of the microbiota–gut–brain axis illustrate how gut microbiota dynamically influence brain function and homeostasis. These communication routes are tightly regulated by the intestinal barriers and BBBs, which protect the CNS from harmful insults. Disruption of these barriers or alterations in microbial signaling may impair neuroimmune balance and neuronal regulation.

3.2. Dysregulation of the microbiota–gut–brain axis in AD

Growing evidence indicates that gut microbiota dysbiosis contributes to AD pathogenesis through multiple interconnected mechanisms, including Aβ accumulation, neuroinflammation, oxidative stress, and tau pathology (Figure 2).

3.2.1. Aβ accumulation

According to the well-established Amyloid–Tau–Neurodegeneration framework, extracellular deposition of Aβ is a core pathological marker of amyloid pathology in AD. Aβ peptides are generated from the sequential proteolytic cleavage of the APP, first by β-secretase and subsequently by γ-secretase, yielding aggregation-prone species, such as Aβ40 and Aβ42. These peptides can oligomerize and form extracellular plaques, contributing to neurotoxicity and synaptic dysfunction.[52,53] Microbial metabolites, notably SCFAs, such as butyrate, and tryptophan derivatives, influence cerebral Aβ dynamics. In AD mouse models, oral administration of butyrate has been shown to reduce brain Aβ levels and enhance cognitive memory performance, with a negative correlation observed between brain Aβ deposition and the levels of butyrate and IL-10.[54,55] Furthermore, SCFAs, such as butyrate, propionate, and pentanoate, can inhibit the formation of Aβ dimers and trimers, with pentanoate also impeding the conversion of Aβ monomers into fibrils.[56] This effect may be partly mediated through 5-HT signaling pathways, as serotonin availability depends on tryptophan metabolism and serotonin transporter function.[57] Dysbiosis of the gut microbiota can impair SCFAs' function and disrupt tryptophan availability, exacerbating brain Aβ deposition due to insufficient 5-HT synthesis in the brain.

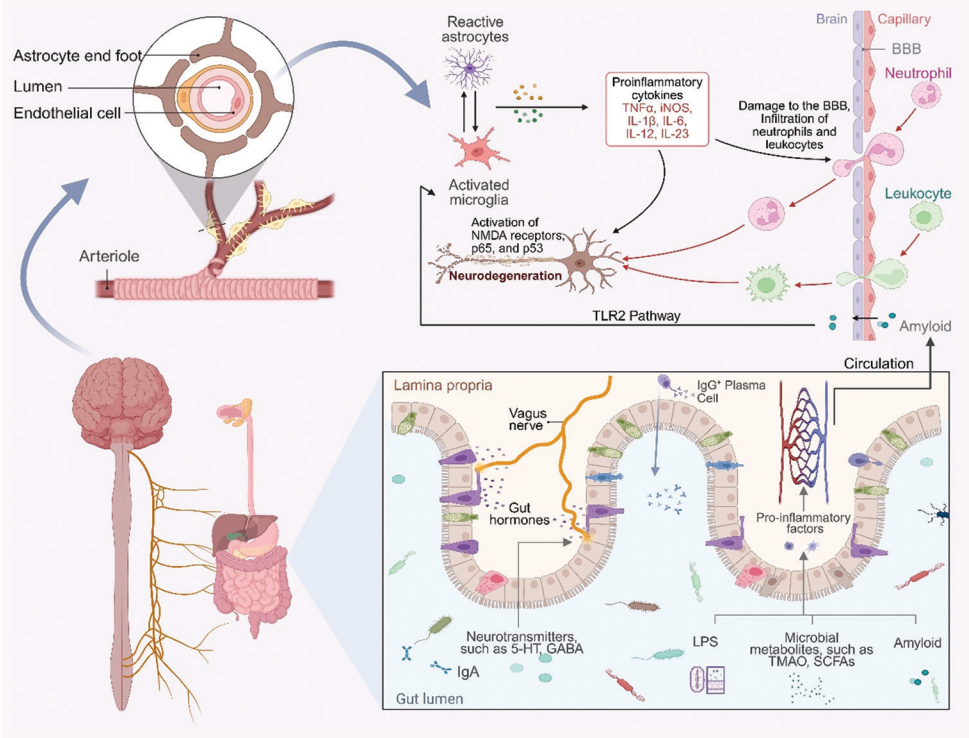

Figure 2. Interplay between gut dysfunction, neuroinflammation, and the blood–brain barrier in the pathogenesis of Alzheimer's disease. Created with BioRender.com. JIANG, H. (2025) https://BioRender.com/izd3ej5.
Abbreviations: 5-HT: Serotonin; BBB: Blood–brain barrier; GABA: Gamma-aminobutyric acid; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LPS: Lipopolysaccharide; NMDA: N-methyl-D-aspartate; SCFAs: Short-chain fatty acids; TLR: Toll-like receptor; TMAO: Trimethylamine N-oxide; TNF: Tumor necrosis factor.

3.2.2. Neuroinflammation and barrier dysfunction

Recent research shows that gut microbiota imbalance plays a critical role in the complex mechanisms of AD, including chronic neuroinflammation, barrier damage, and immune responses. A compromised intestinal barrier ("leaky gut") allows LPS, TMAO, and other proinflammatory molecules to enter circulation, triggering systemic inflammation and BBB dysfunction.[58,59] This facilitates microglial and astrocytic activation and sustained cytokine release (e.g., interleukin [IL]-1β, IL-6, and tumor necrosis factor [TNF]-α), which initially promote Aβ clearance but prolonged activation of microglia leads to the sustained release of proinflammatory cytokines, initiating an inflammatory cascade that damages the BBB barrier, ultimately resulting in neuronal deterioration and death. TNF-α and IL-1β can directly cause synaptic loss through caspase activation, glutamate toxicity, and complement-mediated pruning.[60] In addition, microbial amyloids from *Escherichia coli* and *Staphylococcus aureus* can activate microglia through the toll-like receptor 2 pathway, leading to elevated levels of cytokines IL-17A and IL-22, triggering nuclear factor-κB (NF-κB) signaling and cyclooxygenase-2 activation, inducing inflammatory responses and phagocytosis, thereby exacerbating brain damage.[61] It is well-established that with age, the permeability of the gastrointestinal mucosa and the BBB increases.[10] It has been hypothesized that in this context of increased barrier permeability, microbial components (such as amyloids) could potentially translocate more easily. Crucially, upon entering the brain, these bacterial amyloids are proposed to act as potent seeds that directly catalyze the misfolding and aggregation of endogenous human Aβ through a process of cross-seeding, thereby accelerating the formation of toxic oligomers and fibrils.[62,63] Furthermore, the presence of bacterial amyloids intensifies neuroinflammation, establishing a self-perpetuating loop that destabilizes proteostasis and contributes to AD pathogenesis. While experimental models support this mechanism, the extent of its contribution to human AD requires further robust evidence. However, SCFAs, such as butyrate from the gut microbiota, could help maintain barrier integrity and suppress inflammation, supporting their potential therapeutic role.[55]

3.2.3. Oxidative stress and mitochondrial dysfunction

There is a reciprocal relationship between oxidative stress and Aβ aggregation in AD, with each reinforcing the other.[64] The gut microbiota significantly influences oxidative

stress, mitochondrial dysfunction, and neurodegenerative diseases by producing SCFAs, tryptophan derivatives, and antioxidants, which protect mitochondrial functions. Butyrate, an SCFA, activates Nuclear factor erythroid 2-related factor 2 (Nrf2) by inhibiting histone deacetylases (HDAC) and induces epigenetic modifications of Nrf2 promoters associated with antioxidant responses, thereby mitigating oxidative stress. Hoyles *et al.*[65,66] further demonstrated, using an *in vitro* BBB model with hCMEC/D3 cells, that propionate activates Nrf2, regulates redox homeostasis, and reduces the release of reactive oxygen species, thereby protecting the BBB.[65,66]

3.2.4. Tau pathology and neurofibrillary tangles

Two pathological markers, Tau protein and insoluble neurofibrillary tangles, are primarily found in the neuronal axons of the brain. Proinflammatory cytokines elevated by gut dysbiosis can activate kinases, such as glycogen synthase kinase-3β and cyclin-dependent kinase 5, promoting tau phosphorylation.[67,68] Tau hyperphosphorylation and aggregation are also linked to gut dysbiosis, particularly through microbiota-induced inflammation in apolipoprotein E (APOE)-sensitive models.[69] Animal studies using germ-free or antibiotic-treated models show that modulation of gut microbiota reduces tau pathology, suggesting a causal role.[70] Therapeutic interventions targeting the microbiota have shown promise in attenuating tau-related neurodegeneration in preclinical studies.[69] While mechanisms remain to be fully elucidated, these findings highlight the microbiota–gut–brain axis as a novel target in tau pathology.

In summary, dysregulation of the microbiota–gut–brain axis contributes to AD by promoting neuroinflammation, barrier dysfunction, and oxidative stress. Gut microbiota and their metabolites also influence Aβ deposition and tau pathology, key features of AD. This complex bidirectional communication highlights the important role of gut microbes in disease progression. Understanding these interactions may offer new opportunities for microbiota-targeted therapies to slow or prevent AD.

4. Therapeutics targeted at the gut microbiota in AD

Given the accumulating evidence that gut microbiota dysbiosis contributes to AD pathogenesis through neuroinflammation, amyloid deposition, and barrier dysfunction, therapeutic strategies targeting the gut microbiome have emerged as promising avenues to slow or prevent cognitive decline. These interventions include dietary modification, prebiotics, probiotics, synbiotics, FMT, and other approaches (Figure 3).

4.1. Diet

Recent mechanistic evidence further emphasizes the fundamental role of diet in shaping gut microbiota resilience. Kennedy *et al.*[71] demonstrated that mice treated with antibiotics recovered their gut microbial diversity and function only when fed a balanced, fiber-rich chow diet. In contrast, a Western-style diet, characterized by high fat and low fiber, impaired microbiota recovery and increased vulnerability to *Salmonella* infection. The study revealed that an appropriate dietary environment supports beneficial microbial interactions and metabolic functions, highlighting diet as a necessary condition for restoring gut homeostasis and maintaining host health. Through its influence on gut composition and function, diet plays a central role in regulating the microbiota–gut–brain axis, thereby contributing to cognitive health and potentially mitigating the progression of neurodegenerative diseases.

Several dietary patterns have demonstrated neuroprotective effects partly through microbiota modulation. The Mediterranean diet (MD), rich in fruits, vegetables, whole grains, legumes, nuts, olive oil, and moderate fish intake, is the most extensively studied. Meta-analyses report that adherence to MD correlates with approximately 20% reduced risk of dementia and improvements in global cognition and memory domains.[72] The MD fosters an increase in SCFAs-producing bacteria, such as *Faecalibacterium*, which contribute to anti-inflammatory effects and maintain intestinal barrier integrity.[73] In addition, MD components, such as olive oil, contain polyphenols that attenuate Aβ and tau pathology, reduce oxidative stress, and strengthen BBB function.[74] The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes vegetables, fruits, low-fat dairy, whole grains, and lean proteins. It reduces vascular risk factors for dementia and modulates microbiota toward beneficial taxa, resulting in improved anti-inflammatory profiles and cognitive function.[75] The Mediterranean-DASH intervention for neurodegenerative delay diet combines elements of MD and DASH, focusing on brain-healthy foods. Emerging data indicate its effectiveness in slowing cognitive decline by enriching beneficial gut microbiota and enhancing SCFAs production.[76] The ketogenic diet (KD), high in fat and low in carbohydrates, shifts metabolism to ketone body utilization. A modified Mediterranean-KD was shown to increase beneficial SCFAs and alter gut microbiota composition, such as increasing *Akkermansia*, in association with improved AD biomarkers in individuals with MCI.[77] However, there are also studies presenting opposing viewpoints. Wang *et al.*[78] reported that KD-related dyslipidemia may negatively impact AD neuropathology by initiating the formation

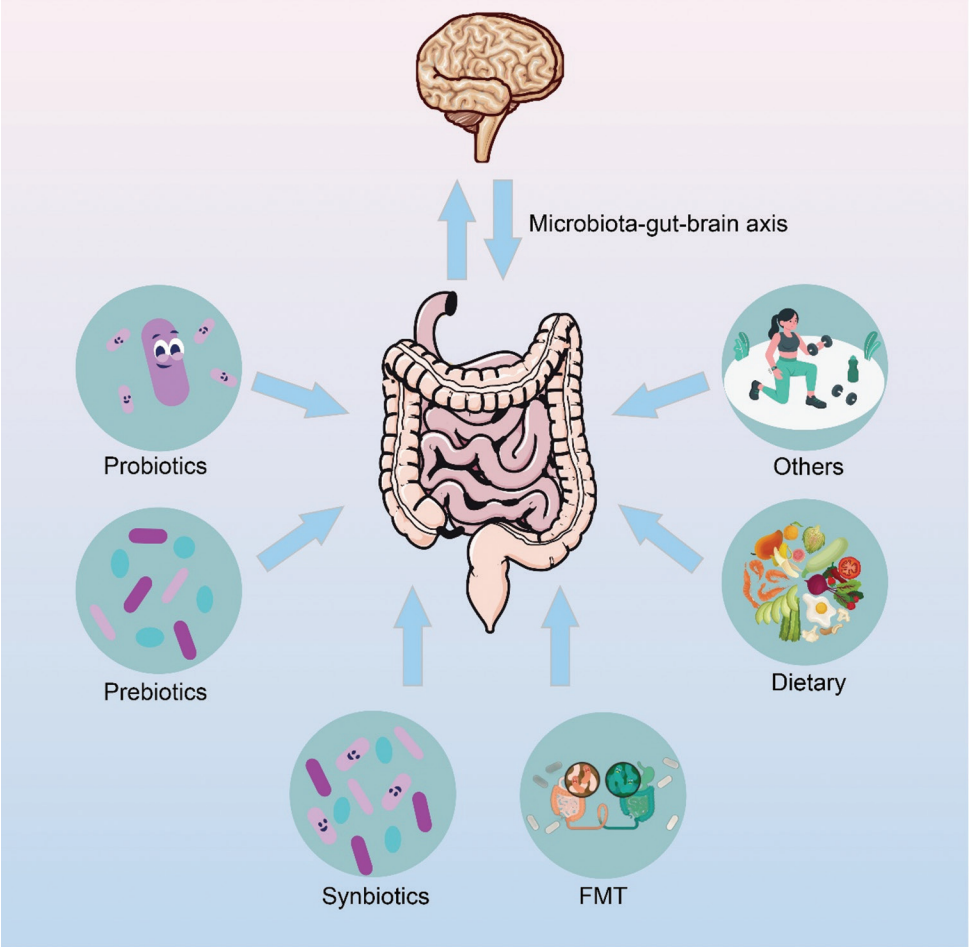

Figure 3. Overview of gut microbiota-targeted interventions in Alzheimer's disease. Image created by the authors.
Abbreviation: FMT: Fecal microbiota transplantation.

of abnormal neural connectivity in individuals with AD. Therefore, the use of the KD diet in AD patients should be approached with caution. Among the various dietary components, dietary fiber plays a particularly important role in modulating the gut microbiota and supporting cognitive health. A diet rich in fiber is associated with increased gut microbial diversity, promoting microbial balance and inhibiting pathogenic bacteria.[79] Fiber in the diet functions as a nutrient source for beneficial microbes, stimulating the production of SCFAs and supporting overall host well-being.[80] Through fiber fermentation, gut acidity increases, supporting the proliferation of beneficial anaerobes and inhibiting microbes linked to inflammation.[81] In contrast, low-fiber, refined-grain-rich diets may diminish these benefits, promoting proinflammatory bacteria, such as Enterobacteriaceae, and elevating circulating LPS. Increased LPS levels can induce systemic and neuroinflammation, leading to BBB impairment and cognitive deterioration.[82]

In summary, these studies mentioned above primarily emphasize the advantages of a diet abundant in vegetables and fruits for individuals with AD. However, the optimal intake levels of these foods have not yet been established in the literature. A previous study conducted by our team examined the basic requirements for fruits and vegetables and found that consuming a minimum of three servings of vegetables and two servings of fruits every day may aid in preventing dementia among older adults.[83] In conclusion, diet significantly affects the composition of the gut microbiota, potentially improving neuroprotection. Overall, a comprehensive mechanistic understanding is needed to elucidate the complex interactions between various diet patterns, gut microbiota, microbial metabolites, and their effects on cognitive function and the progression of AD. Moreover, addressing the need for personalized diets to accommodate significant individual variations and maximize therapeutic efficacy is a critical issue.

4.2. Prebiotics

Prebiotics are currently described as ingredients that are selectively fermented by gut microbiota, not absorbed in the digestive tract, and that positively influence the gut microbiota, thereby benefiting the host's health.[84] Recently, the effect of prebiotic and protein on muscle in older twins randomized controlled trial investigated the effects of a prebiotic supplement on cognition in older adults.[85] In this double-blind, placebo-controlled study, 72 participants aged above 60 received daily prebiotics or a placebo for 12 weeks alongside resistance exercise and branched-chain amino acid supplementation. Prebiotic supplementation significantly improved cognitive performance compared to placebo ($\beta = -0.482$; $p=0.014$), accompanied by increased abundance of beneficial *Bifidobacterium* species. This trial highlights the potential of prebiotics to enhance cognitive function through modulating gut microbiota in aging populations. Supporting the clinical finding, animal studies have demonstrated that prebiotics function as substrates for microbial fermentation, resulting in the generation of SCFAs, which are essential for modulating the host's immune response by inducing T-cell differentiation. Several prebiotics have shown direct benefits on brain function. For example, fructo-oligosaccharides supplementation in transgenic AD mice increased synapsin-1 expression and activated the glucagon-like peptide-1 signaling pathway, leading to improved brain insulin sensitivity and cognitive function.[86] Similarly, xylo-oligosaccharides helped restore BBB integrity, reduced inflammation, and improved cognition by upregulating tight junction proteins, such as zonula ocludens-1, and reshaping gut microbiota.[87] Ferulic acid, a plant-derived compound with prebiotic-like effects, also attenuated neuroinflammation and Aβ burden in AD mice, possibly via improvement of synaptic plasticity.[88] In addition, advances in synthetic chemistry and bioengineering have enabled the development of designed prebiotics.[89] These structures allow targeted fermentation by beneficial microbes closely linked to human health, such as *Faecalibacterium prausnitzii* and *Roseburia* spp. Designed prebiotics offer enhanced specificity, structural consistency, and controllable metabolic outcomes, such as boosting SCFAs production. These precision tools hold promise for personalized nutrition or therapeutic adjuncts in neurodegenerative disease management.

Together, these clinical and preclinical findings underscore the promising role of prebiotics in modulating the gut microbiota to improve cognitive function and counteract neuroinflammation in aging and AD. However, further research is needed to optimize prebiotic formulations, dosages, and long-term efficacy in diverse human populations before widespread clinical application.

4.3. Probiotics and synbiotics

Probiotics are beneficial microorganisms that reside in the human intestines, which could prevent harmful bacteria from establishing themselves and boost the body's immune response.[90] Probiotics improve gut microbiota diversity, maintain intestinal barrier and BBB integrity, reduce Aβ, decrease neuroinflammation, increase butyrate-producing bacteria, such as *F. prausnitzii*, *Ruminococcus*, and *Clostridium*, and enhance cognition.[91,92] They also modulate oxidative stress in AD neuropathology. In Aβ-treated rats, *Lactobacillus* and *Bacillus* strains boosted antioxidant defenses.[93] Neuroinflammation also plays a significant role in this process. Zhu *et al.*[94] showed that *Bifidobacterium breve HNXY26M4* improved cognition, reduced neuroinflammation, restored gut microbiota, increased SCFAs, and enhanced intestinal barrier in APP/PS1 mice. Clinical studies also support the benefits: 24-week *B. breve A1* supplementation improved mini-mental state examination scores (+ 1.7, $p<0.01$), as well as profile of mood states 2nd edition and gastrointestinal symptom rating scale scores, which suggested that *B. breve A1* may enhance cognitive performance and life quality in elderly populations with MCI.[95] In a randomized controlled trial involving 130 patients aged 65–88 years, daily supplementation with *B. breve MCC1274* for 24 weeks resulted in significant improvements in cognitive function compared to the placebo group. While overall gut microbiota composition did not change markedly, probiotic supplementation appeared to suppress brain atrophy progression, particularly in those with advanced brain atrophy. These results suggest that *B. breve MCC1274* may be beneficial in preventing cognitive decline in MCI patients.[96]

Synbiotics are combinations of prebiotics and probiotics that synergistically promote beneficial gut microbes.[84] Arora *et al.*[97] reported that a synbiotic formula containing *Acetobacter*, *Lactobacillus fermentum*, *Bifidobacterium*, *Kluyveromyces*, and others in a 4% kefir matrix improved memory, executive function, and language in humans, while reducing pro-inflammatory cytokines (IL-12, IL-8, TNF-α) and enhancing anti-inflammatory responses. In APP/PS1 mice, Deng *et al.*[98] found that a synbiotic combining inulin with multiple probiotic strains (e.g., *Bacillus coagulans*, *Bifidobacterium longum*) improved cognition, reduced Aβ42 levels, and alleviated inflammation more effectively than inulin alone. Similarly, Westfall showed that synbiotics combining *Trifolium pratense* extract with probiotics improved survival in *Drosophila melanogaster*, outperforming either component alone.[99] Studies in APP/PS1 mice also showed that synbiotics corrected gut dysbiosis, reduced neuroinflammation, and slowed

disease progression through peroxisome proliferator-activated receptor pathway activation.[100,101] These findings suggest synbiotics may offer a more comprehensive strategy than single-agent approaches in AD prevention and management. However, clinical evidence remains scarce. Further research is needed to validate their effects and clarify whether synbiotics outperform probiotics or prebiotics alone.

4.4. Microbiota-derived metabolites

Gut microbiota-derived metabolites include amino acid derivatives (such as tryptophan metabolites, spermidine, and nicotinamide N-oxide), fatty acid metabolites (such as butyrate, propionate, and acetate), and other compounds, such as secondary bile acids, GABA, TMAO, and urolithin A.[102-104] Among these metabolite groups, SCFAs, particularly acetate, propionate, and butyrate, represent one of the most extensively investigated categories. Current evidence suggests these compounds mediate their physiological effects through several distinct molecular mechanisms: (i) Epigenetic regulation: SCFAs act as broad-spectrum HDAC inhibitors, with butyrate exhibiting the highest inhibitory efficiency (~80%) and propionate ~60%.[105,106] HDAC inhibition increases histone acetylation, loosening chromatin structure and enhancing transcription factor access to promoters. This leads to upregulation of genes involved in neuronal survival, synaptic plasticity, oxidative stress defense, and cellular homeostasis, which collectively support cognitive function;[107-109] (ii) Immunomodulation: SCFAs bind to G-protein-coupled receptors (GPR41/FFAR3, GPR43/FFAR2, GPR109A/HCAR2) on immune cells, including neutrophils, monocytes, and lymphocytes.[110,111] Receptor activation triggers downstream pathways (Gαi, Gαq, mitogen-activated protein kinases, extracellular signal-regulated kinase 1/2, β-arrestin2), inhibits nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing protein 3 inflammasome activation, promotes differentiation of regulatory T cells, and reduces proinflammatory cytokines while increasing IL-10.[112] These immunomodulatory effects help maintain systemic and neuroimmune homeostasis, reducing microglial overactivation and neuroinflammation that contribute to AD pathology; (iii) Microglial modulation: Butyrate suppresses microglial overactivation, enhances synaptic plasticity, and improves cognition in 5×FAD mice.[113] Some studies report SCFAs may also increase Aβ deposition through altered microglial phagocytosis, potentially APOE-dependent;[114,115] (iv) Neurotransmitter regulation: SCFAs influence neurotransmitter synthesis through enteroendocrine signaling, enhancing serotonin (via tryptophan hydroxylase), GABA, dopamine, and norepinephrine metabolism. These changes impact cognitive function, supported by SCFA-mediated improvements in AD models.[116,117] Through these mechanisms, SCFAs play critical roles in neuroprotection and cognitive function, suggesting that modulating their levels may represent a targeted therapeutic strategy in AD. In animal models, oral administration of sodium butyrate and sodium propionate has been shown to significantly reduce Aβ accumulation and improve cognitive function in AD mice.[65,118] Supplementation with tauroursodeoxycholic acid, a secondary bile acid, also improved spatial and recognition memory while reducing Aβ deposits in the brain.[119] Conversely, elevated levels of acetate and TMAO have been associated with greater Aβ burden and cognitive decline, suggesting that lowering these metabolites may be beneficial.[120,121]

Compared with administering live bacteria, modulating microbiota-derived metabolites may avoid risks, such as antibiotic resistance, virulence factors, or bloodstream infections. Nonetheless, while several metabolites have shown neuroprotective effects in animal studies, robust clinical trials in humans are still lacking. Further research is needed to validate their therapeutic potential in AD.

4.5. FMT

FMT is a treatment method designed to restore the balance and diversity of the gut microbiota.[122] Today, FMT is used in conditions like *Clostridium difficile* infection and inflammatory bowel diseases, and is gaining interest in neurodegenerative disorders, such as AD,[123] based on the role of gut microbiota in AD pathogenesis.

Animal studies suggest FMT may benefit AD by restoring microbial balance and regulating SCFAs production. For example, D'Amato *et al.*[124] found that FMT from aged to young mice impaired spatial memory, likely due to loss of SCFAs-producing bacteria, such as *Faecalibaculum*, Lachnospiraceae, and Ruminococcaceae. In contrast, FMT in AD mouse models improved cognition, reduced Aβ accumulation, and increased butyrate production.[125,126] Recent evidence also reveals a dose-dependent effect: in 5×FAD mice, FMT given every other day for 8 weeks improved memory and reduced Aβ load, whereas weekly administration showed minimal benefit. These effects were linked to inhibition of the toll-like receptor 4/IκB kinase β/NF-κB pathway and lower LPS levels in the colon and hippocampus.[127] However, cognitive improvements declined over time, suggesting a time-sensitive response. Clinical evidence is limited to two case reports. One described cognitive and mood improvements in an 82-year-old man after receiving FMT from his wife; another reported enhanced

cognition, microbial diversity, and SCFAs in a 90-year-old woman post-FMT from a younger donor.[128,129] Overall, FMT shows promise as a novel AD intervention through gut microbiota modulation. However, the translational challenges are substantial, including interspecies differences in microbiota composition and the difficulty in selecting optimal donors. Therefore, while FMT holds promise as a novel intervention for AD, large-scale, well-controlled clinical trials are urgently needed to evaluate its efficacy, safety, dose-response relationships, and long-term outcomes.

4.6. Others

In addition to the aforementioned interventions, recent studies highlight the potential of exercise and lifestyle changes in modulating the microbiota–gut–brain axis and improving cognitive outcomes in AD. Nicolas *et al.*[130] reported that chronic disruption of gut microbiota using an antibiotic cocktail impaired hippocampal neurogenesis-dependent behaviors in rats. Notably, voluntary exercise attenuated these behavioral deficits and restored adult hippocampal neurogenesis. While changes in the hippocampal metabolome were not observed, improvements were linked to alterations in cecal metabolites, highlighting the critical role of gut microbiota in brain function and the potential of lifestyle factors, such as exercise, to counteract dysbiosis-induced impairments.

5. Considerations and implications

The global rise in the prevalence of AD, alongside challenges in current diagnostics and uncertain long-term efficacy of new amyloid-targeting antibodies,[131] demands alternative strategies. Gut microbiota-based targets show promise but face key obstacles: Microbiota variability influenced by diet, age, medication, and geography complicates biomarker standardization; most studies are cross-sectional, so longitudinal research is needed to confirm causal links with AD. Developing reliable, non-invasive, and affordable diagnostic tools requires standardized sample handling. The complex bidirectional host-microbiota interactions remain underexplored, limiting precise interventions. Comorbidities and medications further confound results. Variability in sampling and analysis hinders reproducibility and clinical translation. Although microbial metabolites hold therapeutic potential, their systemic effects and delivery require in-depth study. Ethical and regulatory considerations are crucial, particularly in protecting vulnerable populations with cognitive impairment during trials, ensuring informed consent and autonomy. The long-term safety of interventions, such as FMT, must be rigorously assessed. Access inequities may worsen disparities in AD care; collaborative efforts should promote fair distribution. Safe, effective microbiota-targeted therapies could slow or reverse cognitive decline, reduce caregiver and societal burdens, and complement existing treatments by targeting neurodegeneration mechanisms. Moreover, microbiota modulation may aid AD prevention, delaying onset and benefiting public health. Realizing this requires interdisciplinary collaboration among neuroscientists, microbiologists, clinicians, regulators, and patient advocates to design rigorous, safe, and effective clinical trials and responsibly translate findings.

6. Conclusion

This review underscores the pivotal role of the microbiota–gut–brain axis in AD, linking gut dysbiosis to key pathological processes. Therapeutic strategies targeting the gut microbiota show promising potential in managing and possibly preventing AD. Future efforts should focus on precise microbial profiling, personalized interventions, and well-designed clinical trials to translate these findings into effective clinical applications. Advancing this field offers hope for improved diagnosis, treatment, and prevention of AD.

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Conflict of interest

Zhilu Xu is Scientist (Diagnostics) of GenieBiome Ltd. Siew C. Ng has served as an advisory board member for Pfizer, Ferring, Janssen and Abbvie and received honoraria as a speaker for Ferring, Tillotts, Menarini, Janssen, Abbvie and Takeda; has received research grants through her affiliated institutions from Olympus, Ferring and Abbvie; is a founder member, non-executive director, non-executive scientific advisor and shareholder of GenieBiome Ltd which is non-remunerative; is a shareholder of MicroSigX Diagnostic Holding Limited; is a founder member, non-executive Board Director, and non-executive scientific advisor of MicroSigX Biotech Diagnostic Limited, which is non-remunerative; and receives patent royalties through her affiliated institutions; is a named inventor of patent applications held by The Chinese University of Hong Kong and MagIC that cover the therapeutic and diagnostic use of the microbiome. All other authors declare that they have no conflicts of interest.

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References

1. Evans-Lacko S, Aguzzoli E, Read S, Comas-Herrera A, Farina N. *World Alzheimer Report 2024: Global Changes in Attitudes to Dementia*. London, UK: Alzheimer's Disease International; 2024. Available from: https://www.alzint.org/resource/world-alzheimer-report-2024 [Last accessed on 2025 Oct 12].
2. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: Review. *JAMA*. 2019;322(16):1589-1599.
   doi: 10.1001/jama.2019.4782
3. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3708-3821.
   doi: 10.1002/alz.13809
4. 2025 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2025;21(4):e70235.
   doi: 10.1002/alz.70235
5. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303-308.
   doi: 10.1001/archneur.56.3.303
6. Zhang T, Gao G, Kwok LY, Sun Z. Gut microbiome-targeted therapies for Alzheimer's disease. *Gut Microbes*. 2023;15(2):2271613.
   doi: 10.1080/19490976.2023.2271613
7. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. *Nature*. 2012;489(7415):220-30.
   doi: 10.1038/nature11550
8. Susmitha G, Kumar R. Role of microbial dysbiosis in the pathogenesis of Alzheimer's disease. *Neuropharmacology*. 2023;229:109478.
   doi: 10.1016/j.neuropharm.2023.109478
9. Sochocka M, Donskow-Łysoniewska K, Diniz BS, Kurpas D, Brzozowska E, Leszek J. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease-a critical review. *Mol Neurobiol*. 2019;56(3):1841-1851.
   doi: 10.1007/s12035-018-1188-4
10. Montagne A, Barnes SR, Sweeney MD, *et al*. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85(2):296-302.
   doi: 10.1016/j.neuron.2014.12.032
11. Lee J, d'Aigle J, Atadja L, *et al*. Gut microbiota-derived short-chain fatty acids promote poststroke recovery in aged mice. *Circ Res*. 2020;127(4):453-465.
   doi: 10.1161/circresaha.119.316448
12. Cattaneo A, Cattane N, Galluzzi S, *et al*. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging*. 2017;49:60-68.
   doi: 10.1016/j.neurobiolaging.2016.08.019
13. Vogt NM, Kerby RL, Dill-McFarland KA, *et al.* Gut microbiome alterations in Alzheimer's disease. *Sci Rep.* 2017;7(1):13537.
   doi: 10.1038/s41598-017-13601-y
14. Zhuang ZQ, Shen LL, Li WW, *et al*. Gut microbiota is altered in patients with Alzheimer's disease. *J Alzheimers Dis*. 2018;63(4):1337-1346.
   doi: 10.3233/jad-180176
15. Haran JP, Bhattarai SK, Foley SE, *et al.* Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-glycoprotein pathway. *mBio*. 2019;10(3):00632-19.
   doi: 10.1128/mBio.00632-19
16. Li B, He Y, Ma J, *et al*. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. *Alzheimers Dement*. 2019;15(10):1357-1366.
   doi: 10.1016/j.jalz.2019.07.002
17. Liu P, Wu L, Peng G, *et al*. Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. *Brain Behav Immun*. 2019;80:633-643.
   doi: 10.1016/j.bbi.2019.05.008
18. Saji N, Murotani K, Hisada T, *et al.* The relationship between the gut microbiome and mild cognitive impairment in patients without dementia: A cross-sectional study conducted in Japan. *Sci Rep.* 2019;9(1):19227.
   doi: 10.1038/s41598-019-55851-y
19. Ling Z, Zhu M, Yan X, *et al*. Structural and functional dysbiosis of fecal microbiota in Chinese patients with Alzheimer's disease. *Front Cell Dev Biol*. 2020;8:634069.
   doi: 10.3389/fcell.2020.634069

20. Zhou Y, Wang Y, Quan M, Zhao H, Jia J. Gut microbiota changes and their correlation with cognitive and neuropsychiatric symptoms in Alzheimer's disease. *J Alzheimers Dis*. 2021;81(2):583-595.

doi: 10.3233/jad-201497

21. Zhang X, Wang Y, Liu W, *et al*. Diet quality, gut microbiota, and micrornas associated with mild cognitive impairment in middle-aged and elderly Chinese population. *Am J Clin Nutr*. 2021;114(2):429-440.

doi: 10.1093/ajcn/nqab078

22. Guo M, Peng J, Huang X, Xiao L, Huang F, Zuo Z. Gut microbiome features of Chinese patients newly diagnosed with Alzheimer's disease or mild cognitive impairment. *J Alzheimers Dis*. 2021;80(1):299-310.

doi: 10.3233/jad-201040

23. Pan Q, Li YQ, Guo K, *et al*. Elderly patients with mild cognitive impairment exhibit altered gut microbiota profiles. *J Immunol Res*. 2021;2021:5578958.

doi: 10.1155/2021/5578958

24. Liu P, Jia XZ, Chen Y, *et al*. Gut microbiota interacts with intrinsic brain activity of patients with amnestic mild cognitive impairment. *CNS Neurosci Ther*. 2021;27(2):163-173.

doi: 10.1111/cns.13451

25. Jung JH, Kim G, Byun MS, *et al*. Gut microbiome alterations in preclinical Alzheimer's disease. *PLoS One*. 2022;17(11):e0278276.

doi: 10.1371/journal.pone.0278276

26. Zhu Z, Ma X, Wu J, *et al*. Altered gut microbiota and its clinical relevance in mild cognitive impairment and Alzheimer's disease: Shanghai aging study and Shanghai memory study. *Nutrients*. 2022;14(19):3959.

doi: 10.3390/nu14193959

27. Sheng C, Yang K, He B, Du W, Cai Y, Han Y. Combination of gut microbiota and plasma amyloid-Buas a potential index for identifying preclinical Alzheimer's disease: A cross-sectional analysis from the silcode study. *Alzheimers Res Ther*. 2022;14(1):35.

doi: 10.1186/s13195-022-00977-x

28. Kaiyrlykyzy A, Kozhakhmetov S, Babenko D, *et al*. Study of gut microbiota alterations in Alzheimer's dementia patients from Kazakhstan. *Sci Rep*. 2022;12(1):15115.

doi: 10.1038/s41598-022-19393-0

29. Ferreiro AL, Choi J, Ryou J, *et al*. Gut microbiome composition may Be an indicator of preclinical Alzheimer's disease. *Sci Transl Med*. 2023;15(700):eabo2984.

doi: 10.1126/scitranslmed.abo2984

30. He B, Sheng C, Yu X, Zhang L, Chen F, Han Y. Alterations of gut microbiota are associated with brain structural changes in the spectrum of Alzheimer's disease: The silcode study in Hainan cohort. *Front Aging Neurosci*. 2023;15:1216509.

doi: 10.3389/fnagi.2023.1216509

31. Jia L, Ke Y, Zhao S, *et al*. Metagenomic analysis characterizes stage-specific gut microbiota in Alzheimer's disease. *Mol Psychiatry*. 2025;30:3951-3962.

doi: 10.1038/s41380-025-02973-7

32. Fan KC, Lin CC, Chiu YL, Koh SH, Liu YC, Chuang YF. Compositional and functional gut microbiota alterations in mild cognitive impairment: Links to Alzheimer's disease pathology. *Alzheimers Res Ther*. 2025;17(1):122.

doi: 10.1186/s13195-025-01769-9

33. Ma C, Li Y, Mei Z, *et al*. Association between bowel movement pattern and cognitive function: Prospective cohort study and a metagenomic analysis of the gut microbiome. *Neurology*. 2023;101(20):e2014-e2025.

doi: 10.1212/wnl.0000000000207849

34. Vogt NM, Romano KA, Darst BF, *et al*. The gut microbiota-derived metabolite trimethylamine N-oxide is elevated in Alzheimer's disease. *Alzheimers Res Ther*. 2018;10(1):124.

doi: 10.1186/s13195-018-0451-2

35. Zhan X, Stamova B, Sharp FR. Lipopolysaccharide associates with amyloid plaques, neurons and oligodendrocytes in Alzheimer's disease brain: A review. *Front Aging Neurosci*. 2018;10:42.

doi: 10.3389/fnagi.2018.00042

36. Huang Y, Wang YF, Miao J, Zheng RF, Li JY. Short-chain fatty acids: Important components of the gut-brain axis against Ad. *Biomed Pharmacother*. 2024;175:116601.

doi: 10.1016/j.biopha.2024.116601

37. Shen L, Liu L, Ji HF. Alzheimer's disease histological and behavioral manifestations in transgenic mice correlate with specific gut microbiome state. *J Alzheimers Dis*. 2017;56(1):385-390.

doi: 10.3233/jad-160884

38. Zhang L, Wang Y, Xiayu X, *et al*. Altered gut microbiota in a mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2017;60(4):1241-1257.

doi: 10.3233/jad-170020

39. Brandscheid C, Schuck F, Reinhardt S, *et al*. Altered gut microbiome composition and tryptic activity of the 5XFAD Alzheimer's mouse model. *J Alzheimers Dis*. 2017;56(2):775-788.

doi: 10.3233/jad-160926

40. Bäuerl C, Collado MC, Diaz Cuevas A, Viña J, P& iña Juevas A92688sition agut microbiota composition in an APP/PSS1 transgenic mouse model of Alzheimer's disease during lifespan. *Lett Appl Microbiol*. 2018;66(6):464-471.

doi: 10.1111/lam.12882

41. Sun BL, Li WW, Wang J, *et al*. Gut microbiota alteration and its time course in a tauopathy mouse model. *J Alzheimers Dis*. 2019;70(2):399-412.

doi: 10.3233/jad-181220

42. Wang X, Sun G, Feng T, *et al*. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res*. 2019;29(10):787-803.

doi: 10.1038/s41422-019-0216-x

43. Chen Y, Fang L, Chen S, *et al*. Gut microbiome alterations precede cerebral amyloidosis and microglial pathology in a mouse model of Alzheimer's disease. *Biomed Res Int*. 2020;2020:8456596.

doi: 10.1155/2020/8456596

44. Tan FHP, Liu G, Lau SA, *et al*. *Lactobacillus* probiotics improved the gut microbiota profile of a *Drosophila melanogaster* Alzheimer's disease model and alleviated neurodegeneration in the eye. *Benef Microbes*. 2020;11(1):79-89.

doi: 10.3920/bm2019.0086

45. Gu X, Zhou J, Zhou Y, *et al*. Huanglian jiedu decoction remodels the periphery microenvironment to inhibit Alzheimer's disease progression based on the "brain-gut" axis through multiple integrated omics. *Alzheimers Res Ther*. 2021;13(1):44.

doi: 10.1186/s13195-021-00779-7

46. Bello-Medina PC, HernMedina P-021-0, PernMedina P-02, *et al*. Spatial memory and gut microbiota alterations are already present in early adulthood in a pre-clinical transgenic model of Alzheimer's disease. *Front Neurosci*. 2021;15:595583.

doi: 10.3389/fnins.2021.595583

47. Jiang H, Ling Z, Zhang Y, *et al*. Altered fecal microbiota composition in patients with major depressive disorder. *Brain Behav Immun*. 2015;48:186-94.

doi: 10.1016/j.bbi.2015.03.016

48. Kunze WA, Mao YK, Wang B, *et al*. *Lactobacillus reuteri* enhances excitability of colonic Ah Neurons by inhibiting calcium-dependent potassium channel opening. *J Cell Mol Med*. 2009;13(8b):2261-2270.

doi: 10.1111/j.1582-4934.2009.00686.x

49. Fock E, Parnova R. Mechanisms of blood-brain barrier protection by microbiota-derived short-chain fatty acids. *Cells*. 2023;12(4):657.

doi: 10.3390/cells12040657

50. Sathyasaikumar KV, Blanco-Ayala T, Zheng Y, *et al*. The tryptophan metabolite indole-3-propionic acid raises kynurenic acid levels in the rat brain *in vivo*. *Int J Tryptophan Res*. 2024;17:11786469241262876.

doi: 10.1177/11786469241262876

51. Hwang YK, Oh JS. Interaction of the vagus nerve and serotonin in the gut-brain axis. *Int J Mol Sci*. 2025;26(3):1160.

doi: 10.3390/ijms26031160

52. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-356.

doi: 10.1126/science.1072994

53. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol*. 2007;8(2):101-112.

doi: 10.1038/nrm2101

54. Marizzoni M, Cattaneo A, Mirabelli P, *et al*. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. *J Alzheimers Dis*. 2020;78(2):683-697.

doi: 10.3233/jad-200306

55. Fernando W, Martins IJ, Morici M, *et al*. Sodium butyrate reduces brain amyloid-utlevels and improves cognitive memory performance in an Alzheimer's disease transgenic mouse model at an early disease stage. *J Alzheimers Dis*. 2020;74(1):91-99.

doi: 10.3233/jad-190120

56. Ho L, Ono K, Tsuji M, Mazzola P, Singh R, Pasinetti GM. Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. *Expert Rev Neurother*. 2018;18(1):83-90.

doi: 10.1080/14737175.2018.1400909

57. Fisher JR, Wallace CE, Tripoli DL, Sheline YI, Cirrito JR. Redundant Gs-coupled serotonin receptors regulate amyloid-edmetabolism *in vivo*. *Mol Neurodegener*. 2016;11(1):45.

doi: 10.1186/s13024-016-0112-5

58. Philippens IH, Ormel PR, Baarends G, Johansson M, Remarque EJ, Doverskog M. Acceleration of amyloidosis by inflammation in the amyloid-beta marmoset monkey model of Alzheimer's disease. *J Alzheimers Dis*. 2017;55(1):101-113.

doi: 10.3233/jad-160673

59. Coquenlorge S, Duchalais E, Chevalier J, Cossais F, Rolli-Derkinderen M, Neunlist M. Modulation of lipopolysaccharide-induced neuronal response by activation of the enteric nervous system. *J Neuroinflammation*. 2014;11:202.

doi: 10.1186/s12974-014-0202-7

60. Prieto GA, Tong L, Smith ED, Cotman CW. Tnfn C129IL-1L-Tnfn C129L-18 suppresses hippocampal long-term potentiation directly at the synapse. *Neurochem Res*.

2019;44(1):49-60.

doi: 10.1007/s11064-018-2517-8

61. Hill JM, Lukiw WJ. Microbial-generated amyloids and Alzheimer's disease (Ad). *Front Aging Neurosci*. 2015;7:9.

doi: 10.3389/fnagi.2015.00009

62. Wang C, Lau CY, Ma F, Zheng C. Genome-wide screen identifies curli amyloid fibril as a bacterial component promoting host neurodegeneration. *Proc Natl Acad Sci U S A*. 2021;118(34):e2106504118.

doi: 10.1073/pnas.2106504118

63. Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. *PLoS Pathog*. 2017;13(12):e1006654.

doi: 10.1371/journal.ppat.1006654

64. Dumitrescu L, Popescu-Olaru I, Cozma L, *et al.* Oxidative stress and the microbiota-gut-brain axis. *Oxid Med Cell Longev*. 2018;2018:2406594.

doi: 10.1155/2018/2406594

65. Wu J, Jiang Z, Zhang H, *et al*. Sodium butyrate attenuates diabetes-induced aortic endothelial dysfunction via P300-mediated transcriptional activation of NRF2. *Free Radic Biol Med*. 2018;124:454-465.

doi: 10.1016/j.freeradbiomed.2018.06.034

66. Hoyles L, Snelling T, Umlai UK, *et al*. Microbiome-host systems interactions: Protective effects of propionate upon the blood-brain barrier. *Microbiome*. 2018;6(1):55.

doi: 10.1186/s40168-018-0439-y

67. Yang S, Wang L, Liang X, *et al.* Radix hedysari polysaccharides modulate the gut-brain axis and improve cognitive impairment in SAMP8 mice. *Int J Biol Macromol*. 2025;306(Pt 4):141715.

doi: 10.1016/j.ijbiomac.2025.141715

68. Flynn CM, Yuan Q. Probiotic supplement as a promising strategy in early tau pathology prevention: Focusing on GSK-3B? *Front Neurosci*. 2023;17:1159314.

doi: 10.3389/fnins.2023.1159314

69. Seo DO, O'Donnell D, Jain N, *et al.* Apoe isoform- and microbiota-dependent progression of neurodegeneration in a mouse model of tauopathy. *Science*. 2023;379(6628):eadd1236.

doi: 10.1126/science.add1236

70. Harach T, Marungruang N, Duthilleul N, *et al.* Reduction of abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. *Sci Rep.* 2017;7:41802.

doi: 10.1038/srep41802

71. Kennedy MS, Freiburger A, Cooper M, *et al.* Diet outperforms microbial transplant to drive microbiome recovery in mice. *Nature*. 2025;642(8068):747-755.

doi: 10.1038/s41586-025-08937-9

72. Nucci D, Sommariva A, Degoni LM, *et al*. Association between mediterranean diet and dementia and Alzheimer disease: A systematic review with meta-analysis. *Aging Clin Exp Res*. 2024;36(1):77.

doi: 10.1007/s40520-024-02718-6

73. Kimble R, Gouinguenet P, Ashor A, *et al*. Effects of a mediterranean diet on the gut microbiota and microbial metabolites: A systematic review of randomized controlled trials and observational studies. *Crit Rev Food Sci Nutr*. 2023;63(27):8698-8719.

doi: 10.1080/10408398.2022.2057416

74. Alkhalifa AE, Al-Ghraiybah NF, Kaddoumi A. Extra-virgin olive oil in Alzheimer's disease: A comprehensive review of cellular, animal, and clinical studies. *Int J Mol Sci*. 2024;25(3).

doi: 10.3390/ijms25031914

75. Kincaid HJ, Nagpal R, Yadav H. Diet-microbiota-brain axis in Alzheimer's disease. *Ann Nutr Metab*. 2021;77 Suppl 2(Suppl 2):21-27.

doi: 10.1159/000515700

76. McEvoy CT, Jennings A, Steves CJ, Macgregor A, Spector T, Cassidy A. Diet patterns and cognitive performance in a UK female twin registry (Twinsuk). *Alzheimers Res Ther*. 2024;16(1):17.

doi: 10.1186/s13195-024-01387-x

77. Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. Modified mediterranean-ketogenic diet modulates gut microbiome and short-Chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. *EBioMedicine*. 2019;47:529-542.

doi: 10.1016/j.ebiom.2019.08.032

78. Wang Q, Zang F, He C, Zhang Z, Xie C. Dyslipidemia induced large-scale network connectivity abnormality facilitates cognitive decline in the Alzheimer's disease. *J Transl Med*. 2022;20(1):567.

doi: 10.1186/s12967-022-03786-w

79. Makki K, Deehan EC, Walter J, Bäckhed F. The impact of dietary fiber on gut microbiota in host health and disease. *Cell Host Microbe*. 2018;23(6):705-715.

doi: 10.1016/j.chom.2018.05.012

80. Koh A, De Vadder F, Kovatcheva-Datchary P, Bäckhed F. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. *Cell*. 2016;165(6):1332-1345.

doi: 10.1016/j.cell.2016.05.041

81. Desai MS, Seekatz AM, Koropatkin NM, *et al.* A dietary fiber-deprived gut microbiota degrades the colonic mucus barrier and enhances pathogen susceptibility. *Cell*. 2016;167(5):1339-1353.e21.

doi: 10.1016/j.cell.2016.10.043

82. Zinöcker MK, Lindseth IA. The Western diet-microbiome-host interaction and its role in metabolic disease. *Nutrients*. 2018;10(3):365.

doi: 10.3390/nu10030365

83. Lee ATC, Richards M, Chan WC, Chiu HFK, Lee RSY, Lam LCW. Lower risk of incident dementia among Chinese older adults having three servings of vegetables and two servings of fruits a day. *Age Ageing*. 2017;46(5):773-779.

doi: 10.1093/ageing/afx018

84. Salminen S, Collado MC, Endo A, *et al*. The international scientific association of probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat Rev Gastroenterol Hepatol*. 2021;18(9):649-667.

doi: 10.1038/s41575-021-00440-6

85. Ni Lochlainn M, Bowyer RCE, Moll JM, *et al*. Effect of gut microbiome modulation on muscle function and cognition: The promote randomised controlled trial. *Nat Commun*. 2024;15(1):1859.

doi: 10.1038/s41467-024-46116-y

86. Sun J, Liu S, Ling Z, *et al*. Fructooligosaccharides ameliorating cognitive deficits and neurodegeneration in APP/PS1 transgenic mice through modulating gut microbiota. *J Agric Food Chem*. 2019;67(10):3006-3017.

doi: 10.1021/acs.jafc.8b07313

87. Han D, Li Z, Liu T, *et al*. Prebiotics regulation of intestinal microbiota attenuates cognitive dysfunction induced by surgery stimulation in APP/PS1 mice. *Aging Dis*. 2020;11(5):1029-1045.

doi: 10.14336/ad.2020.0106

88. Mahaman YAR, Huang F, Salissou MTM, *et al*. Ferulic acid improves synaptic plasticity and cognitive impairments by alleviating the PP2B/DARPP-32/PP1 axis-mediated step increase and AP1burden in Alzheimer's disease. *Neurotherapeutics*. 2023;20(4):1081-1108.

doi: 10.1007/s13311-023-01356-6

89. Gibson GR, Hutkins R, Sanders ME, *et al*. Expert consensus document: The international scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat Rev Gastroenterol Hepatol*. 2017;14(8):491-502.

doi: 10.1038/nrgastro.2017.75

90. Fuller R. Probiotics in man and animals. *J Appl Bacteriol*. 1989;66(5):365-378.

91. Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic supplementation in patients with Alzheimer's dementia - an explorative intervention study. *Curr Alzheimer Res*. 2018;15(12):1106-1113.

doi: 10.2174/1389200219666180813144834

92. Zhu LB, Zhang YC, Huang HH, Lin J. Prospects for clinical applications of butyrate-producing bacteria. *World J Clin Pediatr*. 2021;10(5):84-92.

doi: 10.5409/wjcp.v10.i5.84

93. Athari Nik Azm S, Djazayeri A, Safa M, *et al*. Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in Biamyloid (1-42) injected rats. *Appl Physiol Nutr Metab*. 2018;43(7):718-726.

doi: 10.1139/apnm-2017-0648

94. Zhu G, Zhao J, Wang G, Chen W. *Bifidobacterium breve* HNXY26M4 attenuates cognitive deficits and neuroinflammation by regulating the gut-brain axis in APP/PS1 mice. *J Agric Food Chem*. 2023;71(11):4646-4655.

doi: 10.1021/acs.jafc.3c00652

95. Kobayashi Y, Kinoshita T, Matsumoto A, Yoshino K, Saito I, Xiao JZ. *Bifidobacterium breve* A1 supplementation improved cognitive decline in older adults with mild cognitive impairment: An open-label, single-arm study. *J Prev Alzheimers Dis*. 2019;6(1):70-75.

doi: 10.14283/jpad.2018.32

96. Asaoka D, Xiao J, Takeda T, *et al*. Effect of probiotic *Bifidobacterium breve* in improving cognitive function and preventing brain atrophy in older patients with suspected mild cognitive impairment: Results of a 24-week randomized, double-blind, placebo-controlled trial. *J Alzheimers Dis*. 2022;88(1):75-95.

doi: 10.3233/jad-220148

97. Arora K, Green M, Prakash S. The microbiome and Alzheimer's disease: Potential and limitations of prebiotic, synbiotic, and probiotic formulations. *Front Bioeng Biotechnol*. 2020;8:537847.

doi: 10.3389/fbioe.2020.537847

98. Deng SM, Chen CJ, Lin HL, Cheng IH. The beneficial effect of synbiotics consumption on Alzheimer's disease mouse model via reducing local and systemic inflammation. *IUBMB Life*. 2022;74(8):748-753.

doi: 10.1002/iub.2589

99. Westfall S, Lomis N, Prakash S. A novel synbiotic delays Alzheimer's disease onset via combinatorial gut-brain-axis signaling in *Drosophila melanogaster*. *PLoS One*. 2019;14(4):e0214985.

doi: 10.1371/journal.pone.0214985

100. Tong Y, Lu G, Guo J, *et al*. A new intestinal supplement "synbiotics" therapeutically regulates gut microbiota and activates PPARs pathway to inhibit Alzheimer's disease progression in mouse models. *New Microbiol*. 2024;47(1):68-79.

101. Zhang J, Zhao X, Xu H, *et al*. NMN synbiotics intervention modulates gut microbiota and metabolism in APP/PS1

Alzheimer's disease mouse models. *Biochem Biophys Res Commun*. 2024;726:150274.

doi: 10.1016/j.bbrc.2024.150274

102. Chandra S, Vassar RJ. Gut microbiome-derived metabolites in Alzheimer's disease: Regulation of immunity and potential for therapeutics. *Immunol Rev*. 2024;327:33-42.

doi: 10.1111/imr.13412

103. Kern L, Mastandrea I, Melekhova A, Elinav E. Mechanisms by which microbiome-derived metabolites exert their impacts on neurodegeneration. *Cell Chem Biol*. 2025;32:25-45.

doi: 10.1016/j.chembiol.2024.08.014

104. Connell E, Le Gall G, Pontifex MG, *et al.* Microbial-derived metabolites as a risk factor of age-related cognitive decline and dementia. *Mol Neurodegener*. 2022;17(1):43.

doi: 10.1186/s13024-022-00548-6

105. Licciardi PV, Ververis K, Karagiannis TC. Histone deacetylase inhibition and dietary short-chain fatty acids. *ISRN Allergy*. 2011;2011:869647.

doi: 10.5402/2011/869647

106. Kasubuchi M, Hasegawa S, Hiramatsu T, Ichimura A, Kimura I. Dietary gut microbial metabolites, short-chain fatty acids, and host metabolic regulation. *Nutrients*. 2015;7(4):2839-2849.

doi: 10.3390/nu7042839

107. Wang J, Yu JT, Tan MS, Jiang T, Tan L. Epigenetic mechanisms in Alzheimer's disease: Implications for pathogenesis and therapy. *Ageing Res Rev*. 2013;12(4):1024-1041.

doi: 10.1016/j.arr.2013.05.003

108. Fischer A. Targeting histone-modifications in Alzheimer's disease. What is the evidence that this is a promising therapeutic avenue? *Neuropharmacology*. 2014;80:95-102.

doi: 10.1016/j.neuropharm.2014.01.038

109. Yang SS, Zhang R, Wang G, Zhang YF. The development prospection of hdac inhibitors as a potential therapeutic direction in Alzheimer's disease. *Transl Neurodegener*. 2017;6:19.

doi: 10.1186/s40035-017-0089-1

110. Tang XL, Wang Y, Li DL, Luo J, Liu MY. Orphan G protein-coupled receptors (GPCRS): Biological functions and potential drug targets. *Acta Pharmacol Sin*. 2012;33(3):363-371.

doi: 10.1038/aps.2011.210

111. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol*. 2019;16(8):461-478.

doi: 10.1038/s41575-019-0157-3

112. Layden BT, Angueira AR, Brodsky M, Durai V, Lowe WL Jr. Short chain fatty acids and their receptors: New metabolic targets. *Transl Res*. 2013;161(3):131-140.

doi: 10.1016/j.trsl.2012.10.007

113. Jiang Y, Li K, Li X, Xu L, Yang Z. Sodium butyrate ameliorates the impairment of synaptic plasticity by inhibiting the neuroinflammation in 5XFAD mice. *Chem Biol Interact*. 2021;341:109452.

doi: 10.1016/j.cbi.2021.109452

114. Gold A, Kaye S, Gao J, Zhu J. Propionate decreases microglial activation but impairs phagocytic capacity in response to aggregated fibrillar amyloid beta protein. *ACS Chem Neurosci*. 2024;15(21):4010-4020.

doi: 10.1021/acschemneuro.4c00370

115. Colombo AV, Sadler RK, Llovera G, *et al.* Microbiota-derived short chain fatty acids modulate microglia and promote Aβ plaque deposition. *Elife*. 2021;10:e59826.

doi: 10.7554/eLife.59826

116. Wu M, Tian T, Mao Q, *et al*. Associations between disordered gut microbiota and changes of neurotransmitters and short-chain fatty acids in depressed mice. *Transl Psychiatry*. 2020;10(1):350.

doi: 10.1038/s41398-020-01038-3

117. Mhanna A, Martini N, Hmaydoosh G, *et al*. The correlation between gut microbiota and both neurotransmitters and mental disorders: A narrative review. *Medicine (Baltimore)*. 2024;103(5):e37114.

doi: 10.1097/md.0000000000037114

118. Lang W, Li X, Wang Y, *et al*. Sodium propionate improves cognitive and memory function in mouse models of Alzheimer's disease. *Neurosci Lett*. 2022;791:136887.

doi: 10.1016/j.neulet.2022.136887

119. Lo AC, Callaerts-Vegh Z, Nunes AF, Rodrigues CM, D'Hooge R. Tauroursodeoxycholic acid (Tudca) supplementation prevents cognitive impairment and amyloid deposition in APP/PS1 mice. *Neurobiol Dis*. 2013;50:21-29.

doi: 10.1016/j.nbd.2012.09.003

120. Erny D, Dokalis N, Mezö C, *et al.* Microbiota-derived acetate enables the metabolic fitness of the brain innate immune system during health and disease. *Cell Metab*. 2021;33(11):2260-2276.e7.

doi: 10.1016/j.cmet.2021.10.010

121. Zarbock KR, Han JH, Singh AP, *et al.* Trimethylamine N-oxide reduces neurite density and plaque intensity in a murine model of Alzheimer's disease. *J Alzheimers Dis*. 2022;90(2):585-597.

doi: 10.3233/jad-220413

122. Ooijevaar RE, Terveer EM, Verspaget HW, Kuijper EJ,

Keller JJ. Clinical application and potential of fecal microbiota transplantation. *Annu Rev Med*. 2019;70:335-351.

doi: 10.1146/annurev-med-111717-122956

123. Allegretti JR, Mullish BH, Kelly C, Fischer M. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *Lancet*. 2019;394(10196):420-431.

doi: 10.1016/s0140-6736(19)31266-8

124. D'Amato A, Di Cesare Mannelli L, Lucarini E, *et al*. Faecal microbiota transplant from aged donor mice affects spatial learning and memory via modulating hippocampal synaptic plasticity- and neurotransmission-related proteins in young recipients. *Microbiome*. 2020;8(1):140.

doi: 10.1186/s40168-020-00914-w

125. Sun J, Xu J, Ling Y, *et al*. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. *Transl Psychiatry*. 2019;9(1):189.

doi: 10.1038/s41398-019-0525-3

126. Kim MS, Kim Y, Choi H, *et al*. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut*. 2020;69(2):283-294.

doi: 10.1136/gutjnl-2018-317431

127. Jiang X, Zheng Y, Sun H, *et al*. Fecal microbiota transplantation improves cognitive function of a mouse model of Alzheimer's disease. *CNS Neurosci Ther*. 2025;31(2):e70259.

doi: 10.1111/cns.70259

128. Hazan S. Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation: A case report. *J Int Med Res*. 2020;48(6):300060520925930.

doi: 10.1177/0300060520925930

129. Park SH, Lee JH, Shin J, *et al*. Cognitive function improvement after fecal microbiota transplantation in Alzheimer's dementia patient: A case report. *Curr Med Res Opin*. 2021;37(10):1739-1744.

doi: 10.1080/03007995.2021.1957807

130. Nicolas S, Dohm-Hansen S, Lavelle A, *et al*. Exercise mitigates a gut microbiota-mediated reduction in adult hippocampal neurogenesis and associated behaviours in Rats. *Transl Psychiatry*. 2024;14(1):195.

doi: 10.1038/s41398-024-02904-0

131. Raket LL, Cummings J, Moscoso A, Villain N, Schöll M. Scenarios for the long-term efficacy of amyloid-targeting therapies in the context of the natural history of Alzheimer's disease. *Alzheimers Dement*. 2024;20(9):6374-6383.

doi: 10.1002/alz.14134