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Review

The role of gut microbiota in the neurobiology and treatment of Alzheimer's disease

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Abstract. Alzheimer's disease (AD) is the most common cause of dementia in the elderly population and characterized by progressive cognitive decline. The major pathological features of AD are the accumulation of extracellular amyloid-beta protein as neuritic plaques and intracellular hyperphosphorylated tau protein as neurofibrillary tangles. Studies have shown that gut microbiota are involved in several central nervous system disorders through regulation of neurotransmitter production, blood-brain barrier permeability and immune responses. The gut microbiota establishes a two-way communication between the gut and the brain through neural, endocrine, and immune pathways, which play a role in various neurological diseases, including AD. Alterations in the composition and function of the gut microbiota may influence neuroinflammation, amyloid-beta accumulation, and tau pathology. Targeting the balance of the gut microbiota through probiotics, prebiotics, and fecal microbial transplantation could be promising therapeutic approach against neurodegeneration. Understanding the complex relationship between the gut microbiota and AD pathobiology could pave the way for novel preventive and therapeutic strategies. Here, we summarized advances in the role of gut microbiota in AD pathobiology and updated rising concerns from recent reports. Moreover, the possibility of applying the capability of the gut microbiota as a promising treatment against AD has been discussed in this review.

Key words: Alzheimer's disease — Microbiota — Amyloid-beta — Neuroinflammation — Probiotics

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder highlighted by impaired cognitive functions primarily in the areas of memory, language, visuospatial, and executive domains (Sohrabi et al. 2019; Hong et al. 2024). Epidemiological studies have shown that AD is the most common neurological complication affecting the elderly worldwide. In recent years, the mortalities associated with AD has increased significantly, growing by 145% (Association 2019; Chaddha et al. 2025). Approved treatments for AD are poorly effective, and an extensive and comprehensive understanding of the pathological mechanisms involved in AD is needed to develop novel therapeutic strategies. It is hypothesized that the pathological hallmarks of AD in the brain include the presence of amyloid-beta (Aβ) aggregated plaques and phosphorylated tau protein in neurofibrillary tangles (NFTs), which are associated with neuronal death and the weakening of synaptic connections (Zhang et al. 2024). The gastrointestinal microbiome is one of the most densely populated microbial resource, comprising nearly

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10^{14} microbes from about 1000 different species that differ in diversity and persistence between individuals (Specter 2021). Bacteroidetes and Firmicutes are the two main bacterial phyla in the intestine, with others, including *Proteobacteria, Verrucomicrobia, Actinobacteria, Cyanobacteria, Fusobacteria, Spirochetes,* and other microbes, making up the remains (Ghosh et al. 2021; Philip Mani et al. 2024). Gut microbiota is essential for various beneficial functions of host physiology, such as preserving the integrity of intestinal barrier, suppressing pathogen adhesion to the gut surface, synthesizing vitamin K, salvaging energy from indigestive nutrition, short-chain fatty acid (SCFA) biosynthesis, and intestinal motility (Chok et al. 2021). Recent studies have shown that dysbiosis, the disruption of balance in composition and abundance of microbiota, is associated with central nervous system (CNS) disorders through dysregulation in neuroactive component production, metabolic functions, and immune responses (Wu et al. 2021). In the past decade, clinical and experimental reports have described disruption of microbiota composition in AD, leading to the development of significant questions and knowledge in this field (Seo et al. 2024). Since then, extensive research has focused on exploring the link between the intestinal microbiota and AD pathology, and several mechanisms have been proposed to elucidate the involvement of microbiota in AD pathology, such as neurotransmitter production, regulation of the immune responses, modulation of metabolic pathways, alteration in blood-brain barrier (BBB) permeability and Aβ generation and clearance (Seo et al. 2024). While these mechanisms propose that targeting the microbiota can be a potential therapeutic approach against AD, the field of the "gut microbiota-AD brain axis" yet has several gaps. The pathways associated with microbiota in AD pathobiology remain unknown and need to be addressed before emerging clinical therapies targeting the gut microbiota for the treatment of AD. In Table 1 are summarized pathways involved

Table 1. Pathways involved in microbiota–AD axis and known and unknown mechanisms in these interactions

Pathway	Known mechanisms	Unknown mechanisms	References
Aβ pathology	Microbiota can modulate APP processing; Microbiota can influence Aβ interactions and plaque formation; Bacteria can biosynthesize and assemble functional amyloid proteins.	Specific interactions between gut microbiota and brain metabolism that developed Aβ pathology	Liang et al. 2024
Neuroinflammation	Dysbiosis can increase intestinal permeability, which contribute to neuroinflammation; Microbiota-derived metabolites and surface molecules (including SCFAs and LPS) induce pro-inflammatory responses.	The signaling pathway linking gut inflammation to brain inflammation; Microbial species that directly influence neuroinflammation	Mostafavi Abdolmaleky et al. 2024
Metabolite production	Production of SCFAs like butyrate improves neuroinflammation; Microbial TMAO contribute to cognitive decline and pathological mechanisms in AD; Several microbes including Bifidobacterium species, Akkermansia muciniphila, Saccharomyces and Faecalibacterium prausnitzii reduced neuroinflammation through NF-κB inhibition.	The role of several microbial metabolites including tryptamine and phenolic compounds on AD pathology	Luo et al. 2024
BBB integrity	The function and composition of gut microbiota affect BBB integrity; Dysbiosis can increase pro-inflammatory cytokines in the circulation which increase BBB permeability by disrupting tight junctions; Altering gut microbiota can influence the migration of immune cells across the BBB.	Signaling pathways between microbial metabolites and BBB; Microbiota-induced epigenetic changes in BBB cells, the impact of individual genetic background on BBB integrity changes induced by microbiota	Parker et al. 2020; Yehualashet et al. 2025
Oxidative stress	Gut microbiota including Faecalibacterium prausnitzii and Lactobacillus can induce antioxidant mechanisms to improve cognitive impairment, mitochondrial dysfunctions and oxidative stress in AD; Dysbiosis can suppress Nrf2 signaling leading to ROS production.	Molecular targets that induce or suppress oxidative stress through gut-brain communication; The relationship between microbial profile and brain ROS production	Botchway et al. 2022; Mostafavi Abdolmaleky et al. 2024

SCFA; short chain fatty acid; LPS, lipopolysaccharide; TMAO, trimethylamine N-oxide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; BBB, blood brain barrier; Nrf2, nuclear factor erythroid 2-related factor 2.

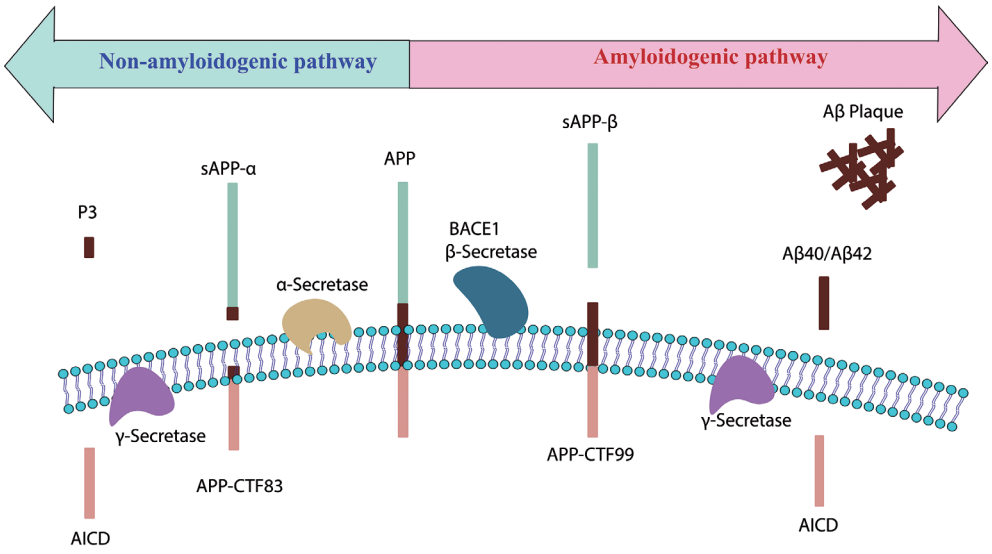


Figure 1. The mechanism of Aβ plaque formation. In non-amyloidogenic pathway, APP is cleaved by α-secretase, which leads to release of soluble APPα ectodomains into the extracellular space and remaining a C-terminal fragment of 83 amino acids within the cell membrane. In amyloidogenic pathway cleavage of APP by the enzyme β-secretase and then γ-secretase leads to Aβ generation.

in microbiota-AD axis and known and unknown mechanisms in these interactions. Here, we review the role of gut microbiota in AD pathological pathways and update rising concerns from recent reports that require further elucidation. Moreover, the possibility of applying the capability of the gut microbiota as a promising treatment against AD is discussed in this review.

The pathobiology of Alzheimer's disease

AD is a neurodegenerative disease and its pathophysiological mechanisms are attributed to the accumulation of extracellular Aβ plaques and intracellular hyperphosphorylated tau tangles in the hippocampus and cortical regions. The accumulation of oligomeric Aβ peptides is implicated in pathophysiology in triggering downstream events such as neuroinflammation and oxidative stress that promote cognitive deficits (Hampel et al. 2021). Amyloid-beta precursor protein (APP), the precursor molecule of Aβ, is a transmembrane protein produced by neurons, astrocytes, and some non-neuronal cells and is involved in cell signaling, synaptic activity, and neuronal development (Cho et al. 2022; Pfundstein et al. 2022). In addition to protecting neurons, the presence of APP in the cell membrane also controls intercellular communication, and regulates neuronal growth and neuroplasticity (Ratan et al. 2023). APP can be processed in amyloidogenic and non-amyloidogenic pathways (Fig. 1). In non-amyloidogenic pathway, APP is cleaved by α-secretase, which leads to soluble APPα ectodomain release into the extracellular space and remaining a C-terminal fragment of 83 amino acids within the cell membrane (Sirisi et al. 2024). The sequential proteolytic cleavage of APP by the enzyme β-secretase (also known as BACE1) and then γ-secretase constitutes the amyloidogenic pathway (Devkota et al. 2021). When APP is degraded in the amyloidogenic pathway, amyloid-beta peptides with different lengths from Aβ-37 to Aβ-43 are produced. Of these, the two main species, Aβ42 and Aβ40, are more involved in AD pathology (Ratan et al. 2023).

Aβ42 is potentially prone to aggregation owing to the hydrophobic fragments in both terminals. Hence, Aβ42 is more likely to contribute to the formation of amyloid plaques, which are neurotoxic (Brand et al. 2022). Furthermore, AD could be differentially diagnosed from other cognitive disorders based on Aβ42/38 and Aβ38/42 ratios in the cerebrospinal fluid (CSF) (Welge et al. 2009; Mulugeta et al. 2011; Tang et al. 2014). By enhancing Aβ production and reducing the Aβ40/Aβ42 ratio, dysregulation of APP degradation pathways potentially contributes to the AD progress. Abnormal Aβ accumulation causes neuroinflammation and neurodegeneration (Fig. 2). Aβ monomeric fragments are soluble but Aβ aggregates form insoluble oligomers that then accumulate to Aβ plaques. Aβ transport by low-density lipoprotein receptor-related protein 1 (LRP1) and receptor for advanced glycation end products (RAGE) is the important strategy used by glial cells to remove Aβ from the extracellular space (Barić 2024). Experimental studies have shown that unbalanced progression of Aβ synthesis and removal results in abnormal aggregation of Aβ, which subsequently leads to Aβ plaque formation (Belder et al. 2023).

Hyperphosphorylation of serine or threonine residues in microtubule-associated protein, tau, increases its intracellular deposition and leads to the formation of NFTs (Iaccarino et al. 2023). Studies on taupathy disorders and

tau transgenic animal models have shown gliosis, neuroinflammation and neurodegeneration even in the absence of Aβ aggregation (Dutta et al. 2023). The accumulation of NFTs causes damage to microtubule organization, leading to insoluble aggregates found in the hippocampus as well as the entorhinal and cerebral cortices (Sánchez et al. 2018). Moreover, tau-mediated microglial activation leads to release of pro-inflammatory cytokines including interleukin-6 (IL-6), IL-1β, , and tumor necrosis factor alpha (TNF-α) (Didonna 2020). Recent transcriptional studies have implicated nuclear factor kappa B (NF-kB) and the nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 (NLRP3) inflammasome in the inflammatory process resulting from microglial activation by tau aggregation (Wang et al. 2018; Stancu et al. 2019). Microglia can significantly enhance tau clearance by uptake and removal of phosphorylated tau. Studies have shown that CX3C motif chemokine receptor 1 (CX3CR1) is involved in phagocytosis and degradation of tau in microglial cells (Bolós et al. 2017; Laurent et al. 2018; Ratan et al. 2023). The absence of CX3CR1 in microglia impaired tau internalization and intensified NFT formation (Bolós et al. 2017; Ratan et al. 2023). In addition to tau clearance, microglia may also be involved in tau release through exosomes, as exosome release can be blocked by microglial depletion (Laurent et al. 2018; Ratan et al. 2023). Consequently, taupathy and pathogenic microglia may drive cyclic pathogenic pathways during the AD development (Ratan et al. 2023). Astrocytes directly affect tau accumulation and metabolism. Tau accumulation has been observed in the nucleus of astrocytes in the CNS of AD affected patients, despite the fact that tau is mainly produced in neurons (Laurent et al. 2018; Ratan et al. 2023). Tau accumulation in astrocytes causes astrocyte dysfunction and apoptosis, leading to BBB breakdown and induction of low molecular weight heat shock protein expression (Togo et al. 2002). Pathogenic tau also disrupted astrocyte-mediated glutamate transport, which subsequently leads to glutamate accumulation in the CNS and further excitotoxicity (Pita-Almenar et al. 2012).

Microbiota and the brain

The CNS and the gut microbiota communicate with each other through complex molecular mechanisms (Mayer et al. 2022). The two-way interaction of the microbiota with the CNS occurs by neural, endocrine, and immune system communications (Fig. 3). Neural pathway is predominantly

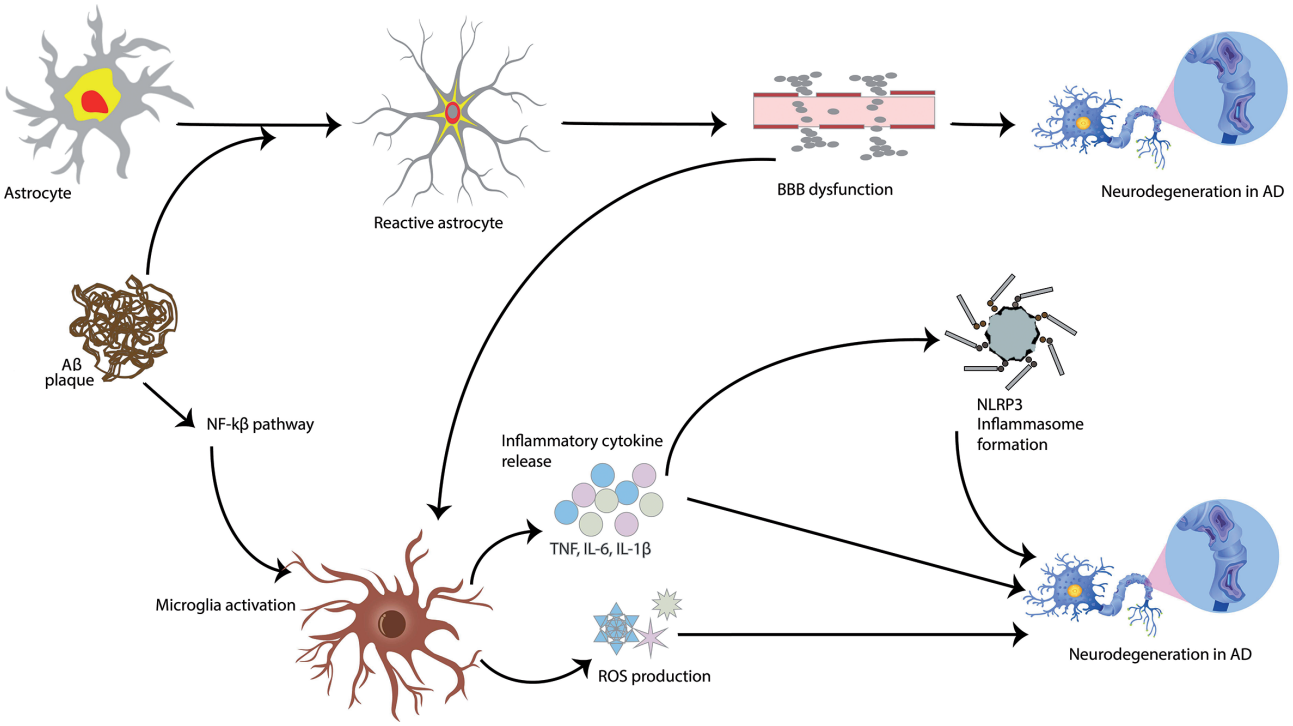


Figure 2. Mechanism of neuroinflammation and neurodegeneration following Aβ accumulation. Plaques of Aβ induce microglia activation, which leads to increased secretion of pro-inflammatory cytokines, activation of the inflammasome pathway in surrounding cells, and increased oxidative stress. All of these events lead to neurodegeneration. Aβ deposition also contributes to neuroinflammation and neurodegeneration by increasing BBB permeability.

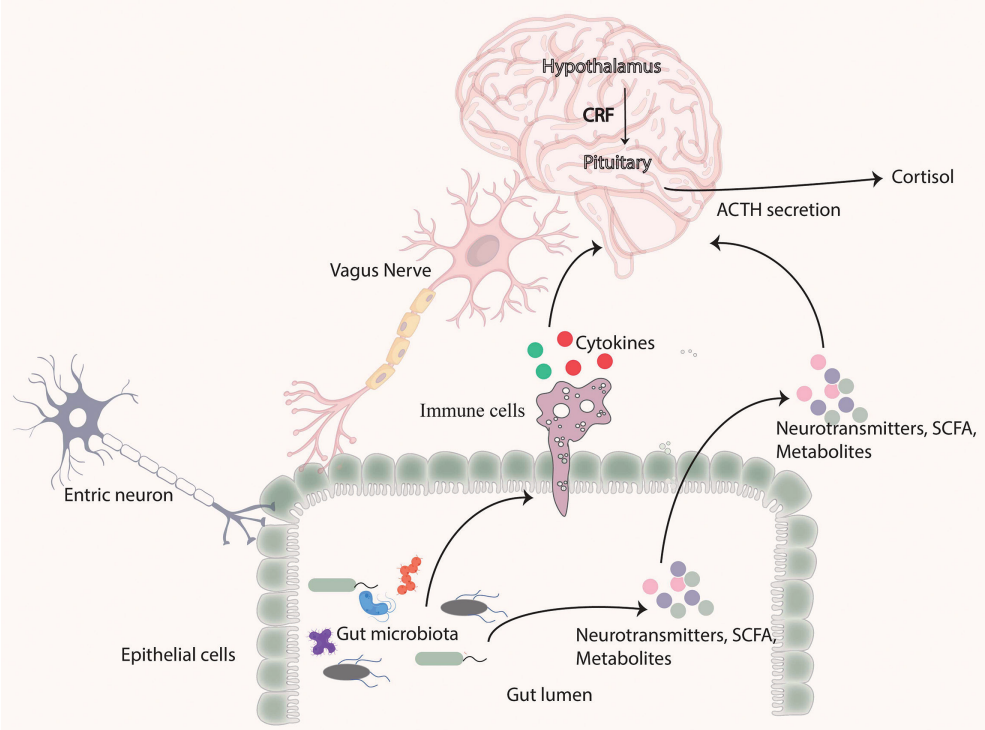


Figure 3. Mechanism of the bidirectional communications between the gut microbiota and the brain. Short chain fatty acids (SCFAs), neurotransmitters (NTs) and metabolites produced by the gut microbiota affect the enteric and vagus nerves, immune cells and hormonal regulation.

mediated by the vagus nerve, which acts as a direct conduit between the CNS and the digestive tract. The vagus nerve plays a key role in regulation of motility, secretion, and permeability of gastrointestinal tract. During stress, the vagus nerve alters intestinal function to adapt to the situation (Décarie-Spain et al. 2024). Another pathway involved in this bidirectional communication is endocrine system. The hypothalamus releases corticotropin releasing hormone (CRH), which induces adrenocorticotropic hormone (ACTH) release from the pituitary gland, ultimately increasing corticosteroids such as cortisol from the adrenal gland (Misiak et al. 2020). Circulating cortisol can alter the composition of the microbiota by affecting secretion, motility and immune responses of gastrointestinal tract (Rusch et al. 2023). In addition, the immune system also plays a role in this bidirectional communication. Since immune cells release pro-inflammatory cytokines in response to inflammation, they can affect intestinal permeability and the BBB integrity to change CNS functions (Zheng et al. 2023). Pro-inflammatory cytokines including IL-6 and TNF-α are released by microglia and can enter the circulation and alter the composition and function of the intestinal microbiota (Potrykus et al. 2021). Neuron-glial-epithelial communication is a complex axis between neurons, glial cells, and epithelial cells that plays a role in regulating CNS activity (Hong et al. 2023). Neurons communicate with each other *via* synaptic structures. Glial cells, including astrocytes and microglia, maintain homeostasis around neurons, operate neuro-immune responses and preserve the BBB integrity (Seguella et al. 2021). Epithelial cells play a role in establishing the BBB to limit the substance transmission between the circulation and CNS and protect CNS from toxins and pathogens (Knox et al. 2022). Moreover, epithelial cells regulate intestinal permeability. The communications between these cell types are regulated by signaling molecules, including neurotransmitters, cytokines, and growth factors (Di Vincenzo et al. 2024). Dysregulation in these communications can lead to diseases including multiple sclerosis and AD. Moreover, these communications could be therapeutic targets in many neurodegenerative diseases (Zheng et al. 2023).

Gut microbes can biosynthesize neurotransmitters including serotonin, dopamine, and gamma-aminobutyric acid (GABA). Moreover, SCFAs are primarily generated through microbial fermentation of dietary fibers and can enter to the circulation and then reach the brain, affecting gene expression and neuronal metabolism (Dezfouli et al. 2025). SCFAs also are important in the regulation of neuroinflammatory pathways. Gut microbiota dysbiosis, can lead to neurological and psychological disorders (Hayer et al. 2024). The gut microbiota in Alzheimer's patients is altered, which results in increased permeability of intestinal tract (Liu et al. 2020). As a result, inflammatory mediators are transported into the brain, exacerbating neuroinflammation and neurodegeneration (Liu et al. 2020). Studies on probiotics, prebiotics, and dietary modifications aimed at improving the microbiota

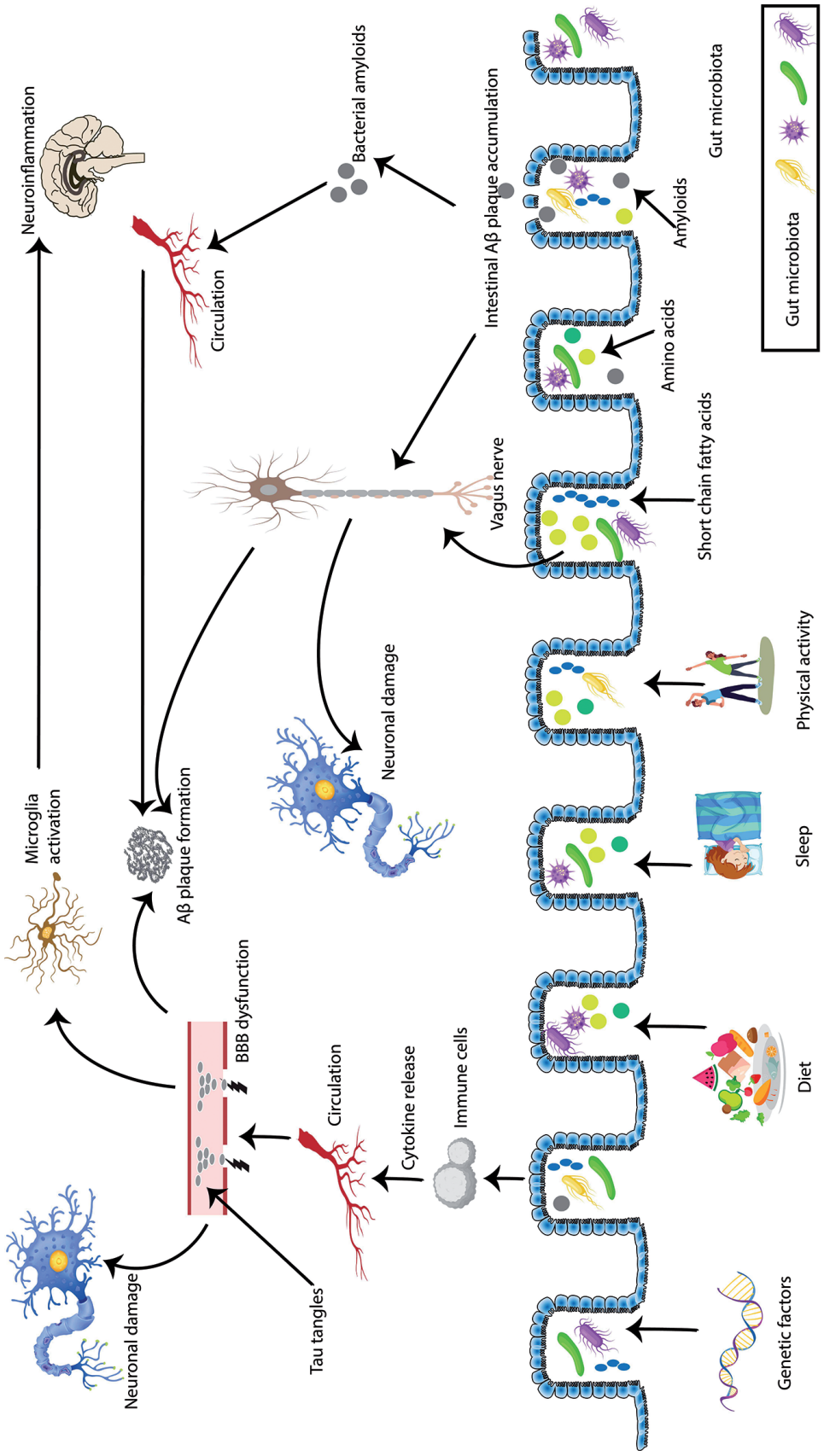


Figure 4. The role of gut microbiota in the pathobiology of AD. Several factors including nutrition, sleep, diet and genetic polymorphisms can influence the function and composition of gut microbiota. Microbiota surface molecules and metabolites affect the release on cytokines including IL-6, IL-1β and TNF-α. Dysbiosis can lead to systemic inflammation, BBB dysfunction and altered immune responses in the brain which can increase Aβ accumulation and neuroinflammation.

and modulating inflammatory pathways have highlighted the significance of preserving a healthy microbiota to protect neural functions (Doifode et al. 2021; Mayer et al. 2022). This two-way connection between the CNS and the microbiota demonstrates the dependence of the brain and gut on each other in maintaining balance and improving their function (Zheng et al. 2023).

In addition to bacteria, which constitute 90–95% of the gut microbiota, gut-resident viruses and fungi also play a role in the gut-brain axis. Dysbiosis in virome composition can damage intestinal epithelial cells, which is associated with increased circulating IL-6 and inflammatory responses (Seth et al. 2020). Most enteric viruses are bacteriophages that contribute in regulation of the gut bacterial population (Wu et al. 2025). In addition, some gut-resident eukaryotic viruses, such as human herpesviruses, can contribute to neuroinflammation by infecting enteric neurons and disrupting the intestinal barrier (Brun et al. 2021; Maes et al. 2024). The fungal population of the microbiota, collectively known as the mycobiome, constitutes only 1–3% of the microbiota population, but plays an important role in regulating host immunity. Candida albicans can migrate to the CNS in inflammatory and dysbiosis conditions and participate in neuroinflammation and cognitive impairment (Fatima et al. 2023). Saccharomyces species protect the integrity of the intestinal barrier and reduce neuroinflammatory processes (Mohammadi et al. 2024; Valizadeh et al. 2025).

Microbiota and pathobiology of Alzheimer's disease

The gut microbiota contributes to AD pathology through immune, neural, endocrine, and metabolic networks in the gut-brain axis. Dysbiosis can lead to increased intestinal permeability and translocation of bacterial products such as lipopolysaccharide (LPS), SCFAs and amyloids, which induce inflammation and microglial activation, contributing to the accumulation of Aβ and tau pathology (Yehualashet et al. 2025). As presented in Figure 4, microbiota can induce neuroinflammation, Aβ accumulation, and neurodegeneration in AD pathobiology.

Microbiota and amyloid-beta generation

The progressive aggregation of misfolded proteins in the brain is an important hallmark of various neurodegenerative disorders, including AD and Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). A hypothesis underlying the pathobiology of PD has been proposed that α-synuclein accumulation may begin in the enteric nervous system and gradually extend to the brain regions, where it is trans-synaptically transmitted from neuron to neuron. An increase in Firmicutes and a decrease in Bacteroidetes and an increase in the Clostridium leptum in the intestine could be involved in intestinal Aβ accumulation and Aβ deposits in the early stages of AD (Brandscheid et al. 2017). Moreover, it has been reported that abundance of *Helicobacteraceae and Desulfovibrionaceae* in the intestine of APP/PS1 transgenic mice was associated with increased brain Aβ levels and cognitive impairments (Shen et al. 2017). Interestingly, Aβ aggregation in the myenteric plexus neurons and intestinal inflammation were observed prior to the brain neuroinflammatory markers in this AD animal model (Semar et al. 2013). Similarly, intestinal dysbiosis, intestinal-epithelial barrier impairment, and vascular Aβ accumulation in the intestine precede the onset of Aβ deposition in the hippocampus in the Tg2576 animal model (Honarpisheh et al. 2020). Deposition of Aβ has been observed in the intestinal tissue of AD patients in postmortem studies (Honarpisheh et al. 2020). Hence, it has been hypothesized that intestinal Aβ deposition occurs prior to its accumulation in the CNS during AD development.

Microbial trimethylamine N-oxide (TMAO) has been reported to contribute to cognitive decline and pathological mechanisms in AD by enhancing β-secretase function and thereby exacerbating Aβ generation (Buawangpong et al. 2022). Furthermore, TMAO produced by microbiota, induced platelet reactivity by increasing calcium release (Krüger-Genge et al. 2020). Since activated platelets contribute to the generation of Aβ, thereby platelet activation increases Aβ in the circulation and the brain (Inyushin et al. 2020). Platelets have a large amount of APP on their surface and their activation increases the amyloidogenic pathway and Aβ secretion in the circulation. In addition, platelet activation leads to cerebral vasculitis and microvascular dysfunction, which exacerbates amyloid pathology in the brain (Ferrer-Raventós et al. 2021). Increased bacterial bile acids in the circulation leads to increase BBB permeability by disrupting tight junctions, allowing bile acids or peripheral cholesterol to enter the CNS (Lirong et al. 2022; Collins et al. 2023). Increased cholesterol in the membrane of neural cells facilitates the incorporation of APP in the phospholipid monolayer of lipid raft, leading to the acceleration of Aβ generation (Gamba et al. 2012; Liu et al. 2020). Furthermore, bile acids also reduce the level of the cholesterol metabolizing enzyme CYP46A in brain, disrupting cholesterol clearance pathways, leading to cholesterol aggregation and expansion of Aβ generation (Jia et al. 2020; Mulak 2021). Butyric acid produced by the gut microbiota can inhibit Aβ1-40 and Aβ1-42 peptides interactions and Aβ plaque formation (Huang et al. 2024).

Many bacteria can biosynthesize and assemble functional amyloid fibrils onto their cell surfaces (Sønderby et al. 2022). Most bacterial amyloids contribute to biofilm formation and other communicating behaviors in which bacteria interact

with a surface or other cells (Jain et al. 2019). Bacterial amyloids are structurally and biochemically similar to pathogenic amyloids in the host (Marcoleta et al. 2019). These amyloid compounds are implicated in the promotion of Aβ amyloidosis (Christensen et al. 2019). Bacterial amyloids also can cross-link and aggregate host amyloid peptides through molecular mimicry (Miller et al. 2021). Moreover, amyloid components from gut microbiota can induce the secretion of pro-inflammatory factors including IL-17A and IL-22 (Wu et al. 2021). Curli is a widely researched extracellular amyloid fiber produced by many Enterobacteriaceae, including E. coli and Salmonella species (Marcoleta et al. 2019). Other bacterial amyloids include FapC by Pseudomonas fluorescens, phenol-soluble modulin by Staphylococcus aureus, chaplin by Streptomyces coelicolor, and MccE492 by Klebsiella pneumonia (Javed et al. 2020; Liu et al. 2020; Salinas et al. 2020).

It has been reported that certain fungi, such as Candida albicans, are increased in the oral and intestinal microbiota of Alzheimer's patients compared to healthy individuals (Yetgin 2024). Candida albicans produces amyloid proteins that induce the formation of Aβ plaques in the brain. The composition of gut bacteria has been shown to inhibit or enhance the production of these amyloid proteins (Yetgin 2024). It has been reported that encapsulated yeast fungus, Cryptococcus, is involved in systemic inflammation, leading to cognitive impairment and deficits in executive functions (Liu et al. 2022). Some fungi can prevent AD pathobiology. For instance, Aspergillus species MPUC239, inhibited BACE1 activity and reduced Aβ accumulation (Fujihara et al. 2023). Intestinal Saccharomyces inhibited Aβ(1-42) accumulation, cognitive impairment and AD progression (Cecarini et al. 2022). Saccharomyces boulardii inhibited amyloid production in mice and reduced Aβ accumulation and memory dysfunction through modulation of the BACE1 pathway (Mohammadi et al. 2024). Interestingly, enteric viruses also are involved in the Aβ pathobiology. Intestinal virome profiles in individuals with amyloid-positive AD patients showed lower bacteriophage diversity. The family Siphoviridae was reduced in these patients. Remarkable reductions in Lactococcus phages were also observed in these patients compared to control individuals (Ghorbani et al. 2023).

Microglia are involved in the regulation of Aβ aggregation, and microglial phagocytic activity is important for the engulfment of monomeric and oligomeric Aβ and the clearance of deposited Aβ fibrils (Dodiya et al. 2021). The accumulation of stimulated microglia nearby amyloid aggregations may provide a barrier that can prevent the fibrilation of soluble Aβ into deposited plaques, reduce damage to neighboring neuropils, and make Aβ deposits more compact (Caradonna et al. 2024; Jazuli et al. 2024). The gut microbiota is crucial for microglial maturation and function under homeostatic conditions (Bano et al. 2024). Germ-free animal models, with disrupted gut microbiota composition, showed defects in microglial proportion and maturation. These impairments can be reversed by reintroduction of viable mixture of gut microbiota (Erny et al. 2015, 2021). Microglia from adult germ-free mice had reduced expression levels of genes involved in microglial maturation (Erny et al. 2015). Supplementation of aged mice with Bacteroides fragilis suppressed microglial phagocytosis and contributed to AD pathogenesis by impairing Aβ clearance (Wasén et al. 2024). These findings indicate that microglial functions are highly affected by microbiota compositions and their metabolites. Thion et al. (2018) reported that microglia are more influenced by the microbiota during the fetal period in males and during adulthood in females.

Microbiota and neuroinflammation in Alzheimer's disease

Gut microbiota regulates host inflammatory responses, and neuroinflammatory pathways are involved in the neurodegenerative processes. Li et al. (2020) showed that microbiota composition had significant differences between transgenic AD and normal mice, and cognitive impairment was increased in specific pathogen-free (SPF) transgenic Alzheimer's mice compared to germ-free Alzheimer's mice, and the MAPK signaling pathway, APP expression, and amyloid deposition were increased in SPF Alzheimer's mice. Therefore, dysregulation in the gut microbiota during AD progression can be involved in the cognitive impairment and Aβ deposition *via* MAPK pathway. Interestingly antibiotic treatment reduced Aβ deposition in hippocampus. Inhibition of colony-stimulating factor 1 receptor (CSF1R) resulted in depletion of microglia in antibiotic-treated animals and inhibited the reduction of cerebral Aβ, suggesting that microglia are involved in the effect of microbiota on AD pathobiology (Dodiya et al. 2021). Transplantation of fecal microbiota from AD transgenic mice to germ-free animals increased Aβ, microglial activation, and neurodegeneration (Dodiya et al. 2021).

The gut microbiota contributed in immune homeostasis by regulating the balance between pro-inflammatory and anti-inflammatory pathways. Stimulation of the immune system is a critical host defense mechanism against pathogens (Pickard et al. 2017). Nevertheless, an overactive inflammation leads to increased cytokines and recruitment of leukocytes, including factors of cellular acquired immunity (B and T lymphocytes), which permeate to the CNS or secrete cytokines that increase inflammation in the CNS (Heneka et al. 2024). Excessive abundance of adverse microorganisms and reduced microbial diversity considerably can alter intestinal-blood barrier. As a result, invading microorganism surface molecules, specifically LPS, and microbial metabolites can pass into the circulation, inducing

the release of pro-inflammatory mediators by the immune cells (Dezfouli et al. 2025).

Chronic or persistent inflammation of the intestinal mucosa can overwhelm the immune responses, resulting in chronic, hyperactive and dysfunctional inflammatory responses, that trigger pathological mechanisms (Di Vincenzo et al. 2024). Long-term changes in the microbial compositions not only induce inflammatory responses in the gastrointestinal tract, but also affect distant organs. Furthermore, the BBB integrity potentially compromised due to increased inflammatory cytokines, subsequently triggering neuroinflammatory cascades (Al Bander et al. 2020; Mostafavi Abdolmaleky and Zhou 2024). Seo et al. (2024) showed that the activity of meningeal γδ T cells, plasmacytoid dendritic cells, and NK cells in a mouse model of tauopathy, is dependent on the compositions of microbiota. These immune cells release cytokines including interleukin-17 and type I interferon, that are involved in the neuroinflammatory pathways.

Neuroinflammatory processes can also be developed by the entrance of microbial LPS and metabolites to the CNS (Džidić-Krivić et al. 2025). Human study has also reported that AD patients showed increased levels of peripheral inflammatory markers such as LPS, cell adhesion molecules (CAMs), IL-1β, IL-6, and TNFα, and decreased level of anti-inflammatory cytokine IL-10 (Marizzoni et al. 2023). Hence, gut microbiota dysbiosis not only has a detrimental effect on the gastrointestinal tract, but also remarkably interrupts the balance between microbiota and immune responses (Teffera et al. 2024). As a result, dysregulation in the reciprocal relationship between the gut and the brain results in diverse neuroinflammatory responses. An increasing number of studies suggest that neuroinflammatory mechanisms play crucial roles in the Aβ deposition, tau protein hyper-phosphorylation, and subsequent neurodegeneration (Guerrero et al. 2021; Twarowski et al. 2023).

Pro-inflammatory cytokines, initially considered for their neuroprotective roles, have been implicated as neurodegenerative factors when produced inappropriately and unbalanced (Guerrero et al. 2021). Consequently, the extent of inflammation-induced nervous system damage depends on the degree of host immune system activation, the stage of disease pathobiology and environmental and genetic factors (Rather et al. 2021). Changes in BBB permeability and intestinal barriers due to intestinal dysbiosis may contribute to the increased brain accumulation of microbial molecules (such as LPS) and metabolites (such as SCFAs), thereby establishing pro-inflammatory environments that serve the pathogenic pathways in AD (Yehualashet et al. 2025). Furthermore, gut dysbiosis induced release of IL-6, IL-8, and other inflammatory mediators generated by triggering receptors expressed on myeloid cells (TREM) signaling in response to specific bacteria including *Fusobacterium, Escherichia Coli and Clostridium species* (Mou et al. 2022; Wu et al. 2023). However, some bacteria in gastrointestinal tract exhibited anti-inflammatory properties including Bifidobacterium species, *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* through metabolites that inhibit NF-κB activation (Liang et al. 2021; Effendi et al. 2022; Mei et al. 2024).

SCFAs, such as acetate, propionate, and butyrate, exert neuroprotective and neurotoxic effects depending on different physiological conditions. Butyrate has been shown to inhibit histone deacetylases (HDACs), thereby reducing the expression of neuroinflammatory genes (Huang et al. 2024). Butyrate increased tight junction protein expression and reduced BBB permeability. This SCFA stimulated the production of BDNF and supported neuronal survival (Ge et al. 2023). Studies have also reported a role for SCFAs in the progression of AD. During dysbiosis, SCFAs including acetate and propionate can stimulate TLR-mediated microglial activation and neuroinflammation. Increased SCFAs in experimental models of AD is associated with increased amyloid plaque burden and microglial clustering (Colombo et al. 2021; Akhtar et al. 2022; Wang et al. 2024). Table 2 presented conditions involved in SCFA effects in the pathobiology of AD.

Restoring intestinal SCFAs in transgenic AD mice could increase microglial recruitment to Aβ plaques, modulate microglia response and increase ApoE expression (Colombo et al. 2021). It has been reported that SCFA-induced microglial modulation was associated with increased plaque burden (Colombo et al. 2021; Dodiya et al. 2022). Some SCFAs, such as butyrate, showed neuroprotective properties by reducing inflammatory microglial responses (Wang et al. 2022). The HDAC inhibitory effects of butyrate can shift microglial gene expression to an anti-inflammatory phenotype, reduce TNF-α and IL-1β production, and increase phagocytic capacity (Huang et al. 2024; Xu et al. 2025). These beneficial effects mostly occurred in the early or pre-symptomatical stages of AD, whereas in conditions where Aβ plaques were extensive, SCFA-induced microglial modification could worsen Aβ accumulation (Fernando et al. 2020; Huang et al. 2024).

Influence of genetic factors on microbiota-brain axis in Alzheimer's disease

The composition and function of the gut microbiota are not only influenced by environmental factors such as diet, antibiotic use, and age, but are also significantly influenced by the genetic profile of host (Loh et al. 2024). Genetic predisposition plays an important role in the onset and progression of AD, and the apolipoprotein E (ApoE) genotype is the strongest known genetic risk factor for late-onset AD (Botchway et al. 2022). Among the isoforms of ApoE gene, the ApoE4 allele is associated with increased

Table 2. Conditions involved in the effects of SCFAs in the pathobiology of AD

Content	Protective mechanisms in AD	Pathological mechanisms in AD	References
Microbiota composition	Balanced microbiota prevents AD *via* HDAC inhibition, anti-inflammatory gene expression, BDNF upregulation.	Gut dysbiosis and germ-free conditions progress pathology *via* TLR activation and pro-inflammatory cytokine release	Akhtar et al. 2022; Liu et al. 2025
SCFA type and ratio	High butyrate ratio prevents AD pathology *via* HDAC inhibition and suppressing inflammation.	High acetate ratio promotes AD pathology *via* impairing Aβ clearance and increasing microglia activation	Perry et al. 2016; Luo et al. 2024
BBB integrity	Intact BBB allows for regulated entry of SCFAs into the brain.	Damaged BBB allows harmful influx of SCFAs	Parker et al. 2020
Stage of the disease	SCFA administration is neuroprotective in the early stages of AD through preserving BBB integrity and reducing neuroinflammation.	Administration of SCFAs in late-stage AD with systemic inflammation can worsen disease progression by increasing Aβ plaques, increasing neuroglial clustering, increasing NLRP3 and IL-1β levels and stimulating tau pathology	Luo et al. 2024; Schaible et al. 2025
SCFA concentration	Physiological concentrations induce neuroprotective effects *via* NF-κB inhibition and GPR41/43 mediated mitophagy.	High doses of SCFAs (especially acetate) increase AD pathology *via* upreglation of ApoE, reducing Aβ reuptake and increasing Aβ plaques	Colombo et al. 2021; Luo et al. 2024

SCFA, short chain fatty acids; HDAC, histone deacetylase; BDNF, brain derived neurotrophic factor; TLR, toll like receptor; NLRP3, nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3; NF-κB, nuclear factor kappa B; GPR41/43, G-protein coupled receptor 41/43.

Aβ accumulation, and increased neuroinflammation (Botchway et al. 2022). ApoE4 status was associated with a decrease in the relative abundance of Ruminococcaceae and an increase in Clostridium in microbiota composition (Tran et al. 2019). In particular, a reduction in beneficial SCFA-producing bacteria such as Faecalibacterium and Roseburia has been reported in ApoE4 genotype (Liaquat et al. 2025). These changes can lead to increased intestinal permeability and systemic inflammation, which increase neuroinflammation and amyloid pathology in the brain (Liaquat et al. 2025). Significant differences in gut microbial signatures have been observed between ApoE4 carriers and noncarriers, even in healthy individuals, suggesting a potential early role in disease risk (Bressa et al. 2025). This highlights gene-microbiota-environment interactions that may influence not only susceptibility but also treatment response in AD.

Bridging integrator 1 (BIN1) has been proposed as another important genetic risk factor for late-onset AD. BIN1 is functionally involved in endocytosis, membrane trafficking, and cytoskeletal organization. Overexpression of BIN1 has been reported to cause microstructural changes in hippocampal synapses (Daudin et al. 2018). In primary neuronal cultures, inhibition of BIN1 resulted in accumulation of phosphorylated tau at synapses, altered synaptic architecture, impaired tau secretion, and increased synaptic toxicity induced by phosphorylated tau (Glennon et al. 2020; Thomas et al. 2023). These findings suggest that BIN1 may play a role in the pathobiology of AD. Increased levels of BIN1 in mouse and human intestinal epithelium has been reported to contribute to impaired intestinal barrier function, and decreased BIN1 level is associated with upregulation of tight junction proteins in the intestine (Thomas et al. 2019; Thomas et al. 2023). Therefore, BIN1 expression and activity are implicated in increased intestinal barrier permeability and increased systemic inflammation and neuroinflammation induced by microbial dysbiosis. BIN1 induces intestinal inflammation and this effect was suppressed by BIN1 Knockout or treatment with an antibody against BIN1. In human studies, BIN1 levels were higher in the inflamed colon than in the normal colon (Thomas et al. 2023). Genetic data have logically suggested that BIN1 could be a therapeutic target for passive immunotherapy in AD (Thomas et al. 2023).

Similarly, variants in the CLU gene have been associated with the risk of late stage AD. This gene encodes Clusterin protein, an extracellular chaperone involved in the clearance of protein aggregates. Clusterin in the gastrointestinal tract is involved in regulating the growth and composition of the microbiota and LPS-induced inflammation, which may influence AD pathology and neuroinflammation (Jun et al. 2023; Seo et al. 2025). PICALM (phosphatidyl inositol-binding clathrin-aggregating protein) polymorphisms, known to regulate APP endocytosis through autophagy, have also been associated with inflammatory responses (Ando et al. 2022). Although a direct link to the gut microbiota remains to be investigated, PICALM variants are likely to play a role in the BBB damages and

neuroinflammation following peripheral inflammatory processes (Ando et al. 2022). Genome-wide studies have also shown that host genetic polymorphisms, along with other factors, account for individual variations in gut microbial profiles. For instance, a large-scale metagenome-level correlation study identified several host gene loci associated with alterations in the frequency of intestinal bacteria, including Bifidobacterium, Faecalibacterium, and Bacteroides (Kurilshikov et al. 2021).

Therapeutic approaches toward microbiota-brain axis in Alzheimer's disease

Targeting the composition of the intestinal microbiota and restoring it to balanced state has been proposed as a promising therapeutic approach in AD (Fig. 5). One of the important strategies is the administration of prebiotics which are food components like indigestible nutritional fibers to induce the functional progression of beneficial microbiota. Another suggested strategy is administration of probiotics, which are live microbiota that are beneficial when administered in sufficient quantities. Moreover, fecal microbial transplantation (FMT), which involves transferring of compounds from the healthy fecal matter into the intestinal tract of the diseased patients also has been proposed to regulate gut microbiota in AD patients (Seo et al. 2024).

Probiotics and prebiotics

It has been shown that supplementation of a probiotic mixture consisting of *Streptococcus thermophiles, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii* subspecies *Bulgaricus* in aged rats improved long term potentiation (LTP), alleviated neuroinflammation, and reduced microglial activity (Distrutti et al. 2014). Administration of this probiotic also increased the brain levels of neuroplasticity mediators, including synapsin and brain derived neurotrophic factor (BDNF) (O'Callaghan et al. 2009). Treatment with butyrate, in a transgenic 5XFAD mice model of AD improved synaptic impairments and prevented AD development *via* upregulation of synaptic proteins (PSD-95, SYP, NR2B) and downregulation of pro-inflammatory markers (TNF-α, IL-6, IL-1β) in the hippocampal tissue (Jiang et al. 2021).

Recently, administration of *Faecalibacterium prausnitzii* has been shown to reduce cognitive impairments in AD (Leblhuber et al. 2018; Ueda et al. 2021). Following intracerebroventricular injection of Aβ, administration of *Faecalibacterium prausnitzii* isolated from healthy individuals indicated that this microorganism is a promising target to improve cognitive impairment, mitochondrial dysfunctions and oxidative stress in AD (Ueda et al. 2021). Future

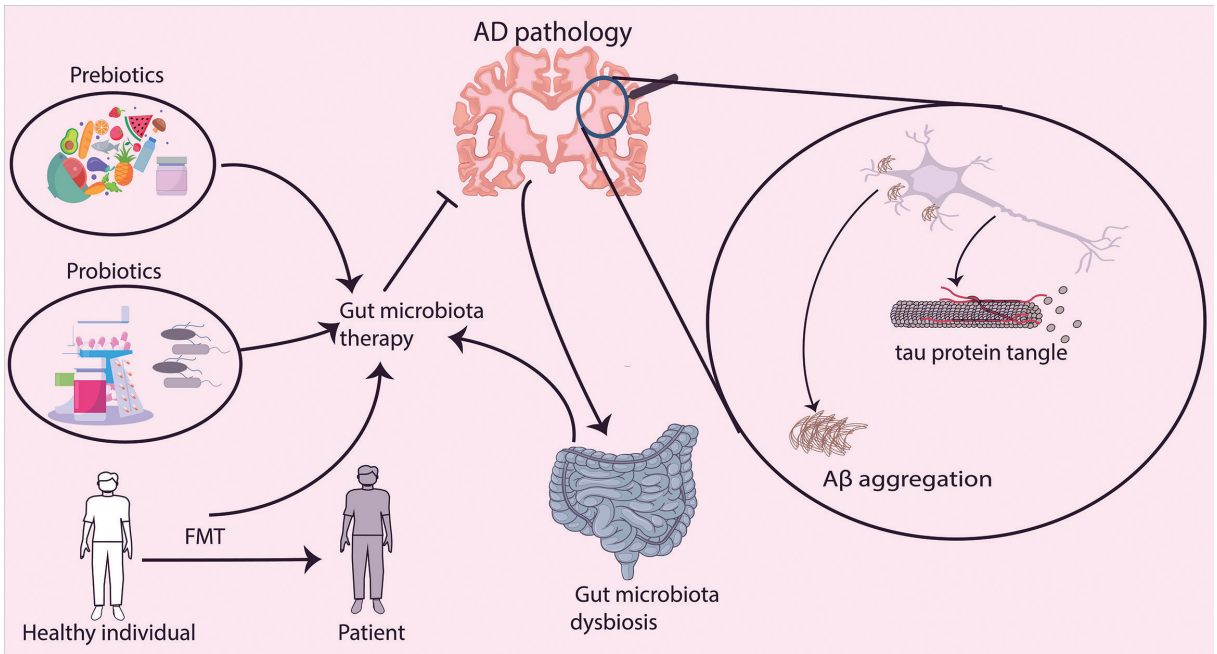


Figure 5. Targeting the composition of the gut microbiota as a promising therapeutic approach for AD. Targeting dysbiosis and restoring the balance of microbiota could be effective in treating AD. Probiotics, probiotics and fecal microbiota transplantation (FMT) are important strategies.

experimental and human studies are required to confirm the beneficial effect of these probiotics on the pathobiology of AD and to elucidate the processes by which they can improve cognitive impairments.

Probiotic administration improves synaptic plasticity through changes in glutamatergic synapses in the hippocampus. Oral administration of the probiotic Enterococcus faecium and the prebiotic inulin for 5 weeks enhanced the NMDAR/AMPAR ratio in hippocampal Schaffer collateral synapses and promoted LTP. This synergistic effects of probiotics and prebiotics enhanced cognitive functions in association with butyrate production, which led to increased BDNF and decreased inflammatory cytokines in the hippocampus (Romo-Araiza et al. 2018). Furthermore, SCFA generation by gut microbiota following probiotic administration enhanced LTP and increased cogitation by histone acetylation, which plays a key role in learning and memory (Silva et al. 2020). Depending on the composition of the microbiota and the pathological pathways activated in the brain, SCFAs may also have detrimental effects on AD progression. Germ-free AD mice showed reduced Aβ plaques in association with lower levels of circulating SCFAs. SCFA administration to these animals increased the deposition of Aβ aggregates and impaired microglial activity by reducing phagocytic functions (Colombo et al. 2021).

Microbial metabolites and prebiotic components have shown beneficial effects against cognitive impairments in the experimental studies, even in advanced stages of AD, where the underlying pathways may contribute to histone acetylation (Sarti et al. 2025; Yehualashet et al. 2025). Six months supplementation of APP/PS1 transgenic mice with oligosaccharides from *Morinda officinalis* improved learning and memory decline. These prebiotics also modulated the synthesis and release of monoaminergic neurotransmitters (Xin et al. 2018). Interestingly, treatment of AD transgenic mice with a combination of probiotics including *Streptococcus thermophilus, Bifidobacteria, and Lactobacillus* increased the fecal content of SCFAs including acetate, propionate and butyrate. Therefore, this probiotic combination may act through SCFAs mediators that improved cognitive functions and restored ubiquitin proteasome and autophagy systems in the brain (Bonfili et al. 2017). Moreover, 3xTg-AD mice supplemented with this probiotic for four months increased Sirtuin-1 dependent antioxidant mechanisms, which induced neuroprotection by reducing reactive oxygen species (ROS) generation and preserving neuronal survival (Bonfili et al. 2018). Long-term treatment with *Agathobaculum butyriciproducens* improved memory impairments in mouse models of AD, which was accompanied by reduced Aβ plaques and microglial activation in the hippocampus and prefrontal cortex. This probiotic downregulated IL-1β and complement component C1QB and increased IGF-1 signaling pathway in the brain (Go et al. 2021).

Probiotics may be promising adjunctive therapeutic strategies against AD. Treatment with the FDA-approved AD drug, memantine, in combination with *Lactobacillus plantarum* in AD transgenic mice improved cognitive function, reduced Aβ aggregation in the hippocampus, and supported neuronal survival and synaptic plasticity. These effects were associated with reduced TMAO generation and neuroinflammatory mechanisms through restoration of the gut microbiota and reduction of Clusterin levels (Wang et al. 2020). It has been reported that combined administration of *Lactobacillus plantarum* and *Bifidobacterium bifidum* with aerobic exercise following intra-cerebroventricular Aβ injection preserved neuronal survival, increased choline acetyltransferase and BDNF in the hippocampus and enhanced learning and memory (Shamsipour et al. 2021).

Several clinical reports have demonstrated beneficial effects of probiotic treatments on cognitive functions in patients with AD. However, these effects depend on the type of probiotic, the stage of the disease, the cognitive assessment methods and the study design. A randomized, double-blind, placebo-controlled trial in 60 AD patients administered a probiotic formula consisting of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum*, and *Bifidobacterium bifidum* for 12 weeks. Patients treated with probiotics showed remarkable improvement in Mini-Mental State Examination (MMSE) cognitive scores compared with the placebo group. Probiotic consumption also reduced serum concentrations of C-reactive protein (CRP), malondialdehyde and triglycerides (Akbari et al. 2016). Moreover, administration of probiotics containing *Lactobacillus rhamnosus* or *Bifidobacterium longum* to AD patients for 12 weeks improved cognitive performance on the MMSE test compared to a group that received placebo. There was no significant difference between the two probiotic interventions in this study (Akhgarjand et al. 2022).

In a study, *Bifidobacterium berve* was administered to 80 elderly people with mild cognitive impairment (MCI) for 16 weeks and it was shown that this probiotic significantly improved the cognitive functions (Xiao et al. 2020). Nishikawa et al. examined the association between dietary prebiotic consumption and the risk of AD occurrence in a seven-year study on 1,837 elderly people aged 65 years and older. They found that fructan intake was remarkably associated with a decreased risk of AD occurrence with each gram of fructan in the diet reducing the risk by 24% (Nishikawa et al. 2021). A randomized, double-blind, controlled trial reported that administration of selenium (200 mg/day) plus probiotics containing *Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium longum* to AD patients showed that the use of probiotics and selenium supplements for 12 weeks increased cognitive performance on the MMSE test. Moreover, CRP levels decreased and glutathione (GSH) levels increased in the serum of these patients.

Conversely, probiotic supplementation with a combination of *Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus fermentum, Lactobacillus lactis, Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus salivarius, Bifidobacterium bifidobacterium, Bifidobacterium bifidobacterium,* and *Bifidobacterium lactis* for 4 weeks in a group of 20 patients had no effect on MMSE scores. However, probiotic treatment increased *Faecalibacterium prausnitzii* and decreased zonuline concentration in fecal specimens compared to baseline. After treatment, serum kynurenine concentrations increased with a concomitant enhancement in the kynurenine/tryptophan ratio, which was associated with an increase in the inflammatory mediator, neopterin in the serum. The report proposed that probiotic intake could induce macrophage and dendritic cell activation. These results should be interpreted with caution, as the sample size was restricted ($n = 20$) and the study was not placebo-controlled (Leblhuber et al. 2018).

Furthermore, in a double-blind trial, treatment of severe AD patients with a probiotic supplement containing *Lactobacillus acidophilus, Lactobacillus fermentum*, *Lactobacillus plantarum*, *Bifidobacterium bifidum, Bifidobacterium longum* and *Bifidobacterium lactis* for 12 weeks had no effect on cognition and serum concentrations of nitric oxide (NO), GSH, total antioxidant capacity (TAC), and cytokines (TNF-α, IL-6, and IL-10) did not change after administration. The authors concluded that cognition and biochemical profile in patients in advanced stages of AD are not sensitive to probiotic treatment, and in addition to the composition and concentration of probiotic supplementation, disease severity and timing of treatment can influence administration outcomes (Agahi et al. 2018). In Table 3 and Table 4 are summarized experimental and clinical studies for prebiotic and probiotic-based therapeutic strategies against AD.

Fecal microbiota transplantation

Several studies have used fecal microbiota transplantation (FMT) to improve AD-related pathobiological pathways. It has been shown that FMT from wild type mice to treatment of APP/PS1 transgenic mice improved cognitive impairment and reduced Aβ aggregation. These improvements were associated with reduced tau phosphorylation and Aβ42 levels. Synaptic plasticity enhanced in FMT-treated transgenic mice, with increased levels of postsynaptic density protein 95 (PSD-95) and synapsin I in synaptic structures. A decrease in cytochrome c oxidase subunit II (COX-2) levels was also observed in AD transgenic mice after FMT. FMT treatment also restored dysregulations in gut microbiota compositions and SCFA levels (Sun et al. 2019). Reciprocally, FMT from aged APPS/PS1 mice (corresponding to the developed pathological stage) to germ-free young APPS/PS1 mice (corresponding to the presymptomatic stage) for seven days accelerated Aβ aggregation, reduced microglial accumulation around Aβ plaques and suppressed Aβ plaque phagocytosis in young mice (Wang et al. 2021). It was consistently observed that FMT from 5xFAD Alzheimer's mice to normal mice resulted in decreased hippocampal neurogenesis and decreased BDNF and increased p21 levels, leading to memory impairment. Microglia were activated in the hippocampus of these animals, which led to increased levels of the inflammatory markers, TNF-α and IL-1β. In addition, gut microbial dysbiosis as well as increased inflammation in the colon and circulation were observed in these animals (Kim et al. 2021).

In another study antibiotic treatment was given to APPPS1 mice before weaning at 2–3 weeks postpartum and FMT was performed one day after the end of antibiotic treatment until 9 weeks of age. Data obtained in APPPS1 mice treated with antibiotics and FMT showed that Aβ amyloidosis and the morphology of plaque-associated microglia and presynaptic (synaptophysin-positive) and postsynaptic (PSD95-positive) neurons were restored, independent of whether the donor was wild-type or transgenic AD mouse fecal material (Dodiya et al. 2022). The reason for the discrepancy between this study and previous studies remained unclear, but is likely related to the developmental stage of the animals at the start of the treatments, different models of AD-like pathology, antibiotic combinations, antibiotic concentrations, and duration of treatments (Dodiya et al. 2022; Bairamian et al. 2022).

Regarding to the clinical studies, FMT is currently FDA-approved for the treatment of severe Clostridioides difficile infection (Obaid 2024). Interestingly, in a case report, it has been presented that an AD patient aged 82 years old underwent FMT treatment for Clostridium difficile, after which his cognitive impairments rapidly improved, with a 6-point improvement in MMSE at four months after FMT and a 9-point improvement in MMSE at six months after FMT (Hazan 2020). In another case report, a 90-year-old woman with AD dementia and severe and recurrent Clostridioides difficile infection underwent two FMT treatments. The MMSE and Montreal Cognitive Assessment (MoCA) tests showed improvement after FMT treatments compared to preoperative tests (15 and 11 before treatment, and 20 and 17 after treatment respectively). FMT changed the composition of the fecal microbiota with *Bacteroidales, Bacteroidia, Tannerellaceae*, and *Actinobacteria* being the most enriched taxa after FMT (Park et al. 2021).

Overall, the available data support the manipulation of microbiota and their metabolites as a promising therapeutic approach against AD, to restore cognitive ability and neural activity, indirectly by modulating immune responses. Future studies are required to assess microbiota changes in primary stages of pathobiology, preparation of the recipient gut environment (antibiotic cleansing and antibiotic combination,

concentration, and duration of administration), optimization of donor microbiota engraftment, and origin of fecal material (from single or multiple donors) and donor genotype before FMT treatment for AD. The lack of sufficient information and standardization can significantly hinder or slow progress in this field.

Table 3. Experimental studies on microbiata-based therapeutic strategies against Alzheimer's disease

Compounds/Approaches	Subject	Tested Parameters	Outcomes	References
Streptococcus thermophiles, Bifidobacterium breve, B. longum, B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus	Aged rats	LTP, microglial activity, synapsin and BDNF levels	Reduced age related LTP deficits, alleviated neuroinflammation and microglial activation, increased neuroplasticity markers	Distrutti et al. 2014
SCFA (butyrate)	5XFAD mice	Memory, Synaptic proteins (PSD-95, SYP, NR2B), pro-inflammatory markers (TNF-α, IL-6, IL-1β), synaptic impairments	Improved memory and synaptic function, prevented AD development by upregulating synaptic proteins and downregulating inflammation	Jiang et al. 2021
Faecalibacterium prausnitzii	Aβ-injected mice	Cognitive function, mitochondrial dysfunction, oxidative stress	Reduced cognitive impairment, improved mitochondrial function and oxidative stress	Ueda et al. 2021
Enterococcus faecium plus Prebiotic (inulin)	Aged rats	NMDAR/AMPAR ratio, LTP, butyrate levels, BDNF, inflammatory cytokines, cognitive functions	Increased synaptic plasticity, enhanced LTP, increased BDNF, decreased inflammation, improved cognition	Romo-Araiza et al. 2018
SCFAs (butyrate, propionate, acetate)	Germ-free AD mice	Aβ plaques, microglial activity	Increased Aβ plaques, increased microglia activation and impaired microglial phagocytosis (detrimental effect)	Colombo et al. 2021
Prebiotic oligosaccharides from *Morinda officinalis*	APP/PS1 transgenic mice	Learning and memory, Aβ1–42 level, histological changes	Improved learning and memory; reduced Aβ1–42, ameliorated neuronal apoptosis	Xin et al. 2018
Agathobaculum butyriciproducens	APP/PS1 transgenic and LPS-induced cognitive impairment mice models	Memory impairments, Aβ plaques, microglial activation, IL-1β, C1QB, IGF-1 signaling	Improved memory, reduced plaques and inflammation, increased IGF-1 signaling	Go et al. 2021
Prebiotics (fibers and plant complexes, containing inulin/fruit-oligosaccharides) and probiotics (*Lactobacillus rhamnosus and Lactobacillus paracasei*)	APP/PS1 transgenic mice	Aβ aggregation, neurohistological changes and microglia activity	Ameliorated Aβ aggregates, reduced neuronal apoptosis and cortical atrophy, increased GFAP level, reduced microglia activity	Sarti et al. 2025
Lactiplantibacillus plantarum	APP/PS1 transgenic mice	Neuroinflammation, neuronal morphology, Aβ plaques, tau phosphorylation, intestinal barrier alteration	Ameliorated neuroinflammation and neuronal damages, decreased Aβ aggregates, reduced tau phosphorylation level, and preserved intestinal barrier	Hu et al. 2024

LTP, long term potentiation; BDNF, brain-derived neurotrophic factor; SCFA, short chain fatty acid; TNF-α, Tumor necrosis factor alpha; IL-6, interleukin 6; PSD95, Postsynaptic density 95; NR2B, N-methyl D-aspartate receptor subtype 2B; C1QB, complement component 1q subunit B; IGF-1, insulin-like growth factor 1; GFAP, glial fibrillary acidic protein.

Table 4. Clinical trials for microbiata-based therapeutic strategies against Alzheimer's disease

Compounds/Approaches	Population	Tested parameters	Outcomes	References
Probiotic milk containing *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum*, and *Lactobacillus fermentum*	60 AD patient (*n* = 30 in probiotic group and *n* = 30 in placebo group)	MMSE cognitive scores, serum CRP, malondialdehyde, triglycerides	Improvement cogitative score, reduced inflammatory and oxidative markers, reduced triglycerides	Akbari et al. 2016
Lactobacillus fermentum, L. plantarum, Bifidobacterium lactis, L. acidophilus, B. bifidum and B.longum	48 AD patient (*n* = 23 in probiotic group and *n* = 25 in placebo group)	Cognitive TYM scores, NO, glutathione, total antioxidant capacity, malondialdehyde, TNF-α, IL-6, and IL-10	No effect on cognition and biochemical markers	Agahi et al. 2018
Mixed probiotics (various *Lactobacillus* and *Bifidobacterium* strains)	18 AD patients in probiotic group (no placebo treatment)	MMSE and CDT cognitive scores, fecal zonulin, serum kynurenine, neopterin	Lack of improvement in cognition, increased beneficial gut bacteria; increased activation of macrophages and dendritic cells	Leblhuber et al. 2018
Lactobacillus rhamnosus or *Bifidobacterium longum*	90 AD patients (30 in L.rhamnosus group, 30 in B. longum group and 30 in placebo group)	MMSE and CFT cognitive scores, ADL and IADL functional scales and GAD-7 anxiety score	Improved cognitive scores, improved IADL scale, reduced anxiety	Akhgarjand et al. 2022
Lactobacillus rhamnosus	169 people over 52 years old (*n* = 86 in probiotic group, *n* = 33 in placebo group)	cognitive performance score, 16S rRNA-based microbiota quantification	Improved cognition, decreased the relative abundance of Prevotella and Dehalobacterium	Aljumaah et al. 2022
Bifidobacterium longum subsp. *Infantis, B breve, B. animalis subsp. Lactis, and Lactobacillus plantarum*	32 AD patients (*n* = 16 in active control group receiving probiotic 5×10^7 CFU/day and *n* = 16 in treatment group receiving probiotic 1×10^{10} CFU/day).	MMSE and ADAS-Cog cognitive scores, ADL score,BDNF, IL-1β, SOD	Lack of improvement in cognition, increased BDNF levels and reduced inflammation and oxidative stress	Hsu et al. 2023
Selenium plus probiotic containing *Lactobacillus acidophilus, Bifidobacterium bifidum, and B. longum*	53 AD patient (*n* = 27 in probiotic group and *n* = 26 in placebo group)	MMSE score, LDL cholesterol, total/HDL cholesterol, glutathione, serum CRP	Improved cognition, reduced LDL and total/HDL cholesterol, reduced CRP, increased glutathione	Tamtaji et al. 2019
Bifidobacterium breve	130 MCI patients (*n* = 65 in probiotic group and *n* = 65 in placebo group)	Cognitive function in ADAS-Cog and MMSE tests and brain atrophy	Improved cognition and prevented brain atrophy	Asaoka et al. 2022
Lacticaseibacillus rhamnosus and *B. longum*	90 AD patients (30 in L.rhamnosus group, 30 in B. longum group and 30 in placebo group)	Inflammatory cytokines, quality of life and physical activity	Reduced inflammation and improved quality of life and physical activity	Akhgarjand et al. 2024

MMSE, mini-mental state examination; CRP, c-reactive protein; TYM, test your memory; TNF-α, tumor necrosis factor alpha; IL-6, interleukin 6; CFT, cognitive function test; ADL, activities of daily living; IADL, instrumental activities of daily living; GAD-7, generalized anxiety disorder; BDNF, brain-derived neurotrophic factor; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale.

Conclusion

The complex and bidirectional connections between the microbiota and the brain along the gut-brain axis present logical propositions for noninvasive and costeffective therapeutic innovation for neurological and psychiatric disorders. This could be widely used not only for AD but also for other CNS disorders. Although gut microbiota dysregulation leads to disruption in the balance between pro-inflammatory and anti-inflammatory pathways and involves several species in different neurodegenerative diseases, that seem to contribute to neurodegeneration through similar pathways. These changes can induce inflammation in the gastrointestinal tract that damages intestinal barrier integrity and subsequently stimulates a peripheral pro-inflammatory responses leading to increased neuroinflammation and impaired CNS functions. In this regard, targeting the intestinal microbiota to regulate immune system indirectly, rather than directly targeting immunomodulatory pathways, seems to be an appealing option because inflammatory pathways are affected by gut microbiota. Nevertheless, immune response-modulating approaches targeting both the microbiota and the immune cells that are more effective than a single-target approach should not be rule-out.

Future research on the gut-brain axis in AD requires integrated experimental platforms to uncover underlying mechanisms and therapeutic targets. Among the most important experimental models are germ-free animals, which allow for the controlled introduction of human-derived microbiota to study their precise effects on cognition, neuroinflammation, and Aβ deposition, as well as transgenic mouse models of AD (including APP/PS1, 3xTg-AD) colonized with the microbiota of Alzheimer's patients to study disease progression in human-relevant microbial environments. In addition, the development and use of advanced experimental models, including gut-brain organoids, will be beneficial to assess efficacy, safety, and mechanistic pathways. In recent years, advances in molecular technologies and bioinformatic analyses have made extensive advantages in determining mechanisms of microbiota effects on neurodegenerative disorders. Omics technology can extent the understanding on microbiota-host interactions for future studies. Metagenomics is beneficial for recognizing microbial taxonomy and functional potential of AD-driven gut microbiota in AD pathology (Tilocca et al. 2020). Metabolomics can provide the promising approaches for profiling microbial metabolites such as SCFAs, bile acids, and tryptophan derivatives involved in neuroinflammation and neurodegeneration. Transcriptomics and single-cell RNA sequencing are important tools for analyzing gene expression changes in gut immune cells and neural cells in response to microbiota compositions and metabolites (Verma et al. 2024).

Recent studies emphasize the crucial role of the gut microbiota in the pathogenesis of AD and position it as a promising target for therapeutic intervention. Modulation of the gut microbiota may offer novel strategies to slow or prevent the progression of AD-related pathological processes such as neuroinflammation, Aβ accumulation, and tau hyperphosphorylation. Among the therapeutic approaches being investigated, FMT and probiotic administration presented more promising options due to their ability to induce profound and long-lasting changes in gut microbial composition and immunomodulation. Other interventions, including prebiotics and targeted antibiotic regimens, also have potential but require precious regulation to avoid unwanted disruptions in beneficial microbial populations. Furthermore, dietary interventions rich in polyphenols and fermentable fibers, which support beneficial microbial species (including *Bifidobacterium*) and increase the production of beneficial SCFAs (including butyrate), offer a noninvasive and sustainable approach with broad translational potential. Finally, establishing a mechanistic framework linking gut microbial changes to AD pathobiology is critical for the development of microbiota-based clinical interventions.

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