Gut microbiota-driven neuroinflammation in Alzheimer's disease: from mechanisms to therapeutic opportunities

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-beta (Aβ) plaques, tau hyperphosphorylation, and chronic neuroinflammation. While neuroinflammation—mediated by microglial and astrocyte activation—has long been considered a secondary response to Aβ pathology, emerging evidence positions it as a primary driver of cognitive decline. Notably, the gut microbiota, through the microbiota-gut-brain axis (MGBA), is crucial in modulating neuroinflammation. Dysbiosis disrupts gut barrier integrity, promotes systemic inflammation, and exacerbates neuroinflammatory responses, thereby accelerating AD progression. Recent advances reveal that gut microbiota-derived metabolites (e.g., short-chain fatty acids, lipopolysaccharides) directly influence microglial activation and Aβ aggregation. These findings have opened new therapeutic possibilities, with microbiota-targeted approaches such as probiotics, prebiotics, and fecal microbiota transplantation demonstrating promising neuroprotective effects in preclinical studies by reducing neuroinflammation and preserving cognitive function. However, translating these findings into clinical applications requires further validation through randomized controlled trials. This review summarizes the current understanding of gut microbiota-driven neuroinflammation in AD, from molecular mechanisms to potential therapeutic strategies. Targeting the

MGBA represents a paradigm shift in AD management, emphasizing the modulation of neuroinflammation and pathological progression through gut microbiota interventions. The discussion also addresses existing research challenges and outlines future directions to advance this promising field.

1 Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder primarily affecting aging individuals and a leading cause of dementia (1). It is characterized by memory loss, cognitive decline, and behavioral changes. Currently, approximately 6.7 million Americans aged 65+ live with AD, with projections reaching 13.8 million by 2060 (1). The global prevalence of AD and related dementias has witnessed a striking 160.8% increase between 1990 and 2019, nearly tripling over this period. Notably, the most substantial rises in age-standardized prevalence rates were observed in East Asia and high-income Asia-Pacific regions, including Brunei, Japan, South Korea, and Singapore (2). The increasing prevalence poses significant financial challenges, as those with severe AD require extensive long-term care (3). In 2015, the global economic burden of dementia was estimated at $818 billion (4).

The "amyloid hypothesis" suggests that misfolded β-amyloid (Aβ) peptides trigger amyloid plaques and tau protein deposits, leading to neurofibrillary tangles (NFTs). However, evidence indicates this alone cannot fully explain AD. Increasing inflammation in AD patients and the association of AD risk genes with immune function highlight neuroinflammation as a critical factor in disease progression (5). Neuroinflammation, an inflammatory response in the central nervous system (CNS) triggered by neuronal damage, initially serves a protective role through glial cells like microglia and astrocytes (6). However, chronic injury leads to sustained glial activation (7), releasing pro-inflammatory cytokines and damaging molecules, thereby perpetuating neuronal damage (8). In AD, Aβ accumulation activates microglia and astrocytes, resulting in the release of reactive oxygen species (ROS), nitric oxide (NO), and cytokines (6), which not only exacerbate neuroinflammation but also promote further Aβ deposition and tau-related NFT formation.

Recent research highlights the gut microbiota's role in AD, with dysbiosis linked to neuroinflammation through pro-inflammatory metabolites. The microbiota-gut-brain axis, a bidirectional communication network, is crucial for maintaining homeostasis between the gut and brain (9). In AD, microbial imbalance promotes harmful bacteria that produce metabolites like lipopolysaccharides (LPS), which disrupt the blood-brain barrier

(BBB) and trigger brain inflammation (10). Reduced production of short-chain fatty acids (SCFAs), such as butyrate, exacerbates chronic neuroinflammation (11). Additionally, gut-derived metabolites activate microglia, amplifying neuroinflammation and accelerating Aβ plaque and tau tangle accumulation (12).

This review investigates the interplay between gut microbiota and neuroinflammation in AD, emphasizing how chronic neuroinflammation accelerates disease progression. It explores the role of gut microbiota and its metabolites in modulating neuroinflammatory processes, highlighting the significance of the gut-brain axis. By analyzing these interactions, the review underscores the potential of targeting the microbiota-gut-brain axis as a therapeutic strategy to mitigate neuroinflammation and slow the progression of AD.

2 Roles of neuroinflammation in AD pathogenesis

In the early stages of AD, the accumulation of Aβ and tau proteins activates microglia and astrocytes, which initially play a protective role by clearing these proteins through phagocytosis, thereby temporarily slowing disease progression (13–15). However, as AD advances, the efficiency of these glial cells in clearing Aβ and tau diminishes, and their response becomes increasingly harmful to the brain. This leads to the accumulation of these proteins and the formation of neural plaques (NPs) and NFTs. The persistent buildup of Aβ and tau chronically activates microglia and astrocytes, triggering the release of pro-inflammatory mediators such as cytokines, complement components, and neurotoxic molecules. This ongoing neuroinflammation results in neuronal dysfunction and cell death, establishing a vicious cycle that accelerates the progression of AD (16) (Figure 1).

2.1 Evidence for neuroinflammation in AD

CNS neuroinflammation in AD is characterized by complex interactions between microglia and astrocytes. Microglia, which make up about 10% of CNS cells, act as resident macrophages and can shift between pro-inflammatory (M1) and anti-inflammatory
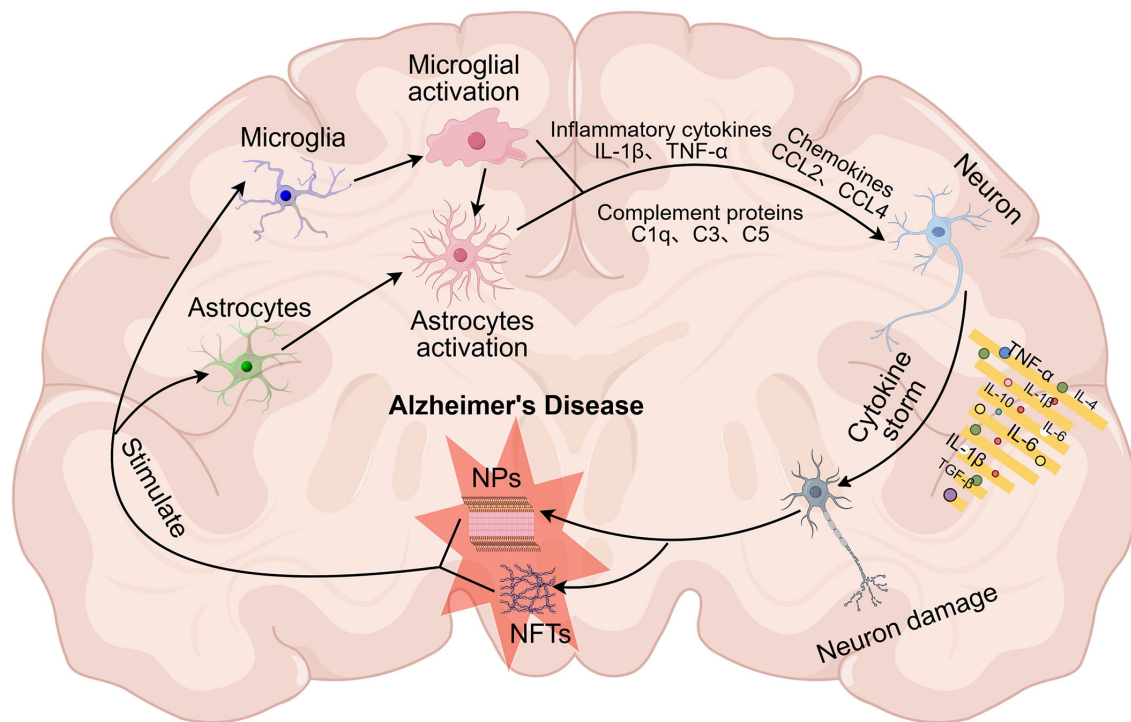
FIGURE 1

Neuroinflammation and its feedback loops in Alzheimer's disease. In the context of brain injury, pathological signals such as amyloid-beta (Aβ) and tau proteins can activate resting microglia and astrocytes. This activation triggers the release of pro-inflammatory cytokines and the activation of the complement system, which contributes to neuronal damage. In turn, the damaged neurons release more Aβ and tau, promoting their aggregation into amyloid plaques (NPs) and neurofibrillary tangles (NFTs). These pathological products serve as signals of neuronal injury, initiating a positive feedback loop that further exacerbates neurodegeneration.

(M2) states (17). M1 microglia, activated by stimuli such as LPS and interferon-γ (IFN-γ), release pro-inflammatory cytokines like IL-1β, TNF-α, and inducible nitric oxide synthase (iNOS), leading to chronic inflammation. In contrast, M2 microglia support inflammation resolution and regulate immune responses, with subtypes (M2a, M2b, M2c) involved in suppressing pro-inflammatory cytokines (18, 19). In AD, neuroinflammation plays a significant role in disease progression. For example, Yan et al. demonstrated that Aβ activates microglia by binding to the receptor for advanced glycation end products (RAGE), leading to the release of cytokines such as TNF-α and IL-6 (20). Additionally, Aβ exposure stimulates RAGE-expressing neurons to produce macrophage colony-stimulating factor (M-CSF), which recruits peripheral microglia to the site of accumulation. These microglia further activate inflammatory signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway and NF-κB, thereby amplifying the inflammatory response (21). Aβ also activates the NLRP3 inflammasome, which leads to caspase-1 activation and the release of IL-1β, exacerbating neuroinflammation (22). Furthermore, tau pathology also contributes to microglial activation through PQBP1-cGAS-STING signaling. The deletion of PQBP1 worsens inflammation and cognitive decline, underscoring the role of tau in neuroinflammation (13). Both Aβ and tau pathologies play

critical roles in activating microglia and triggering inflammatory pathways that accelerate the progression of AD (23–25).

Astrocytes, the most abundant glial cells in the CNS (comprising about 25% of brain volume), also show significant activation in AD, especially around amyloid plaques. Astrocytes are essential for maintaining CNS homeostasis, supporting synaptogenesis, providing nutrients and neurotrophic factors to neurons, and regulating extracellular ion balance and BBB integrity (26, 27). Wyss-Coray et al. demonstrated that astrocytes can clear Aβ deposits in the brain. However, their accumulation around Aβ plaques can trigger their transformation into reactive astrocytes (28). A1 astrocytes, a reactive subtype, have been found in AD brains. These cells lose their homeostatic functions and contribute to the apoptosis of neurons and oligodendrocytes, further aggravating neuroinflammation (29). Additionally, A1 astrocytes can disrupt microcirculation and damage the BBB, facilitating the accumulation of Aβ and promoting disease progression (30, 31). Tau internalization via integrin αV/β1 receptors activates astrocytic NF-κB signaling, which upregulates inflammatory mediators, while signals derived from microglia further promote A1 astrocyte differentiation (32, 33). Thus, the progression of AD involves a dysregulation of microglial M1/M2 polarization and a shift in astrocytes from homeostatic to neurotoxic states. The interactions between microglia and astrocytes create a self-perpetuating

inflammatory cascade, which accelerates neuronal damage and cognitive decline.

2.2 Molecular mechanisms underlying neuroinflammation in AD

In AD, neuroinflammation is driven by the activation of the innate immune system, primarily mediated by Aβ plaques, tau protein pathology, and dysregulation of the complement system. The aggregation of Aβ and tau proteins stimulates the release of proinflammatory cytokines, thereby exacerbating neuronal damage. Complement proteins interact with Aβ deposits, recruiting microglia to facilitate their clearance. However, chronic complement activation can lead to pathological synaptic pruning and neurotoxic inflammation. This inflammatory cascade is further amplified through cytokine-driven feed-forward loops, accelerating neurodegeneration. Consequently, the interplay between Aβ/tau pathologies, complement activation, and cytokine signaling establishes a self-perpetuating cycle that drives AD progression through sustained neuroinflammation and synaptic loss.

2.2.1 Cytokines

Cytokines play a pivotal role in regulating the initiation, progression, and immune crosstalk of neuroinflammation in AD, influencing both localized CNS responses and systemic immune signaling (34). Pro-inflammatory cytokines, such as TNF-α and IL-1β, exacerbate neuroinflammation by activating immune cells, amplifying cytokine cascades, and inducing neuronal damage. In contrast, anti-inflammatory cytokines like IL-10 help to counterbalance this inflammation and promote neuroprotection (35). Disruption of this delicate balance accelerates neurodegeneration through mechanisms such as the bystander effect, where inflammatory mediators indiscriminately harm adjacent neurons. Chemokines, including CXCL1, CCL2, and CX3CL1, direct immune cell chemotaxis toward Aβ plaques, aiding amyloid clearance but perpetuating neurotoxicity under chronic activation (17).

In AD, microglia and astrocytes are the primary sources of cytokines, including TNF-α, IL-1β, IL-6, IL-2, IL-12, and IFN-γ, which drive neuroinflammatory cascades (35). M1-polarized microglia exacerbate inflammation through the secretion of pro-inflammatory cytokines (such as IL-1β, TNF-α, and IL-6) and ROS production, both of which are strongly associated with neuronal degeneration. Conversely, M2-polarized microglia help to attenuate inflammation and promote tissue repair by secreting anti-inflammatory cytokines (IL-10, IL-4, IL-13, TGF-β) while suppressing pro-inflammatory mediators. The phenotypic shift between M1 and M2 microglial states is crucial for maintaining a balance between inflammatory responses and reparative processes in the AD brain. A meta-analysis by Chen et al., which included 2,629 AD patients and 2,049 controls, found that cerebrospinal fluid (CSF) levels of IL-1β, IL-6, IL-8, TNF-α, TGF-β, and MCP-1 were significantly higher in AD patients compared to controls (36).

Chemokines play a pivotal role in AD by regulating microglial migration to sites of neuroinflammation, where they amplify the inflammatory response. In AD patients, chemokines such as CCL2 and their receptors CCR3 and CCR5 are upregulated in reactive microglia, leading to increased immune cell recruitment and further exacerbating neuronal damage. Moreover, CCL4, expressed by astrocytes surrounding Aβ plaques, underscores the involvement of glial cell interactions in the inflammatory process. This chronic inflammatory environment promotes the accumulation of toxic substances like Aβ and tau. In transgenic mice, overexpression of CCL2 resulted in increased microglial accumulation in areas of neuroinflammation, worsening the inflammatory response. This overexpression was also associated with higher Aβ deposition, potentially linked to elevated apolipoprotein E (ApoE) levels, a protein that affects Aβ metabolism and clearance (37, 38). These findings highlight the intricate relationship between chemokines, inflammation, and Aβ accumulation, suggesting that targeting chemokine signaling could serve as a promising therapeutic strategy to slow the progression of AD.

2.2.2 Complement system

The complement system, a cornerstone of innate immunity, contributes critically to AD pathology through immune surveillance and synaptic remodeling (39). Activated via classical, lectin, or alternative pathways, it amplifies inflammation, facilitates pathogen clearance, and mediates synaptic elimination. The classical pathway, initiated by C1q binding to pathogens or apoptotic cells, triggers a protease cascade culminating in C3 deposition. C3 cleavage products (C3b, iC3b) promote phagocytosis via microglial receptors or induce cell lysis via membrane attack complexes (MACs) (40). The complement system also supports brain development, including cortical neuronal migration (41), CNS development (42), and synaptic pruning (43). Microglia primarily produce complement proteins in the brain, with astrocytes also contributing. Dysregulation of the complement system is linked to various neurodegenerative diseases. In the mature brain, early synaptic loss is common in many such conditions, with studies showing that complement proteins are often upregulated before neuronal loss (44). This suggests that reactivation of complement-mediated synaptic elimination may contribute to disease progression.

In AD, the activation of the complement system is closely linked to Aβ deposition. Complement proteins, such as C1q, C3 (including its activated forms C3b, C3c, and C3d), and C4, are produced by glial cells surrounding these plaques and contribute to the disease's progression (40). These proteins are commonly found near Aβ plaques and NFTs in brain regions associated with memory, indicating that complement activation may facilitate the persistence and spread of these pathological features (43, 45). When complement components interact with other inflammatory pathways, they trigger a cascade of events that increase the production of pro-inflammatory cytokines and toxic molecules, further damaging neurons and accelerating cognitive decline (46).

Hence, neuroinflammation is central to AD, driven by microglial and astrocytic activation due to Aβ and tau accumulation. Initially protective, these cells eventually adopt a pro-inflammatory state, exacerbating neuronal damage and cognitive decline. Microglial polarization from M1 to M2 illustrates their dual role in inflammation and repair. Neurotoxic A1 astrocytes further increase inflammation, leading to neuronal death and blood-brain barrier disruption. Pro-inflammatory cytokines and complement proteins are critical mediators of neurodegeneration, perpetuating the inflammatory cycle. Targeting these immune pathways presents therapeutic potential to mitigate disease progression. Future research should elucidate the signaling mechanisms behind glial activation and develop therapies that modulate inflammation while preserving neuroprotection.

3 Gut microbiota-driven neuroinflammation

Recent studies have emphasized the crucial role of gut microbiota in overall health and disease prevention (47–50). The gut hosts a diverse ecosystem of microorganisms—bacteria, fungi, archaea, and viruses—that contribute to digestion, metabolism, and immune function. Beyond these traditional roles, gut microbiota also affects the brain and nervous system, particularly in neuropsychiatric disorders. Alterations in the gut microbiota have been linked to neurodegenerative diseases, such as AD. These microorganisms influence neuroinflammation through various mechanisms, including the production of metabolites, modulation of immune responses, and the maintenance of intestinal barrier integrity.

3.1 Gut microbiota and microbiota–gut–brain axis

3.1.1 Composition and functional dynamics of gut microbiota

The gut harbors a diverse community of microbiota that can influence the risk of neuropsychiatric disorders (51). The microbiota consists of approximately 3.8×10^{13} microorganisms, roughly equal to the number of human cells, and contains over 4 million genes—150 times more than the human genome (52, 53). It hosts around 1,000 bacterial species and 7,000 strains, with Firmicutes and Bacteroidetes being the most predominant (54). Gut microbiota plays a crucial role in health by regulating metabolism, breaking down complex food polysaccharides, modulating intestinal motility, supporting the gut barrier, and influencing fat distribution. Additionally, gut microbiota interacts with the CNS through the microbiota–gut–brain axis, affecting neuronal function and potentially contributing to neurodegenerative diseases such as AD, and Parkinson's disease. Emerging research has shown that gut microbiota composition can be influenced by diet, lifestyle, and even environmental factors, with alterations in microbiota diversity linked to various neurological

and psychiatric conditions. For instance, recent studies found that dysbiosis—an imbalance in microbiota composition—can lead to increased gut permeability, a condition often referred to as "leaky gut". This allows harmful substances to enter the bloodstream, triggering systemic inflammation, which can then impact brain function and contribute to conditions such as autism spectrum disorders and multiple sclerosis (55–57). Moreover, recent studies have highlighted the role of microbial metabolites, particularly short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These are produced by gut bacteria during the fermentation of dietary fiber and have been shown to have significant anti-inflammatory effects. SCFAs not only help maintain gut integrity but also play a critical role in regulating brain function by influencing neuronal activity and modulating immune responses in the CNS (58, 59). Given these insights, current research is increasingly focused on understanding how microbiota diversity and composition affect both gut and brain health. This knowledge holds promise for novel therapeutic approaches aimed at preventing or treating neuropsychiatric disorders through microbiota modulation.

3.1.2 Mechanisms of the microbiota-gut-brain axis

The gut is not only one of the largest immune organs in the body, housing over 70% of immune cells, but it also possesses neural functions similar to those of the brain. A variety of microorganisms within the gut produce metabolic byproducts that significantly influence overall health. Recent research has revealed the complex mechanisms behind the gut's bidirectional communication with the brain, known as the gut-brain axis (GBA) (60, 61). This communication is mediated through neural, endocrine, and immune pathways that are crucial for maintaining physiological homeostasis. The microbiota-gut-brain axis (MGBA) represents the continuous dialogue between the gut and the brain, involving interconnected systems such as the autonomic nervous system, neuroendocrine pathways, the vagus nerve, immune responses, and metabolites produced by gut microbiota (62). The Enteric Nervous System (ENS), often called the "second brain," serves as the primary integrative hub for bidirectional GBA signaling. Comprising a dense network of neurons and glial cells, the ENS is a specialized, semi-autonomous subdivision of the peripheral nervous system (63, 64). Distributed along the gastrointestinal tract, ENS neurons form ganglionated plexuses—most notably the myenteric and submucosal plexuses (63–65), which regulate motility, secretion, and absorption to ensure digestive efficiency and maintain intestinal microbiota homeostasis (66). As a critical interface between gut microbiota and the CNS, the ENS responds to microbial signals through direct interactions with metabolites and indirect pathways involving enteroendocrine signaling, immune mediators, and bidirectional vagal afferents (67). This crosstalk enables constant brain-gut communication, with microbiota playing a central role in its regulation. Notably, microbiota influence neurotransmitter synthesis and neuromodulation, impacting gut-brain signaling and broader brain functions like cognition, emotional regulation, and stress responses (68, 69).

There is growing evidence that the gut microbiota plays a significant role in modulating brain function, primarily through the production of specific metabolites. The microbiota also influences immune responses and the gut microenvironment through Toll-like receptors (TLRs), which detect microbial components and trigger immune reactions that extend beyond the gut to other organs, including the brain. This immune activation can lead to systemic inflammation, a process linked to the development of neurodegenerative diseases, such as AD (70). Animal studies, particularly those conducted in rodents, have provided valuable insights into how specific gut microbes impact both brain function and immune activity (71, 72). For instance, *Bifidobacterium infantis* has been shown to support neuroimmune responses, offering protection to the brain from neuroinflammation (73). Similarly, increased populations of *Lactobacillus casei*, *Anaplasma fragilis*, and *Streptococcus thermophilus* positively affect brain activity and cognition (74–76). Conversely, certain pathogenic bacteria, such as *Fusobacterium rectum*, *Porphyromonas gingivalis*, and *Lactobacillus rhamnosus*, have been implicated in the development of AD, suggesting a detrimental role in brain health (77, 78). These findings revealed the significant influence of the gut microbiota on neurodegenerative diseases and brain function, suggesting that modulating the gut microbiome could offer potential therapeutic strategies for improving brain health and managing related diseases (9, 79, 80).

3.2 AD-associated gut microbiota alterations

The gut microbiota plays a critical role in the pathogenesis of AD. Recent studies have linked gut dysbiosis to various conditions, including AD, obesity, diabetes, and neuropsychiatric disorders (81–83). This imbalance disrupts the normal microbial ecosystem, leading to improper metabolite production and harmful byproducts, which can negatively affect overall health, including the CNS. In AD, gut dysbiosis has been shown to contribute to cognitive decline, suggesting it plays a central role in both the onset and progression of the disease (11, 84).

Studies on the gut microbiota of AD patients have identified significant differences compared to healthy individuals. For example, Vogt et al. discovered changes in bacterial composition, such as a reduction in Firmicutes, an increase in Cyanobacteria, and a decline in beneficial *Bifidobacteria*, indicating a shift toward a more inflammatory microbiota in AD (85). Additionally, studies have shown that AD patients exhibit lower gut microbial diversity, characterized by an increase in pro-inflammatory bacteria and a decrease in beneficial species (84, 86, 87). Ling et al. also observed a decrease in *Faecalibacterium* and an increase in *Lactobacillus* and *Bifidobacterium*, suggesting that these changes may contribute to the neuroinflammation seen in AD (11). Furthermore, differences in microbiota composition are observed between patients with mild cognitive impairment (MCI) and those with advanced AD, indicating a gradual microbiota shift as the disease progresses (87). This progression suggests that gut microbiota alterations may not only be a characteristic of AD but could also provide insight into the disease's early stages and progression.

Dysbiosis is thought to contribute to early AD pathology by promoting immune aging, cytokine imbalances, and neuroinflammation (88). For example, Cattaneo et al. found an increase in pro-inflammatory bacteria, such as *Escherichia/Shigella*, and a decrease in anti-inflammatory species, such as Enterobacteriaceae, which correlated with amyloid plaque accumulation and a heightened inflammatory response (84). The decline in beneficial gut bacteria, such as those producing butyrate, further exacerbates the inflammatory state in AD. Animal studies show that AD mice have lower levels of butyrate-producing bacteria and reduced SCFAs like butyrate, propionate, and acetate (89, 90). These SCFAs are crucial for energy production, immune regulation, and gut homeostasis (91). Impaired SCFA production leads to amyloid plaque accumulation, metabolic dysfunction, and microglial impairment, all of which accelerate cognitive decline (92–94).

Moreover, the decline in butyrate-producing bacteria is often accompanied by an increase in pro-inflammatory bacteria, triggering both local and systemic inflammation, further exacerbating neuroinflammation (95). This microbial shift is also linked to altered T cell function, increased gut permeability, and bacterial translocation (96, 97). These changes facilitate the entry of pro-inflammatory substances, like LPS, into the bloodstream, triggering systemic inflammation and disrupting the BBB, intensifying neuroinflammation (98). Additionally, reduced gut microbiota diversity can alter tryptophan and serotonin levels, impacting the production of critical brain molecules such as dopamine and brain-derived neurotrophic factor (BDNF) (96, 99, 100). Overall, these microbial imbalances play a significant role in the neurodegenerative processes of AD, with gut dysbiosis closely linked to disease progression and neuroinflammation.

3.3 MGBA-mediated neuroinflammation

Recent studies have highlighted the increased risk of AD in patients with inflammatory bowel disease (IBD). A Taiwanese study of 1,742 IBD patients and 17,420 healthy controls found that 5.5% of IBD patients developed dementia, compared to just 1.4% in healthy individuals (101). This significant difference suggests that intestinal inflammation may influence brain inflammation. A key factor in this link is the disruption of the gut-blood barrier. Research has shown that tight junction proteins, such as occludin and zonula occludens-1 (ZO-1), are reduced in AD animal models, leading to increased gut permeability (102–105). This breakdown may allow harmful bacterial metabolites to enter the bloodstream, potentially affecting the CNS and contributing to AD.

The gut microbiota produces various microbial byproducts, including LPS, amyloid, and trimethylamine N-oxide (TMAO). Gram-negative bacteria, such as *Bacteroides fragilis* and *Escherichia coli*, secrete LPS (106, 107), which, when disrupted or released via outer membrane vesicles, can damage the gut-blood barrier (108). This damage impacts intercellular proteins like E-

cadherin, allowing LPS to enter circulation. Once in the bloodstream, LPS can cross the BBB, increasing the risk of pro-inflammatory substances entering the CNS. Elevated LPS levels have been found in the hippocampus, cortex, and plasma of AD patients, compared to healthy individuals (109). LPS is highly immunogenic and induces potent pro-inflammatory effects on neurons (110). In AD, LPS exposure activates TLRs on microglia, triggering an inflammatory response through interactions with proteins like CD14 and MD-2. TLR4 receptors, activated by CD14, are critical in the brain's response to Aβ (111, 112). This inflammatory cascade not only modulates immune responses but also exacerbates neuroinflammation, accelerating the progression of AD.

Recent research has revealed that LPS derived from *Bacteroides fragilis* (BF-LPS) activate neuroinflammatory pathways that are linked to AD. BF-LPS has been shown to significantly activate the NF-κB signaling pathway in human brain cells, which leads to an inflammatory cascade that contributes to neuroinflammation associated with AD (113). The presence of LPS in amyloid plaques suggests an interaction between microbial LPS and Aβ, further intensifying neuroinflammatory responses (114). In AD, LPS from *E. coli* has been detected in critical regions such as the hippocampus and cortex, areas essential for memory and learning. These regions are particularly susceptible to neuroinflammatory damage due to the presence of LPS (115). Animal studies confirm these findings, showing that LPS injections impair hippocampal-dependent cognitive functions, including learning and memory. Repeated LPS administration also leads to increased Aβ accumulation and plaque formation in the hippocampus (116). Additionally, LPS injections into the fourth ventricle of mice induce inflammatory responses and brain changes similar to those seen in AD, such as microglial activation and neuronal dysfunction. LPS also increases the levels of pro-inflammatory cytokines like IL-1β, IL-6, IL-10, and TNF-α, both in the brain and the bloodstream (117). These cytokines contribute to AD by promoting the expression of β-amyloid precursor protein (β-APP) and increasing the activity of β-secretase 1 (BACE1), crucial steps in the production of Aβ (118). Moreover, LPS activates the NLRP3 inflammasome in microglia, enhancing the processing of pro-inflammatory cytokines like IL-1β and IL-18, further amplifying neuroinflammation and Aβ aggregation (119, 120). This inflammatory cascade recruits additional immune cells, accelerating the progression of AD. Recent studies also highlight the potent pro-inflammatory and neurotoxic effects of gut-derived LPS, suggesting that the gut-brain axis plays a crucial role in AD pathology. The neurotoxic effects of gut-derived LPS on cultured human neurons underscore its potential contribution to neurodegenerative processes (121, 122).

In addition to LPS, various gut bacteria, including *Escherichia coli*, *Bacillus subtilis*, *Salmonella* spp., *Mycobacterium tuberculosis*, and *Staphylococcus aureus*, contribute to amyloid protein accumulation by producing misfolded Aβ oligomers and fibers (123, 124). This process may play a key role in AD pathology. Amyloids are insoluble, protein-rich aggregates that form deposits in tissues, and they can promote biofilm formation among bacteria,

enhancing their aggregation and resistance to physical and immune challenges. Bacterial amyloids, especially those found in the gut, can activate the immune system, potentially leading to the formation of amyloid deposits in the brain (124). This may further amplify immune responses, contributing to neuroinflammation. Research into microbial-derived amyloids is still ongoing, but some bacterial proteins, such as Frizzled, may influence Aβ accumulation in the brain through prion-like mechanisms. These mechanisms initiate inflammatory responses both in the brain and peripherally. Additionally, bacterial amyloids in the gut may trigger the immune system, increasing responses against endogenous neuronal amyloids in the brain (124). As pathogen-associated molecular patterns (PAMPs), these bacterial amyloids activate the innate immune system by stimulating pathways such as TLR2, NF-κB, and CD14, ultimately leading to neuroinflammation. This cascade of immune activation can further exacerbate the progression of AD (125).

The gut microbiota-derived metabolite TMAO plays a significant role in the development of AD (126). Elevated levels of TMAO have been observed in CSF of AD dementia patients compared to healthy individuals (127). These increased TMAO levels are correlated with key AD biomarkers, such as phosphorylated tau protein, the tau to amyloid-beta (Aβ42) ratio, and markers of neuronal degeneration, including total tau and neurofilament light chain proteins (127). In addition, TMAO levels also increase with age in both wild-type and APP/PS1 transgenic mice, which are commonly used as AD models (128). TMAO contributes to cognitive decline and the progression of AD by enhancing the activity of BACE, an enzyme that accelerates Aβ accumulation in the brain. Furthermore, TMAO promotes platelet hyperreactivity by releasing calcium ions from intracellular stores, which is linked to AD-related neuroinflammation and vascular changes (129). This suggests that TMAO may not only influence amyloid pathology but also contribute to the vascular and inflammatory components of AD.

Bile acids (BAs), produced by circulating bacteria, have been linked to increased Aβ production in AD. BAs may disrupt the BBB by impairing tight junctions between endothelial cells, which facilitates the entry of both BAs and peripheral cholesterol into the CNS (130). Once inside, elevated cholesterol levels play a pivotal role in AD pathology. Cholesterol binds to amyloid precursor protein (APP) and promotes its integration into lipid rafts, specialized membrane microdomains involved in APP processing. This interaction facilitates the cleavage of APP by β-secretase, leading to increased production of Aβ (131). Additionally, BAs may interfere with the brain's cholesterol clearance mechanisms, further accumulating cholesterol. This accumulation promotes Aβ formation, linking cholesterol dysregulation to AD progression. Thus, BAs contribute not only to Aβ production but also to the processes that foster the formation of toxic Aβ aggregates.

The immune system plays a critical role in shaping the gut microbiota, influencing its structure, composition, and function (132). This regulation is driven by feedback from microbial symbionts that interact with the host's immune system (133, 134), maintaining gut homeostasis and impacting broader

processes such as neuroinflammation and aging. Research in rodent models shows how changes in the gut microbiota can affect immune responses and neuroinflammation (135–138). For example, Boehme et al. found that modifying the gut microbiota in young and middle-aged mice reversed stress-induced immune activation in middle-aged mice, reducing the infiltration of Ly-6Chi monocytes in the brain—a marker of neuroinflammation related to aging. This suggests that the microbiota not only influences local immune responses but also affects systemic processes that impact brain health and aging (139).

The inflammatory response begins when immune cells detect PAMPs and microbe-associated molecular patterns (MAMPs) through pattern recognition receptors (PRRs). Host cells, such as tumor or apoptotic cells, also release damage-associated molecular patterns (DAMPs), which are recognized by PRRs and activate the immune system. This activation triggers the production of pro-inflammatory cytokines and chemokines by immune cells like macrophages and mast cells, often accompanied by complement activation. Dendritic cells and macrophages present antigens to

local immune cells via major histocompatibility complex (MHC) molecules, activating the adaptive immune system, including T cells, to mount a targeted response (12). If inflammation persists, additional immune cells, including effector T-cells, infiltrate tissues, exacerbating the inflammation and contributing to a chronic inflammatory state. Chronic neuroinflammation is linked to neurodegenerative diseases, highlighting the need for immune balance in maintaining brain health.

The evidence above emphasizes the important role of the gut microbiota and its metabolites in influencing inflammatory processes within the CNS, thereby influencing neuroinflammation and the progression of AD. Disruptions to the gut-blood barrier, which permit harmful microbial metabolites like LPS, BAs, TMAO, and amyloids to leak into the brain, play a significant role in neuroinflammation. This inflammation accelerates the accumulation of amyloid plaques and tau tangles, which in turn disrupt neuronal function and advance the progression of AD. A better understanding of the relationship between the gut microbiota, immune responses, and brain health could open up
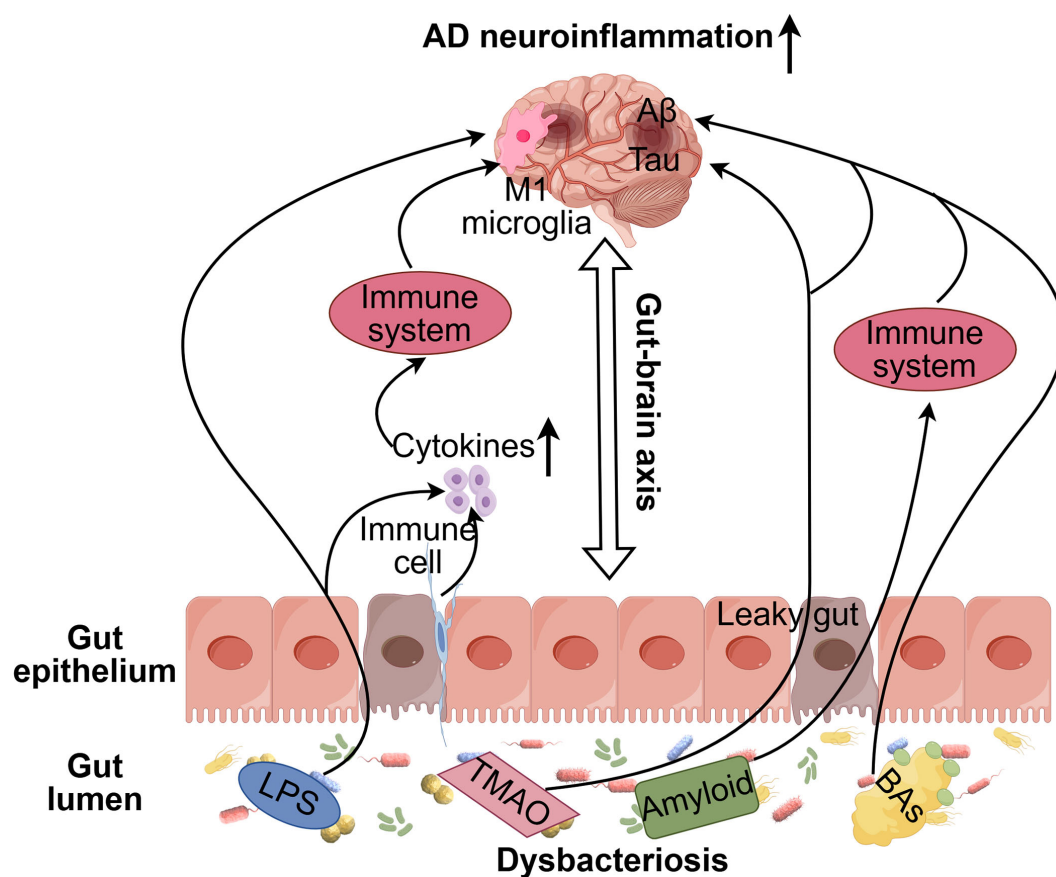

FIGURE 2
Schematic diagram illustrating the regulatory mechanism of gut dysbiosis in AD neuroinflammation. In AD, gut dysbiosis triggers immune responses and the production of harmful metabolites, including lipopolysaccharides (LPS), amyloid, Bile acids (BAs), and trimethylamine N-oxide (TMAO). These metabolites disrupt the integrity of the intestinal mucosal barrier, allowing LPS to enter systemic circulation. This, in turn, promotes systemic inflammation and activates microglia via the microbiota-gut-brain axis (MGBA). Additionally, amyloid accumulation accelerates the formation of neuronal amyloid plaques by enhancing immune system activity. Elevated levels of BAs and TMAO are associated with increased brain Aβ concentrations, while the interaction between TMAO and tau pathology may further intensify neuroinflammation, contributing to AD progression in the brain.

new therapeutic avenues, particularly those targeting the gut microbiome to slow or prevent the onset and progression of AD (Figure 2).

4 Targeting gut microbiota to mitigate neuroinflammation in AD

Emerging evidence has established the gut microbiota as a key modulator of neuroinflammation in AD pathogenesis. The bidirectional communication network of the gut-brain axis serves as a critical interface linking microbial communities to CNS homeostasis. Current therapeutic approaches targeting this axis include probiotics, prebiotics, synbiotics, postbiotics, and fecal microbiota transplantation (FMT). These interventions exert their beneficial effects by restoring microbial homeostasis, reinforcing intestinal barrier integrity, and modulating systemic and neuroimmune responses, thereby potentially ameliorating AD-related pathological processes (Table 1). While challenges remain in clinical translation, optimizing microbial formulations and personalizing treatment strategies may unlock novel, disease-modifying therapies for AD.

4.1 Probiotics

Probiotics, particularly *Lactobacilli* and *Bifidobacteria* strains, are live microorganisms that support gut health and offer several benefits, including immune regulation, stress resistance, pathogen inhibition, and improved intestinal barrier function (103, 140–142). In a BALB/c mouse model, *B. longum* supplementation improved cognitive performance, as demonstrated by better performance in tasks like the NOR and Barnes maze tests (143). Other probiotics, such as *L. spiralis*, *B. breve* A1, and *L. casei* Shirota, have been shown to promote APP metabolism, enhance memory, and lower Aβ levels in rats, helping to reduce neuroinflammation—crucial in preventing AD progression (144–146). *Clostridium butyricum* has also been found to prevent cognitive decline and reduce Aβ accumulation while inhibiting microglial activation and inflammatory cytokines in APP/PS1 mice (147). Additionally, probiotics can modulate the hypothalamic-pituitary-adrenal (HPA) axis and restore neuronal activation under stress, as seen in increased c-Fos and BDNF expression in the hippocampus (148). *Akkermansia muciniphila* alleviates inflammatory responses and enhances immune function through the enzymatic degradation of mucin, yielding SCFAs and oligosaccharides. The release of SCFAs further reduces intestinal permeability, thereby reinforcing intestinal barrier integrity and promoting overall gut health (149).

Combining multiple probiotic strains often confers greater benefits than single-strain interventions. For example, Hang et al. demonstrated that administration of probiotics-2 (P2; *B. lactis* and *L. rhamnosus*) and probiotics-3 (P3; *B. lactis*, *L. acidophilus*, and *L. rhamnosus*) to 6-month-old SAMP8 mice significantly ameliorated AD-like cognitive impairment. This intervention concurrently mitigated neuronal damage, reduced the pathological deposition

of Aβ and tau proteins, and attenuated neuroinflammatory responses within the hippocampus and cerebral cortex (150). VSL#3, a blend of eight Gram-positive strains, promotes beneficial gut microbiota changes in AD models, improving long-term memory, reducing inflammation, and enhancing neuroplasticity (151). Similarly, SLAB51, a mixture of nine bacterial strains, has been shown to reduce brain damage, Aβ accumulation, and amyloid plaque formation in transgenic AD mice (152). Probiotics-4, a combination of *L. casei*, *L. acidophilus*, *B. lactis*, and *B. bifidum*, improved memory, reduced neuronal damage, and protected the gut and blood-brain barrier in aging mice. It also lowered inflammatory markers like IL-6 and TNF-α, as well as plasma and brain LPS levels (153). Likewise, a combination of *L. acidophilus, L. fermentum, B. lactis, and B. longum* improved learning and reduced oxidative stress in rats following Aβ1–42 injection, highlighting the potential of probiotic combinations in AD therapy (154).

Probiotics have gained attention as a potential treatment for AD due to their influence on the MGBA, which may help clear amyloid buildup and reduce neuroinflammation. While animal models have shown promising results, clinical trials in AD patients have yielded inconsistent outcomes. Some studies report improvements in cognitive function, such as higher Mini-Mental State Examination (MMSE) scores after probiotic supplementation (155). For example, a clinical trial with 20 advanced AD patients found that a 4-week regimen of a specific probiotic mixture (including *L. lactis* W19, *L. paracasei* W20, *L. acidophilus* W22, *L. alialius* W24, *L. casei* W56, *L. plantarum* W62, *B. bifidum* W23, *B. lactis* W51, and *B. lactis* W52) led to significant decreases in fecal zonulin levels, a marker of intestinal inflammation. The intervention also increased levels of *Faecalibacterium prausnitzii*, an anti-inflammatory bacterium, and elevated serum levels of inflammatory markers such as neopterin and kynurenine, suggesting an immunomodulatory effect on macrophages and dendritic cells (156). Furthermore, a 12-week, double-blind, placebo-controlled trial involving 90 patients with mild-to-moderate AD demonstrated that administration of two distinct single-strain probiotics (*L. rhamnosus* HA-114 or *B. longum* R0175) significantly improved subjects' average MMSE scores (157). Further studies indicate preventive benefits in healthy elderly individuals. For example, a 12-week supplementation with probiotics containing *B. bifidum* BGN4 and *B. longidum* BORI led to a reduction in pro-inflammatory gut bacteria, along with improvements in mental flexibility, stress performance, and elevated serum levels of BDNF, a protein linked to neuroplasticity (158). However, the exact mechanisms by which probiotics impact AD remain unclear. Some trials show that mixed probiotic therapies do not significantly improve cognitive function or biochemical markers, especially in patients with severe AD. For instance, research on fermented milk products containing *B. animalis* did not lead to notable changes in bacterial composition or gene expression in fecal samples, questioning the consistency of probiotic effects (159). These mixed results suggest that while probiotics can influence gut microbial function, they do not always lead to significant changes in microbiota composition or cognitive outcomes. Further research is needed to identify the most

TABLE 1 Targeting gut microbiota to mitigate neuroinflammation in AD.

Therapy	Experimental subject	Major finding	References
Probiotics	*B. breve A1*	Male 10-week-old ddY mice	• Ameliorates Aβ-induced memory dysfunction • Plasma acetate↑	(144)
	L. casei Shirota	Male R1.40 mice	• Enhanced spatial memory • APP and BACE-1 mRNA↑	(146)
	C. butyricum	APP/PS1 mice	• Ameliorated cognitive deficits • Improve the degenerated neurons • Aβ42↓, IL-1β and TNF-α↑ • Suppressed the Activation of Microglia • Helicobacteraceae and Porphyromonadaceae ↓ • Butyrate↑	(147)
	VSL#3	Aged male Wistar rats	• Actinobacteria↑, Firmicutes↓ • Reverses aging gene effects • Promotes synaptogenesis via BDNF	(151)
	SLAB51 probiotic formulation	3×Tg-AD mice	• Mitigates AD cognitive damage • *Bifidobacterium* spp. ↑, Campylobacterales↓ • Acetic, propionic and butyric acids↑ • IL-1α, IL-1β, IL2, IL-12, IFN-γ, and TNF-α↓ • Ghrelin, leptin, GLP-1 and GIP↑ • $A\beta_{1-42}$↓	(152)
	Probiotics-4 (*B. lactis, L. casei, B. bifidum*, and *L. acidophilus*)	Senescence-accelerated mouse prone 8 (SAMP8) mice.	• Ameliorates neurocognitive deficits • Proteobacteria, *Pseudomonas* and Lachnospiraceae_NK4A136↓ • Reduces intestinal barrier injury • LPS↓, IL-6 and TNF-α↓ • Improves BBB, neuroinflammation via TLR4/NF-κB	(153)
	Probiotics (*L. acidophilus, L. fermentum, B. lactis*, and *B. longum*)	$A\beta_{1-42}$ injected rats	• Improved spatial memory • Improve oxidative stress	(154)
	Multi-strain probiotic supplements	AD Patients	• BDNF↑, IL-1β↓ • Cognitive decline reduction trend • *Bifidobacterium, Lactobacillus, Ruminococcus, Clostridium* and *Akkermansia*↑	(155)
	B. bifidum BGN4 and *B. longum* BORI	Community-dwelling older Adults	• *Eubacterium, Allisonella*, Clostridiales, and Prevotellaceae↓ • BDNF↑	(158)
Prebiotics	FOS from Morinda officinalis	Adult male Sprague–Dawley rats	• Ameliorate learning and memory dysfunction • Improve oxidative stress and inflammation disorder • Regulate the synthesis and secretion of neurotransmitter • Ameliorates cerebral edema, apoptosis • Tau and $A\beta_{1-42}$↓	(164)
	FOS	APP/PS1 mice	• Ameliorates cognitive and pathology • Synapsin I and PSD-95↑ • GLP-1↑, GLP-1R↓ • Helicobacteraceae and Deferribacteraceae↓	(165)
	Mannan oligosaccharide	5×FAD mice	• Alleviates cognitive/neuropsychiatric deficits • Aβ↓ • Modulates redox, neuroinflammation • Prevents gut barrier damage/LPS leak • *Lactobacillus*↑, *Helicobacter*↓ • Butyrate↑	(166)
	Oligosaccharides From Morinda	APP/PS1 mice	• Alleviates cognitive deficits • Ameliorates cerebral edema, apoptosis • $A\beta_{1-42}$ ↓	(167)
	Fructan	Multiethnic population	• Dietary fructan reduces AD risk	(169)

(Continued)

TABLE 1 Continued

Therapy	Experimental subject	Major finding	References
Synbiotics	NMN Synbiotics	APP/PS1 mice	• Aβ↓ • Ameliorates colon histopathology, upregulates barrier proteins • IL-1β, IL-6, and TNF-α↓ • Reduce ROS/oxidative stress	(173)
	Novel synbiotic	Drosophila genetic model of AD	• Increased survivability and motility • Aβ↓ • Acetylcholinesterase activity↑	(174)
	Vitalon Probiotics and inulin	The APP transgenic mouse line J20	• Ameliorated cognitive impairment • Aβ↓ • IL-1β and TNF-α↓	(175)
	Probiotic and selenium	AD patients	• Improve MMSE • Total antioxidant capacity↑	(176)
	Probiotic-fermented milk supplementation	AD patients	• Ameliorated cognitive impairment • Inflammation and oxidative markers↓	(177)
Postbiotics	Sodium butyrate	5×FAD mice	• Attenuates memory deficits • Aβ↓	(189)
	Sodium butyrate	C57BL/6J mice with lead chloride	• Alleviates neurobehavioral impairment • IL-1β, TNFα, and IL-6↓ • BDNF↑	(190)
	Butyrate	Caco-2/PBMC Co-Culture Model	• Improved intestinal barrier function	(197)
FMT	Fresh fecal solution of wild-type mice	APP/PS1 mice	• Attenuate spatial learning impairment • Aβ accumulation and Tau hyperphosphorylation↓ • Attenuate synaptic dysfunction • Attenuate neuroinflammation • Proteobacteria and Verrucomicrobia↓ Bacteroidetes↑ • Butyrate↑	(90)
	Fresh fecal solution of wild-type mice	ADLP[APT] mice	• Attenuate cognitive impairment • Aβ accumulation and Tau hyperphosphorylation↓ • Normalize Ly6G−Ly6CCD115 myeloid overpopulation	(207)
	Fecal matter from healthy B6SJL wildtype donor mice	5xFAD mice	• Attenuate cognitive impairment • Aβ↓	(210)
	FMT from 5×FAD mice	Wild-type mice	• Induce memory dysfunction • Neuroinflammation↑ • Inflammation in the colon↑	(209)
	FMT from healthy spouse	Male AD patient	• Improve memory and cognition	(211)
	FMT from healthy young man	An old woman with AD	• Improve cognitive functions	(212)
Others	Grape seed polyphenol extract	Male Sprague-Dawley rats	• Accumulation of GSPE phenolic acid metabolites in GI • Brain phenolic acid metabolites inhibit neurotoxic Aβ42 aggregation	(216)
	Anthocyanins	Healthy adults	• Inhibit NF-κB reducing chronic inflammatory mediators	(221)

APP, Amyloid precursor protein; Aβ, β-amyloid; BACE-1, Beta-site APP cleaving enzyme 1; BBB, Blood-brain barrier; BDNF, Brain-derived neurotrophic factor; GI, Gastrointestine; GIP, Gastric inhibitory polypeptide; GLP-1, Glucagon-like peptide-1; IFN-γ, Interferon γ; IL-1β, Interleukin-1β; LPS, lipopolysaccharides; MMSE, Mini-Mental State Examination; NF-κB, Nuclear factor kappa B; PS1, Presenilin 1; TLR4, Toll-like receptor 4; TNF-α, Tumor Necrosis Factor-α.

effective probiotic strains and mechanisms for preventing or treating AD.

4.2 Prebiotics

Prebiotics are compounds that promote the growth of beneficial gut bacteria and are found in various foods (160, 161). They are linked to improvements in cognitive function and the management of neurodegenerative diseases like AD. Examples include resistant starch (RS), inulin, oligosaccharides (e.g., fructooligosaccharides [FOS] and alginate), galactose, and oligo-xylulose (162). Studies suggest RS boosts butyrate production, which supports gut health and may reduce inflammation (163). Fructose and alginate have been shown to enhance cognitive function by improving short-term memory and inhibiting the proliferation of astrocytes triggered by Aβ accumulation. FOS, in particular, have shown promise in AD animal models, enhancing gut microbiota diversity, protecting neurons, and reducing Aβ1–42 and tau protein levels, which are linked to AD pathology (164). FOS may also modulate the GLP-1/GLP-1 receptor pathway, offering neuroprotective effects (165). In a study with 5×FAD mice, mannan-oligosaccharides promoted beneficial bacteria like *Lactobacillus*, reduced harmful bacteria like *Helicobacter*, and strengthened the intestinal and blood-brain barriers. This resulted in decreased Aβ accumulation, restored redox balance, and increased butyrate levels in key brain regions (166). Similarly, Malinda oligosaccharides improved memory, reduced plaque formation, and alleviated oxidative stress and inflammation in AD models (164, 167).

While human studies are ongoing, prebiotic supplementation shows potential in the elderly, particularly in regulating cytokine gene expression, which affects inflammation and immune responses (168). A study of 1,837 participants found that each 1g increase in dietary fructose intake was associated with a 24% reduction in AD risk, suggesting that prebiotics like FOS may help reduce the risk of clinical AD in older adults (169).

4.3 Synbiotics

Synbiotics are combinations of probiotics and prebiotics introduced by Gibson and Roberfroid (170). They are classified into two types: complementary synbiotics, which are simple mixtures of probiotics and prebiotics, and synergistic synbiotics, where the prebiotic enhances the growth of specific probiotics (171). The goal is to help probiotics survive the gastrointestinal tract and maximize the benefits of both components (172). Synbiotics often provide more effective health benefits than probiotics or prebiotics alone (173–176). Studies suggest synbiotics can regulate gut microbiota, reduce inflammation, and improve intestinal barrier function, offering neuroprotective effects for AD. For example, a nicotinamide mononucleotide (NMN) synbiotic, containing NMN, *Lactiplantibacillus plantarum* CGMCC 1.16089, and lactulose, reduced Aβ deposition in the cerebral cortex and hippocampus in APP/PS1 mouse models. It

also improved colon health, restored goblet cells, and increased tight junction proteins like Claudin-1 and ZO-1, strengthening the intestinal barrier while reducing proinflammatory cytokines and oxidative stress (173). Another study using transgenic AD Drosophila melanogaster found that a synbiotic formula with *L. plantarum* NCIMB 8826, *L. fermatus* NCIMB 5221, and *B. longum* spp. *infantis* NCIMB 702255combined with polyphenol-rich plant extracts improved survival, mobility, reduced Aβ deposition, and acetylcholinesterase activity (174). Additionally, a complementary synbiotic with inulin and probiotics like *Bacillus natto*, *Bacillus coagulans*, *L. casei*, *L. acidophilus*, *B. longum*, *B. breve* improved memory, neurogenesis, and reduced Aβ42 levels and neuroinflammation in AD mice (175).

While human clinical studies on synbiotics are limited, some promising results have been observed. A study of 79 AD patients showed that supplementing with 200 mg of selenium and specific probiotics for 12 weeks improved cognitive and metabolic functions, as indicated by higher MMSE scores, and reduced inflammation and oxidative stress markers (176). Another study using probiotic-fermented kefir milk in elderly AD patients showed significant improvements in cognitive function, including memory, language skills, and executive function, as well as reduced inflammation, oxidative stress, and blood cell damage (177). Although still in the early stages, these studies suggest that synbiotics could be a promising approach for improving cognitive function and overall health in AD patients. Further clinical research is needed to fully understand their therapeutic potential in neuroprotection and AD management.

4.4 Postbiotics

Postbiotics are a promising approach for treating inflammatory diseases, offering the benefits of probiotics without the risks of live microorganisms. This makes them particularly suitable for individuals with compromised immune systems (178). Key components of postbiotics include SCFAs, produced during fiber fermentation, and neuroactive substances that influence both the gut and the CNS. These substances have the potential to modulate cognitive and behavioral functions in animals and humans (179, 180).

SCFAs, fatty acids with 2 to 6 carbon atoms, are primarily produced by colonic bacteria like *Bacillus* spp., *Bifidobacterium* spp., and *Clostridium* spp (181, 182). SCFAs activate G-protein-coupled receptors (GPCRs), triggering signaling pathways that regulate immune and inflammatory responses, such as the release of cytokines like TNF-α, IL-1, and IL-6. Notably, butyrate has shown significant promise in improving cognitive function in AD mouse models (183). As a histone deacetylase (HDAC) inhibitor, butyrate attenuates histone deacetylation (184), thereby suppressing the expression of genes encoding pattern recognition receptors, kinases, transcriptional regulators, cytokines, and chemokines (185, 186). Concurrently, butyrate enhances chromatin accessibility, enabling the aryl hydrocarbon receptor (AhR)-ligand complex to bind regulatory elements within target gene promoters (187). This

triggers AhR activation, which suppresses pro-inflammatory cytokines (e.g., IFN-γ, IL-6, IL-12, TNF-α, IL-7, and IL-17), inhibits microbial translocation and tissue fibrosis, and enhances mucosal protection by inducing anti-inflammatory cytokines (IL-10, IL-22), stimulating antimicrobial peptides, and promoting intestinal epithelial repair (185, 188).

In AD, both clinical and preclinical studies have shown that SCFAs, particularly butyrate, play significant roles at various stages of the disease (189, 190). In the immune system, SCFAs influence neutrophil and lymphocyte migration, promote the production of Tregs, and modulate T cell activity (96, 191, 192). They also affect neutrophil recruitment and the production of inflammatory mediators like TNF-α (191, 193). SCFAs strengthen BBB by increasing tight junction proteins like occludin, improving barrier integrity (194, 195). Butyrate has been particularly effective in enhancing cognition and immune function (196, 197).

Gut microbiota also play a critical role in producing neurotransmitters and neuromodulators that affect gut-brain communication and brain function (68, 69, 198). Gut bacteria metabolize amino acids like tryptophan and tyrosine to produce neurotransmitter precursors, which influence immune function and T cell differentiation (199, 200). Bacterial strains such as *E. coli*, *Lactobacillus* spp., and *Saccharomyces cerevisiae* produce neurotransmitters like GABA, serotonin (5-HT), and dopamine, which regulate emotional health, stress, mood, and cognition. Imbalances in these neurotransmitters can affect mental health (201). These neurotransmitters can enter the bloodstream and impact brain function by influencing microglial activation (202). Additionally, some gut microbes regulate BDNF, crucial for neuronal growth (203). This highlights the complex gut-brain connection, offering potential therapies for neurological and psychiatric disorders.

4.5 FMT

FMT involves transferring carefully selected donor feces into a patient's gastrointestinal tract to restore microbiota diversity and functionality. It has shown promise in treating inflammatory diseases linked to microbiota imbalance, such as AD (204, 205). Studies suggest FMT can reduce key AD features like Aβ deposition, tau protein formation, memory impairment, and microglial activation, while also lowering neuroinflammation biomarkers. Mechanisms include anti-inflammatory effects, regulation of Aβ accumulation, improved synaptic plasticity, and increased production of SCFAs (90, 206–210). In animal models, such as the APP/PS1 transgenic mouse model, FMT from healthy mice improved cognitive function, reduced Aβ and tau protein levels, and increased synaptic protein expression. Pro-inflammatory microglia and cyclooxygenase-2 (COX-2) were reduced, and SCFA-producing bacteria increased (90). Similarly, daily FMT in the ADPL^{APT} transgenic model for four months improved cognition, reduced Aβ and tau, and decreased activated microglia, astrocytes, and inflammatory markers (207). In familial AD models like 5×FAD mice, FMT decreased amyloid plaques and improved

cognitive performance (210). FMT also suppressed pro-inflammatory cytokines while boosting anti-inflammatory cytokines such as IL-10, IL-22, IL-2, and TGF-β. However, microbiota from AD patients increased gut NLRP3 expression and peripheral inflammatory markers, worsening cognitive decline, indicating that AD-derived microbiota may promote inflammation (209).

Though animal studies are promising, clinical evidence is limited. One case report described an AD patient who improved cognitive function after receiving FMT for recurrent *C. difficile* infection (211). Another case involved a 90-year-old woman with AD and *C. difficile* infection, who showed improved cognition and microbiome diversity after FMT from a healthy donor (212). Despite these positive outcomes, further research is needed to confirm FMT as a viable treatment for AD.

4.6 Others

Phenolic compounds, polyphenols, and tannins (PPT) influence microbial metabolism and offer potential benefits for neural health. These bioactive compounds regulate neuron-glial cell interactions, essential for brain homeostasis. PPT also enhance blood flow, improving nutrient and oxygen delivery while aiding metabolic waste clearance, helping protect neurons from neurotoxins and inflammation, which may offer therapeutic benefits for neurodegenerative diseases (213, 214).

Flavan-3-ols, a key component of dietary flavonoids, support neural health by scavenging free radicals, chelating metals, and modulating enzyme activity. They possess anti-inflammatory properties that reduce oxidative damage (215). After absorption, flavonoids are metabolized by gut microbiota into phenolic acids and metabolites that accumulate in the brain. These metabolites inhibit the self-assembly of Aβ peptides, preventing toxic amyloid aggregation in neurodegenerative diseases like AD (216). Flavonoids also cross the blood-brain barrier, reduce microglial activation, and lower pro-inflammatory cytokines such as TNF-α and IL-1β, promoting a healthier neural environment (217, 218).

Anthocyanins, a subclass of flavonoids, modulate inflammation and provide neuroprotective effects. They regulate pro-inflammatory cytokines and inhibit neuroinflammation pathways (219). Studies in older mice show that blueberry anthocyanins improve cognitive function, enhance memory, and reduce inflammation associated with aging and neurodegeneration (220). Human clinical trials further support these findings, showing reduced plasma inflammatory markers, suggesting potential benefits for mitigating chronic inflammation, a risk factor for cognitive decline (221).

Thus, modulating the microbiota through probiotics, prebiotics, postbiotics, FMT, and other bioactive compounds offers a promising approach for managing AD and neuroinflammation. Both preclinical and clinical studies highlight the complex gut-brain relationship, showing how these interventions may reduce AD-related pathologies like Aβ accumulation and cognitive decline. However, much of the research is based on animal models, and
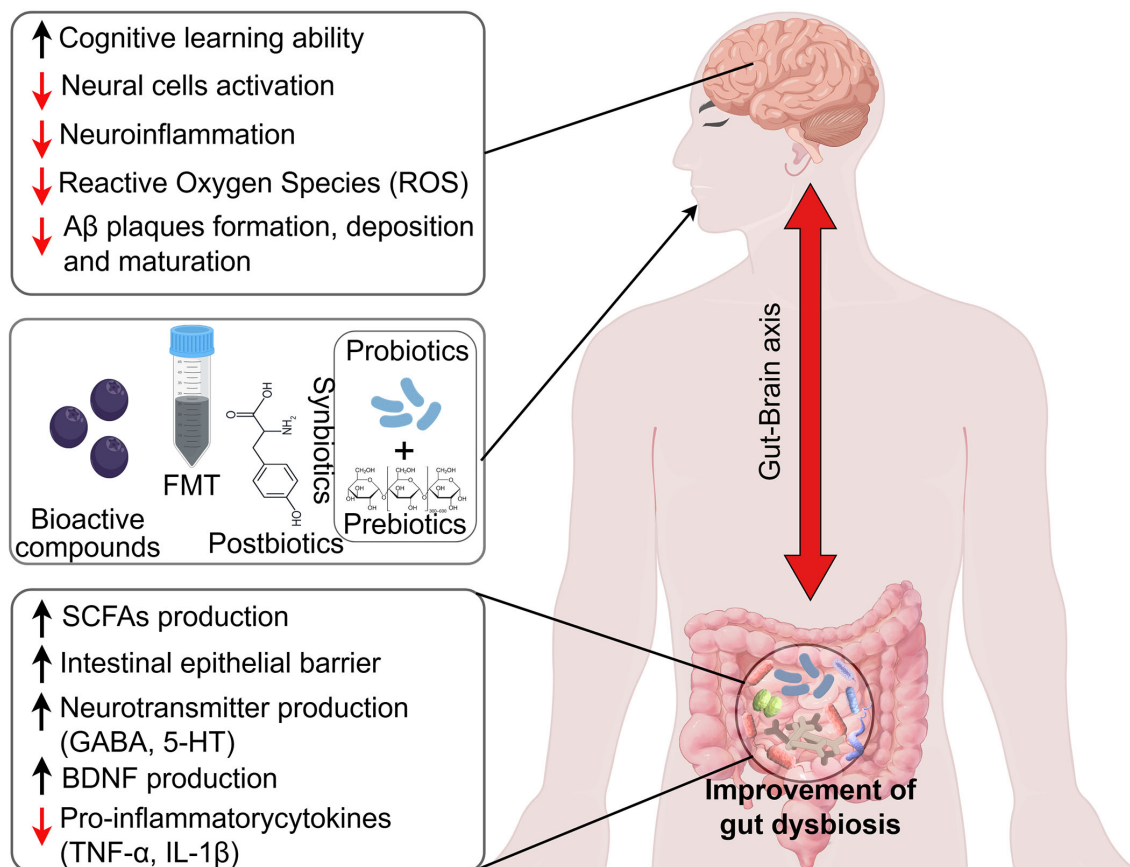
FIGURE 3
Schematic diagram illustrating the therapeutic potential of gut microbiota in AD neuroinflammation. Interventions targeting gut microbiota (such as probiotics, prebiotics, synbiotics, postbiotics, and FMT) have been shown to restore the gut microbiota imbalance commonly found in AD patients. These interventions are linked to increased production of short-chain fatty acids (SCFAs), improved intestinal mucosal barrier function, reduced levels of pro-inflammatory factors, and enhanced intestinal neurotransmitters. By correcting the gut dysbiosis and modulating the gut-brain axis, these treatments have been shown to improve the neuropathological status of AD. This is reflected in enhanced cognitive function, reduced activation of neural cells, and a significant decline in amyloid-beta (Aβ) and tau protein levels, ultimately helping to alleviate AD-related neuroinflammation.

further clinical trials are needed to confirm these findings in humans. Future research should focus on identifying specific microbial strains and metabolites with neuroprotective effects and optimizing delivery methods, with the goal of developing personalized treatments for AD. Understanding the MGBA could lead to innovative strategies for preventing and treating AD, improving quality of life for affected individuals (Figure 3).

5 Conclusion

This review underscores the crucial role of gut microbiota-driven neuroinflammation in AD, shedding light on how this interaction contributes to disease mechanisms such as the accumulation of Aβ and tau proteins and the activation of glial cells. The persistent activation of microglia and astrocytes leads to a chronic inflammatory environment that accelerates neurodegeneration. The emerging link between gut dysbiosis and neuroinflammation offers promising therapeutic opportunities, as dysbiosis has been shown to drive both neuroinflammation and cognitive decline. While preclinical

studies suggest potential for probiotics, prebiotics, postbiotics, and FMT, clinical efficacy remains to be proven. Future research should focus on identifying neuroprotective microbial strains and metabolites, refining delivery methods, and developing personalized treatments. A deeper understanding of the MGBA could revolutionize AD treatment, offering new ways to prevent or delay onset, improve quality of life, and alleviate healthcare burdens. Integrating insights into neuroinflammatory mechanisms and gut microbiota dynamics is key to developing more targeted and effective therapeutic strategies for combating this devastating disease.

Author contributions

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draft, Writing – review & editing. JG: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. ZZ: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. WD: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. XX: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. YL: Data curation, Formal analysis, Methodology, Writing – original draft. ZL: Data curation, Formal analysis, Methodology, Writing – original draft, Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Writing – review & editing. RJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. XC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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References

1. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement.* (2024) 20:3708–821. doi: 10.1002/alz.13809

2. Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. *Front Aging Neurosci.* (2022) 14:937486. doi: 10.3389/fnagi.2022.937486

3. Nizami S, Hall-Roberts H, Warrier S, Cowley SA, Di Daniel E. Microglial inflammation and phagocytosis in Alzheimer's disease: Potential therapeutic targets. *Br J Pharmacol.* (2019) 176:3515–32. doi: 10.1111/bph.14618

4. Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimers Dement.* (2017) 13:1–7. doi: 10.1016/j.jalz.2016.07.150

5. Boyd RJ, Avramopoulos D, Jantzie LL, Mccallion AS. Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases. *J Neuroinflamm.* (2022) 19:223. doi: 10.1186/s12974-022-02584-x

6. Singh D. Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. *J Neuroinflamm.* (2022) 19:206. doi: 10.1186/s12974-022-02565-0

7. Zhang W, Xiao D, Mao Q, Xia H. Role of neuroinflammation in neurodegeneration development. *Signal Transduct Target Ther.* (2023) 8:267. doi: 10.1038/s41392-023-01486-5

8. Kinney JW, Bemiller SM, Murtishaw AS, Leisgang AM, Salazar AM, Lamb BT. Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement (N Y).* (2018) 4:575–90. doi: 10.1016/j.trci.2018.06.014

9. Kowalski K, Mulak A. Brain-gut-microbiota axis in alzheimer's disease. *J Neurogastroenterol Motil.* (2019) 25:48–60. doi: 10.5056/jnm18087

10. Qian X, Hai W, Chen S, Zhang M, Jiang X, Tang H. Multi-omics data reveals aberrant gut microbiota-host glycerophospholipid metabolism in association with neuroinflammation in APP/PS1 mice. *Gut Microbes.* (2023) 15:2282790. doi: 10.1080/19490976.2023.2282790

11. Ling Z, Zhu M, Yan X, Cheng Y, Shao L, Liu 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

12. Bairamian D, Sha S, Rolhion N, Sokol H, Dorothée G, Lemere CA, et al. Microbiota in neuroinflammation and synaptic dysfunction: a focus on Alzheimer's disease. *Mol Neurodegener.* (2022) 17:19. doi: 10.1186/s13024-022-00522-2

13. Jin M, Shiwaku H, Tanaka H, Obita T, Ohuchi S, Yoshioka Y, et al. Tau activates microglia via the PQBP1-cGAS-STING pathway to promote brain inflammation. *Nat Commun.* (2021) 12:6565. doi: 10.1038/s41467-021-26851-2

14. Stancu IC, Cremers N, Vanrusselt H, Couturier J, Vanoosthuyse A, Kessels S, et al. Aggregated Tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology *in vivo*. *Acta Neuropathol.* (2019) 137:599–617. doi: 10.1007/s00401-018-01957-y

15. Wang C, Fan L, Khawaja RR, Liu B, Zhan L, Kodama L, et al. Microglial NF-kappaB drives tau spreading and toxicity in a mouse model of tauopathy. *Nat Commun.* (2022) 13:1969. doi: 10.1038/s41467-022-29552-6

16. Thakur S, Dhapola R, Sarma P, Medhi B, Reddy DH. Neuroinflammation in alzheimer's disease: current progress in molecular signaling and therapeutics. *Inflammation.* (2023) 46:1–17. doi: 10.1007/s10753-022-01721-1

17. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduct Target Ther.* (2023) 8:359. doi: 10.1038/s41392-023-01588-0

18. Nakai K. Multiple roles of macrophage in skin. *J Dermatol Sci.* (2021) 104:2–10. doi: 10.1016/j.jdermsci.2021.08.008

19. Willemsen L, De Winther MP. Macrophage subsets in atherosclerosis as defined by single-cell technologies. *J Pathol.* (2020) 250:705–14. doi: 10.1002/path.5392

20. Yan SD, Chen X, Fu J, Chen M, Zhu H, Roher A, et al. RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature.* (1996) 382:685–91. doi: 10.1038/382685a0

21. Wendt T, Tanji N, Guo J, Hudson BI, Bierhaus A, Ramasamy R, et al. Glucose, glycation, and RAGE: implications for amplification of cellular dysfunction in diabetic nephropathy. *J Am Soc Nephrol*. (2003) 14:1383–95. doi: 10.1097/01.asn.0000065100.17349.ca

22. Van Zeller M, Dias D, Sebastião AM, Valente CA. NLRP3 inflammasome: A starring role in amyloid-β- and tau-driven pathological events in alzheimer's disease. *J Alzheimers Dis*. (2021) 83:939–61. doi: 10.3233/jad-210268

23. Kurmi S, Doshi G, Parab SB. The NLRP3-P2X7 axis and cytokine crosstalk in alzheimer's disease: mechanisms, implications, and therapeutic opportunities. *CNS Neurol Disord Drug Targets*. (2025) 292:1265–81. doi: 10.2174/0118715273377780250505115039

24. Ali M, Garcia P, Lunkes LP, Sciortino A, Thomas MH, Heurtaux T, et al. Temporal transcriptomic changes in the THY-Tau22 mouse model of tauopathy display cell type- and sex-specific differences. *Acta Neuropathol Commun*. (2025) 13:93. doi: 10.1186/s40478-025-02013-z

25. Ding S, Choi SH, Miller YI. Amyloid β-Induced inflammarafts in alzheimer's disease. *Int J Mol Sci*. (2025) 26:4592. doi: 10.3390/ijms26104592

26. Liddelow S, Barres B. SnapShot: astrocytes in health and disease. *Cell*. (2015) 162:1170–1170.e1171. doi: 10.1016/j.cell.2015.08.029

27. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. *Alzheimers Dement*. (2016) 12:719–32. doi: 10.1016/j.jalz.2016.02.010

28. Price BR, Johnson LA, Norris CM. Reactive astrocytes: The nexus of pathological and clinical hallmarks of Alzheimer's disease. *Ageing Res Rev*. (2021) 68:101335. doi: 10.1016/j.arr.2021.101335

29. Lee HG, Wheeler MA, Quintana FJ. Function and therapeutic value of astrocytes in neurological diseases. *Nat Rev Drug Discov*. (2022) 21:339–58. doi: 10.1038/s41573-022-00390-x

30. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci*. (2017) 18:419–34. doi: 10.1038/nrn.2017.48

31. Winkler EA, Nishida Y, Sagare AP, Rege SV, Bell RD, Perlmutter D, et al. GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration. *Nat Neurosci*. (2015) 18:521–30. doi: 10.1038/nn.3966

32. Wang P, Ye Y. Filamentous recombinant human Tau activates primary astrocytes via an integrin receptor complex. *Nat Commun*. (2021) 12:95. doi: 10.1038/s41467-020-20322-w

33. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. (2017) 541:481–7. doi: 10.1038/nature21029

34. Saxton RA, Glassman CR, Garcia KC. Emerging principles of cytokine pharmacology and therapeutics. *Nat Rev Drug Discov*. (2023) 22:21–37. doi: 10.1038/s41573-022-00557-6

35. Liu Y, Tan Y, Zhang Z, Li H, Yi M, Zhang Z, et al. Neuroimmune mechanisms underlying Alzheimer's disease: Insights into central and peripheral immune cell crosstalk. *Ageing Res Rev*. (2023) 84:101831. doi: 10.1016/j.arr.2022.101831

36. Chen X, Hu Y, Cao Z, Liu Q, Cheng Y. Cerebrospinal fluid inflammatory cytokine aberrations in alzheimer's disease, parkinson's disease and amyotrophic lateral sclerosis: A systematic review and meta-analysis. *Front Immunol*. (2018) 9:2122. doi: 10.3389/fimmu.2018.02122

37. Loch RA, Wang H, Perálvarez-Marín A, Berger P, Nielsen H, Chroni A, et al. Cross interactions between Apolipoprotein E and amyloid proteins in neurodegenerative diseases. *Comput Struct Biotechnol J*. (2023) 21:1189–204. doi: 10.1016/j.csbj.2023.01.022

38. Chen Y, Strickland MR, Soranno A, Holtzman DM. Apolipoprotein E: structural insights and links to alzheimer disease pathogenesis. *Neuron*. (2021) 109:205–21. doi: 10.1016/j.neuron.2020.10.008

39. Negro-Demontel L, Maleki AF, Reich DS, Kemper C. The complement system in neurodegenerative and inflammatory diseases of the central nervous system. *Front Neurol*. (2024) 15:1396520. doi: 10.3389/fneur.2024.1396520

40. Shi Q, Chowdhury S, Ma R, Le KX, Hong S, Caldarone BJ, et al. Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Sci Transl Med*. (2017) 9:eaaf6295. doi: 10.1126/scitranslmed.aaf6295

41. Gorelik A, Sapir T, Haffner-Krausz R, Olender T, Woodruff TM, Reiner O. Developmental activities of the complement pathway in migrating neurons. *Nat Commun*. (2017) 8:15096. doi: 10.1038/ncomms15096

42. Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N, et al. The classical complement cascade mediates CNS synapse elimination. *Cell*. (2007) 131:1164–78. doi: 10.1016/j.cell.2007.10.036

43. Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*. (2016) 352:712–6. doi: 10.1126/science.aad8373

44. Heneka MT, Carson MJ, Khoury JE, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in alzheimer's disease. *Lancet Neurol*. (2015) 14:388–405. doi: 10.1016/s1474-4422(15)70016-5

45. Batista AF, Khan KA, Papavergi MT, Lemere CA. The importance of complement-Mediated immune signaling in alzheimer's disease pathogenesis. *Int J Mol Sci*. (2024) 25:817. doi: 10.3390/ijms25020817

46. Bohlson SS, Tenner AJ. Complement in the brain: contributions to neuroprotection, neuronal plasticity, and neuroinflammation. *Annu Rev Immunol*. (2023) 41:431–52. doi: 10.1146/annurev-immunol-101921-035639

47. Wu Y, Wang CZ, Wan JY, Yao H, Yuan CS. Dissecting the interplay mechanism between epigenetics and gut microbiota: health maintenance and disease prevention. *Int J Mol Sci*. (2021) 22:6933. doi: 10.3390/ijms22136933

48. El Boukhari R, Matin M, Bouissane L, Ławiński M, Lushchak O, Singla RK, et al. Enhancing human gut health: Global innovations in dysbiosis management. *Imeta*. (2025) 4:e70028. doi: 10.1002/imt2.70028

49. Beikmohammadi M, Halimi S, Fard NA, Wen W. Therapeutic potential of probiotics: A review of their role in modulating inflammation. *Probiot Antimicrob Proteins*. (2025). doi: 10.1007/s12602-025-10609-z

50. Origüela V, Lopez-Zaplana A. Gut microbiota: an immersion in dysbiosis, associated pathologies, and probiotics. *Microorganisms*. (2025) 13:1084. doi: 10.3390/microorganisms13051084

51. Hashimoto K. Emerging role of the host microbiome in neuropsychiatric disorders: overview and future directions. *Mol Psychiatry*. (2023) 28:3625–37. doi: 10.1038/s41380-023-02287-6

52. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. (2010) 464:59–65. doi: 10.1038/nature08821

53. Humanmicrobiomeprojectconsortium. A framework for human microbiome research. *Nature*. (2012) 486:215–21. doi: 10.1038/nature11209

54. Askarova S, Umbayev B, Masoud AR, Kaiyrlykyzy A, Safarova Y, Tsoy A, et al. The links between the gut microbiome, aging, modern lifestyle and alzheimer's disease. *Front Cell Infect Microbiol*. (2020) 10:104. doi: 10.3389/fcimb.2020.00104

55. Dan Z, Mao X, Liu Q, Guo M, Zhuang Y, Liu Z, et al. Altered gut microbial profile is associated with abnormal metabolism activity of Autism Spectrum Disorder. *Gut Microbes*. (2020) 11:1246–67. doi: 10.1080/19490976.2020.1747329

56. Lou M, Cao A, Jin C, Mi K, Xiong X, Zeng Z, et al. Deviated and early unsustainable stunted development of gut microbiota in children with autism spectrum disorder. *Gut*. (2022) 71:1588–99. doi: 10.1136/gutjnl-2021-325115

57. Thirion F, Sellebjerg F, Fan Y, Lyu L, Hansen TH, Pons N, et al. The gut microbiota in multiple sclerosis varies with disease activity. *Genome Med*. (2023) 15:1. doi: 10.1186/s13073-022-01148-1

58. Guo B, Zhang J, Zhang W, Chen F, Liu B. Gut microbiota-derived short chain fatty acids act as mediators of the gut-brain axis targeting age-related neurodegenerative disorders: a narrative review. *Crit Rev Food Sci Nutr*. (2025) 65:265–86. doi: 10.1080/10408398.2023.2272769

59. Cheng Y, Liu J, Ling Z. Short-chain fatty acids-producing probiotics: A novel source of psychobiotics. *Crit Rev Food Sci Nutr*. (2022) 62:7929–59. doi: 10.1080/10408398.2021.1920884

60. Cryan JF, O'riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. *Physiol Rev*. (2019) 99:1877–2013. doi: 10.1152/physrev.00018.2018

61. Giau VV, Wu SY, Jamerlan A, An SSA, Kim SY, Hulme J. Gut microbiota and their neuroinflammatory implications in alzheimer's disease. *Nutrients*. (2018) 10:1765. doi: 10.3390/nu10111765

62. Luca M, Di Mauro M, Di Mauro M, Luca A. Gut microbiota in alzheimer's disease, depression, and type 2 diabetes mellitus: the role of oxidative stress. *Oxid Med Cell Longev*. (2019) 2019:4730539. doi: 10.1155/2019/4730539

63. Spencer NJ, Hu H. Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. *Nat Rev Gastroenterol Hepatol*. (2020) 17:338–51. doi: 10.1038/s41575-020-0271-2

64. Sharkey KA, Mawe GM. The enteric nervous system. *Physiol Rev*. (2023) 103:1487–564. doi: 10.1152/physrev.00018.2022

65. Benarroch EE. Enteric nervous system: functional organization and neurologic implications. *Neurology*. (2007) 69:1953–7. doi: 10.1212/01.wnl.0000281999.56102.b5

66. Lake JI, Heuckeroth RO. Enteric nervous system development: migration, differentiation, and disease. *Am J Physiol Gastrointest Liver Physiol*. (2013) 305:G1–24. doi: 10.1152/ajpgi.00452.2012

67. Hyland NP, Cryan JF. Microbe-host interactions: Influence of the gut microbiota on the enteric nervous system. *Dev Biol*. (2016) 417:182–7. doi: 10.1016/j.ydbio.2016.06.027

68. Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, et al. Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. *Biol Psychiatry*. (2017) 82:472–87. doi: 10.1016/j.biopsych.2016.12.031

69. Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Res*. (2018) 1693:128–33. doi: 10.1016/j.brainres.2018.03.015

70. Silver J, Schwab ME, Popovich PG. Central nervous system regenerative failure: role of oligodendrocytes, astrocytes, and microglia. *Cold Spring Harb Perspect Biol*. (2014) 6:a020602. doi: 10.1101/cshperspect.a020602

71. Rea K, Dinan TG, Cryan JF. The microbiome: A key regulator of stress and neuroinflammation. *Neurobiol Stress*. (2016) 4:23–33. doi: 10.1016/j.ynstr.2016.03.001

72. Wen L, Duffy A. Factors influencing the gut microbiota, inflammation, and type 2 diabetes. *J Nutr*. (2017) 147:1468s–75s. doi: 10.3945/jn.116.240754

73. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. *Neuroscience*. (2010) 170:1179–88. doi: 10.1016/j.neuroscience.2010.08.005

74. Cerovic M, Forloni G, Balducci C. Neuroinflammation and the gut microbiota: possible alternative therapeutic targets to counteract alzheimer's disease? *Front Aging Neurosci*. (2019) 11:284. doi: 10.3389/fnagi.2019.00284

75. Colpitts SL, Kasper EJ, Keever A, Liljenberg C, Kirby T, Magori K, et al. A bidirectional association between the gut microbiota and CNS disease in a biphasic murine model of multiple sclerosis. *Gut Microbes*. (2017) 8:561–73. doi: 10.1080/19490976.2017.1353843

76. Farzi A, Fröhlich EE, Holzer P. Gut microbiota and the neuroendocrine system. *Neurotherapeutics*. (2018) 15:5–22. doi: 10.1007/s13311-017-0600-5

77. Mehrabadi S, Sadr SS. Assessment of probiotics mixture on memory function, inflammation markers, and oxidative stress in an alzheimer's disease model of rats. *Iran BioMed J*. (2020) 24:220–8. doi: 10.29252/ibj.24.4.220

78. Chang CH, Lin CH, Lane HY. d-glutamate and Gut Microbiota in Alzheimer's Disease. *Int J Mol Sci*. (2020) 21:2676. doi: 10.3390/ijms21082676

79. Liu S, Gao J, Zhu M, Liu K, Zhang HL. Gut microbiota and dysbiosis in alzheimer's disease: implications for pathogenesis and treatment. *Mol Neurobiol*. (2020) 57:5026–43. doi: 10.1007/s12035-020-02073-3

80. De JRD-PV, Forlenza AS, Forlenza OV. Relevance of gutmicrobiota in cognition, behaviour and Alzheimer's disease. *Pharmacol Res*. (2018) 136:29–34. doi: 10.1016/j.phrs.2018.07.007

81. Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's Disease. *Ageing Res Rev*. (2018) 45:53–61. doi: 10.1016/j.arr.2018.04.004

82. Jiang H, Ling Z, Zhang Y, Mao H, Ma Z, Yin 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

83. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci*. (2020) 21:6275. doi: 10.3390/ijms21176275

84. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging*. (2017) 49:60–8. doi: 10.1016/j.neurobiolaging.2016.08.019

85. Vogt NM, Kerby RL, Dill-Mcfarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. *Sci Rep*. (2017) 7:13537. doi: 10.1038/s41598-017-13601-y

86. Pascale A, Marchesi N, Govoni S, Barbieri A. Targeting the microbiota in pharmacology of psychiatric disorders. *Pharmacol Res*. (2020) 157:104856. doi: 10.1016/j.phrs.2020.104856

87. Liu P, Wu L, Peng G, Han Y, Tang R, Ge J, et al. Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. *Brain Behav Immun*. (2019) 80:633–43. doi: 10.1016/j.bbi.2019.05.008

88. Leblhuber F, Steiner K, Geisler S, Fuchs D, Gostner JM. On the possible relevance of bottom-up pathways in the pathogenesis of alzheimer's disease. *Curr Top Med Chem*. (2020) 20:1415–21. doi: 10.2174/1568026620666200514090359

89. Zhang L, Wang Y, Xiayu X, Shi C, Chen W, Song N, et al. Altered gut microbiota in a mouse model of alzheimer's disease. *J Alzheimers Dis*. (2017) 60:1241–57. doi: 10.3233/jad-170020

90. Sun J, Xu J, Ling Y, Wang F, Gong T, Yang C, et al. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. *Transl Psychiatry*. (2019) 9:189. doi: 10.1038/s41398-019-0525-3

91. Parada Venegas D, de la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, et al. Corrigendum: short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. *Front Immunol*. (2019) 10:1486. doi: 10.3389/fimmu.2019.01486

92. Colombo AV, Sadler RK, Llovera G, Singh V, Roth S, Heindl S, et al. Microbiota-derived short chain fatty acids modulate microglia and promote Aβ plaque deposition. *Elife*. (2021) 10:e59826. doi: 10.7554/eLife.59826

93. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*. (2016) 7:189–200. doi: 10.1080/19490976.2015.1134082

94. Wenzel TJ, Gates EJ, Ranger AL, Klegeris A. Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells. *Mol Cell Neurosci*. (2020) 105:103493. doi: 10.1016/j.mcn.2020.103493

95. Haran JP, Bhattarai SK, Foley SE, Dutta P, Ward DV, Bucci V, et al. Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-glycoprotein pathway. *mBio*. (2019) 10:e00632–00619. doi: 10.1128/mBio.00632-19

96. Morris G, Berk M, Carvalho A, Caso JR, Sanz Y, Walder K, et al. The role of microbial metabolites including tryptophan catabolites and short chain fatty acids in the pathophysiology of immune-inflammatory and neuroimmune disease. *Mol Neurobiol*. (2017) 54:4432–51. doi: 10.1007/s12035-016-0004-2

97. Fuke N, Nagata N, Suganuma H, Ota T. Regulation of gut microbiota and metabolic endotoxemia with dietary factors. *Nutrients*. (2019) 11:2277. doi: 10.3390/nu11102277

98. Bonfili L, Cecarini V, Gogoi O, Gong C, Cuccioloni M, Angeletti M, et al. Microbiota modulation as preventative and therapeutic approach in Alzheimer's disease. *FEBS J*. (2021) 288:2836–55. doi: 10.1111/febs.15571

99. Lee HJ, Lee KE, Kim JK, Kim DH. Suppression of gut dysbiosis by Bifidobacterium longum alleviates cognitive decline in 5XFAD transgenic and aged mice. *Sci Rep*. (2019) 9:11814. doi: 10.1038/s41598-019-48342-7

100. Doifode T, Giridharan VV, Generoso JS, Bhatti G, Collodel A, Schulz PE, et al. The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. *Pharmacol Res*. (2021) 164:105314. doi: 10.1016/j.phrs.2020.105314

101. Zhang B, Wang HE, Bai YM, Tsai SJ, Su TP, Chen TJ, et al. Inflammatory bowel disease is associated with higher dementia risk: a nationwide longitudinal study. *Gut*. (2021) 70:85–91. doi: 10.1136/gutjnl-2020-320789

102. Xie Z, Lu H, Yang S, Zeng Y, Li W, Wang L, et al. Salidroside attenuates cognitive dysfunction in senescence-accelerated mouse prone 8 (SAMP8) mice and modulates inflammation of the gut-brain axis. *Front Pharmacol*. (2020) 11:568423. doi: 10.3389/fphar.2020.568423

103. Kaur H, Nagamoto-Combs K, Golovko S, Golovko MY, Klug MG, Combs CK. Probiotics ameliorate intestinal pathophysiology in a mouse model of Alzheimer's disease. *Neurobiol Aging*. (2020) 92:114–34. doi: 10.1016/j.neurobiolaging.2020.04.009

104. Honarpisheh P, Reynolds CR, Blasco Conesa MP, Moruno Manchon JF, Putluri N, Bhattacharjee MB, et al. Dysregulated gut homeostasis observed prior to the accumulation of the brain amyloid-β in tg2576 mice. *Int J Mol Sci*. (2020) 21:1711. doi: 10.3390/ijms21051711

105. Shukla PK, Delotterie DF, Xiao J, Pierre JF, Rao R, Mcdonald MP, et al. Alterations in the gut-microbial-inflammasome-brain axis in a mouse model of alzheimer's disease. *Cells*. (2021) 10:779. doi: 10.3390/cells10040779

106. Alkasir R, Li J, Li X, Jin M, Zhu B. Human gut microbiota: the links with dementia development. *Protein Cell*. (2017) 8:90–102. doi: 10.1007/s13238-016-0338-6

107. Ghaisas S, Maher J, Kanthasamy A. Gut microbiome in health and disease: Linking the microbiome-gut-brain axis and environmental factors in the pathogenesis of systemic and neurodegenerative diseases. *Pharmacol Ther*. (2016) 158:52–62. doi: 10.1016/j.pharmthera.2015.11.012

108. Brown GC, Heneka MT. The endotoxin hypothesis of Alzheimer's disease. *Mol Neurodegener*. (2024) 19:30. doi: 10.1186/s13024-024-00722-y

109. Fox M, Knorr DA, Haptonstall KM. Alzheimer's disease and symbiotic microbiota: an evolutionary medicine perspective. *Ann N Y Acad Sci*. (2019) 1449:3–24. doi: 10.1111/nyas.14129

110. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The central nervous system and the gut microbiome. *Cell*. (2016) 167:915–32. doi: 10.1016/j.cell.2016.10.027

111. Fassbender K, Walter S, Kühl S, Landmann R, Ishii K, Bertsch T, et al. The LPS receptor (CD14) links innate immunity with Alzheimer's disease. *FASEB J*. (2004) 18:203–5. doi: 10.1096/fj.03-0364fje

112. Muendlein HI, Connolly WM, Cameron J, Jetton D, Magri Z, Smirnova I, et al. Neutrophils and macrophages drive TNF-induced lethality via TRIF/CD14-mediated responses. *Sci Immunol*. (2022) 7:eadd0665. doi: 10.1126/sciimmunol.add0665

113. Xia Y, Xiao Y, Wang ZH, Liu X, Alam AM, Haran JP, et al. Bacteroides Fragilis in the gut microbiomes of Alzheimer's disease activates microglia and triggers pathogenesis in neuronal C/EBPβ transgenic mice. *Nat Commun*. (2023) 14:5471. doi: 10.1038/s41467-023-41283-w

114. Kim HS, Kim S, Shin SJ, Park YH, Nam Y, Kim CW, et al. Gram-negative bacteria and their lipopolysaccharides in Alzheimer's disease: pathologic roles and therapeutic implications. *Transl Neurodegener*. (2021) 10:49. doi: 10.1186/s40035-021-00273-y

115. Lin L, Zheng LJ, Zhang LJ. Neuroinflammation, gut microbiome, and alzheimer's disease. *Mol Neurobiol*. (2018) 55:8243–50. doi: 10.1007/s12035-018-0983-2

116. Kahn MS, Kranjac D, Alonzo CA, Haase JH, Cedillos RO, Mclinden KA, et al. Prolonged elevation in hippocampal Aβ and cognitive deficits following repeated endotoxin exposure in the mouse. *Behav Brain Res*. (2012) 229:176–84. doi: 10.1016/j.bbr.2012.01.010

117. O'neill E, Griffin É W, O'sullivan R, Murray C, Ryan L, Yssel J, et al. Acute neuroinflammation, sickness behavior and working memory responses to acute systemic LPS challenge following noradrenergic lesion in mice. *Brain Behav Immun*. (2021) 94:357–68. doi: 10.1016/j.bbi.2020.12.002

118. 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

119. Falcão AS, Carvalho LA, Lidónio G, Vaz AR, Lucas SD, Moreira R, et al. Dipeptidyl vinyl sulfone as a novel chemical tool to inhibit HMGB1/NLRP3-inflammasome and inflamma-miRs in Aβ-mediated microglial inflammation. *ACS Chem Neurosci*. (2017) 8:89–99. doi: 10.1021/acschemneuro.6b00250

120. Wang K, Yao Y, Zhu X, Zhang K, Zhou F, Zhu L. Amyloid β induces NLRP3 inflammasome activation in retinal pigment epithelial cells via NADPH oxidase- and mitochondria-dependent ROS production. *J Biochem Mol Toxicol*. (2017) 31:e21887. doi: 10.1002/jbt.21887

121. Lukiw WJ. Bacteroides fragilis lipopolysaccharide and inflammatory signaling in alzheimer's disease. *Front Microbiol*. (2016) 7:1544. doi: 10.3389/fmicb.2016.01544

122. Li CQ, Zheng Q, Wang Q, Zeng QP. Biotic/Abiotic stress-Driven alzheimer's disease. *Front Cell Neurosci.* (2016) 10:269. doi: 10.3389/fncel.2016.00269

123. Zhou Y, Smith D, Leong BJ, Brännström K, Almqvist F, Chapman MR. Promiscuous cross-seeding between bacterial amyloids promotes interspecies biofilms. *J Biol Chem.* (2012) 287:35092–103. doi: 10.1074/jbc.M112.383737

124. Sampson T. Microbial amyloids in neurodegenerative amyloid diseases. *FEBS J.* (2023) 292:1265–81. doi: 10.1111/febs.17023

125. Pistollato F, Sumalla Cano S, Elio I, Masias Vergara M, Giampieri F, Battino M. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. *Nutr Rev.* (2016) 74:624–34. doi: 10.1093/nutrit/nuw023

126. Praveenraj SS, Sonali S, Anand N, Tousif HA, Vichitra C, Kalyan M, et al. The role of a gut microbial-derived metabolite, trimethylamine N-oxide (TMAO), in neurological disorders. *Mol Neurobiol.* (2022) 59:6684–700. doi: 10.1007/s12035-022-02990-5

127. Vogt NM, Romano KA, Darst BF, Engelman CD, Johnson SC, Carlsson CM, et al. The gut microbiota-derived metabolite trimethylamine N-oxide is elevated in Alzheimer's disease. *Alzheimers Res Ther.* (2018) 10:124. doi: 10.1186/s13195-018-0451-2

128. Zhang L, Yu F, Xia J. Trimethylamine N-oxide: role in cell senescence and age-related diseases. *Eur J Nutr.* (2023) 62:525–41. doi: 10.1007/s00394-022-03011-w

129. Zhu W, Gregory JC, Org E, Buffa JA, Gupta N, Wang Z, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell.* (2016) 165:111–24. doi: 10.1016/j.cell.2016.02.011

130. Wang S, Xu C, Liu H, Wei W, Zhou X, Qian H, et al. Connecting the gut microbiota and neurodegenerative diseases: the role of bile acids. *Mol Neurobiol.* (2023) 60:4618–40. doi: 10.1007/s12035-023-03340-9

131. Mulak A. Bile acids as key modulators of the brain-gut-microbiota axis in alzheimer's disease. *J Alzheimers Dis.* (2021) 84:461–77. doi: 10.3233/jad-210608

132. Shahab M, Shahab N. Coevolution of the human host and gut microbiome: metagenomics of microbiota. *Cureus.* (2022) 14:e26310. doi: 10.7759/cureus.26310

133. Schluter J, Peled JU, Taylor BP, Markey KA, Smith M, Taur Y, et al. The gut microbiota is associated with immune cell dynamics in humans. *Nature.* (2020) 588:303–7. doi: 10.1038/s41586-020-2971-8

134. Yang W, Cong Y. Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. *Cell Mol Immunol.* (2021) 18:866–77. doi: 10.1038/s41423-021-00661-4

135. Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. *Nat Rev Immunol.* (2013) 13:321–35. doi: 10.1038/nri3430

136. Khosravi A, Yáñez A, Price JG, Chow A, Merad M, Goodridge HS, et al. Gut microbiota promote hematopoiesis to control bacterial infection. *Cell Host Microbe.* (2014) 15:374–81. doi: 10.1016/j.chom.2014.02.006

137. Fülling C, Lach G, Bastiaanssen TFS, Fouhy F, O'donovan AN, Ventura-Silva AP, et al. Adolescent dietary manipulations differentially affect gut microbiota composition and amygdala neuroimmune gene expression in male mice in adulthood. *Brain Behav Immun.* (2020) 87:666–78. doi: 10.1016/j.bbi.2020.02.013

138. Yan H, Walker FC, Ali A, Han H, Tan L, Veillon L, et al. The bacterial microbiota regulates normal hematopoiesis via metabolite-induced type 1 interferon signaling. *Blood Adv.* (2022) 6:1754–65. doi: 10.1182/bloodadvances.2021006816

139. Boehme M, Van De Wouw M, Bastiaanssen TFS, Olavarría-Ramírez L, Lyons K, Fouhy F, et al. Mid-life microbiota crises: middle age is associated with pervasive neuroimmune alterations that are reversed by targeting the gut microbiome. *Mol Psychiatry.* (2020) 25:2567–83. doi: 10.1038/s41380-019-0425-1

140. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. *Nat Med.* (2019) 25:716–29. doi: 10.1038/s41591-019-0439-x

141. Liu X, Cao S, Zhang X. Modulation of gut microbiota-brain axis by probiotics, prebiotics, and diet. *J Agric Food Chem.* (2015) 63:7885–95. doi: 10.1021/acs.jafc.5b02404

142. Flynn CM, Omoluabi T, Janes AM, Rodgers EJ, Torraville SE, Negandhi BL, et al. Targeting early tau pathology: probiotic diet enhances cognitive function and reduces inflammation in a preclinical Alzheimer's model. *Alzheimers Res Ther.* (2025) 17:24. doi: 10.1186/s13195-025-01674-1

143. Savignac HM, Kiely B, Dinan TG, Cryan JF. Bifidobacteria exert strain-specific effects on stress-related behavior and physiology in BALB/c mice. *Neurogastroenterol Motil.* (2014) 26:1615–27. doi: 10.1111/nmo.12427

144. Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A, et al. Therapeutic potential of Bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. *Sci Rep.* (2017) 7:13510. doi: 10.1038/s41598-017-13368-2

145. Kobayashi T, Suzuki T, Kaji R, Serata M, Nagata T, Ando M, et al. Probiotic upregulation of peripheral IL-17 responses does not exacerbate neurological symptoms in experimental autoimmune encephalomyelitis mouse models. *Immunopharmacol Immunotoxicol.* (2012) 34:423–33. doi: 10.3109/08923973.2010.617755

146. Ahmad Alwi NA, Lim SM, Mani V, Ramasamy K. Lactobacillus spp.-enhanced memory is strain-dependent and associated, in part, with amyloidogenic and anti-oxidant/oxidative stress interplay in amyloid beta precursor protein transgenic mice. *J Diet Suppl.* (2023) 20:717–34. doi: 10.1080/19390211.2022.2103608

147. Sun J, Xu J, Yang B, Chen K, Kong Y, Fang N, et al. Effect of Clostridium butyricum against Microglia-Mediated Neuroinflammation in Alzheimer's Disease via Regulating Gut Microbiota and Metabolites Butyrate. *Mol Nutr Food Res.* (2020) 64: e1900636. doi: 10.1002/mnfr.201900636

148. Gareau MG, Wine E, Rodrigues DM, Cho JH, Whary MT, Philpott DJ, et al. Bacterial infection causes stress-induced memory dysfunction in mice. *Gut.* (2011) 60:307–17. doi: 10.1136/gut.2009.202515

149. Li B, He Y, Ma J, Huang P, Du J, Cao L, et al. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. *Alzheimers Dement.* (2019) 15:1357–66. doi: 10.1016/j.jalz.2019.07.002

150. Xiao-Hang Q, Si-Yue C, Hui-Dong T. Multi-strain probiotics ameliorate Alzheimer's-like cognitive impairment and pathological changes through the AKT/GSK-3β pathway in senescence-accelerated mouse prone 8 mice. *Brain Behav Immun.* (2024) 119:14–27. doi: 10.1016/j.bbi.2024.03.031

151. Distrutti E, O'reilly JA, Mcdonald C, Cipriani S, Renga B, Lynch MA, et al. Modulation of intestinal microbiota by the probiotic VSL3 resets brain gene expression and ameliorates the age-related deficit in LTP. *PloS One.* (2014) 9:e106503. doi: 10.1371/journal.pone.0106503

152. Bonfili L, Cecarini V, Berardi S, Scarpona S, Suchodolski JS, Nasuti C, et al. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. *Sci Rep.* (2017) 7:2426. doi: 10.1038/s41598-017-02587-2

153. Yang X, Yu D, Xue L, Li H, Du J. Probiotics modulate the microbiota-gut-brain axis and improve memory deficits in aged SAMP8 mice. *Acta Pharm Sin B.* (2020) 10:475–87. doi: 10.1016/j.apsb.2019.07.001

154. Athari Nik Azm S, Djazayeri A, Safa M, Azami K, Ahmadvand B, Sabbaghziarani F, et al. Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in β-amyloid (1-42) injected rats. *Appl Physiol Nutr Metab.* (2018) 43:718–26. doi: 10.1139/apnm-2017-0648

155. Hsu YC, Huang YY, Tsai SY, Kuo YW, Lin JH, Ho HH, et al. Efficacy of probiotic supplements on brain-derived neurotrophic factor, inflammatory biomarkers, oxidative stress and cognitive function in patients with alzheimer's dementia: A 12-week randomized, double-blind active-controlled study. *Nutrients.* (2023) 16:16. doi: 10.3390/nu16010016

156. Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L. Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies. *Signal Transduct Target Ther.* (2024) 9:211. doi: 10.1038/s41392-024-01911-3

157. Akhgarjand C, Tavakoli A, Samavat S, Bagheri A, Anoushirvani A, Mirzababaei A, et al. The effect of conjugated linoleic acid supplementation in comparison with omega-6 and omega-9 on lipid profile: a graded, dose-response systematic review and meta-analysis of randomized controlled trials. *Front Nutr.* (2024) 11:1336889. doi: 10.3389/fnut.2024.1336889

158. Kim CS, Cha L, Sim M, Jung S, Chun WY, Baik HW, et al. Probiotic supplementation improves cognitive function and mood with changes in gut microbiota in community-dwelling older adults: A randomized, double-blind, placebo-controlled, multicenter trial. *J Gerontol A Biol Sci Med Sci.* (2021) 76:32–40. doi: 10.1093/gerona/glaa090

159. Mcnulty NP, Yatsunenko T, Hsiao A, Faith JJ, Muegge BD, Goodman AL, et al. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. *Sci Transl Med.* (2011) 3:106ra106. doi: 10.1126/scitranslmed.3002701

160. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, 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) 14:491–502. doi: 10.1038/nrgastro.2017.75

161. Hutkins R, Walter J, Gibson GR, Bedu-Ferrari C, Scott K, Tancredi DJ, et al. Classifying compounds as prebiotics - scientific perspectives and recommendations. *Nat Rev Gastroenterol Hepatol.* (2025) 22:54–70. doi: 10.1038/s41575-024-00981-6

162. Al-Habsi N, Al-Khalili M, Haque SA, Elias M, Olqi NA, Al Uraimi T. Health benefits of prebiotics, probiotics, synbiotics, and postbiotics. *Nutrients.* (2024) 16:3955. doi: 10.3390/nu16223955

163. Dobranowski PA, Stintzi A. Resistant starch, microbiome, and precision modulation. *Gut Microbes.* (2021) 13:1926842. doi: 10.1080/19490976.2021.1926842

164. Chen D, Yang X, Yang J, Lai G, Yong T, Tang X, et al. Prebiotic effect of fructooligosaccharides from morinda officinalis on alzheimer's disease in rodent models by targeting the microbiota-gut-brain axis. *Front Aging Neurosci.* (2017) 9:403. doi: 10.3389/fnagi.2017.00403

165. Sun J, Liu S, Ling Z, Wang F, Ling Y, Gong T, et al. Fructooligosaccharides ameliorating cognitive deficits and neurodegeneration in APP/PS1 transgenic mice through modulating gut microbiota. *J Agric Food Chem.* (2019) 67:3006–17. doi: 10.1021/acs.jafc.8b07313

166. Liu Q, Xi Y, Wang Q, Liu J, Li P, Meng X, et al. Mannan oligosaccharide attenuates cognitive and behavioral disorders in the 5xFAD Alzheimer's disease mouse model via regulating the gut microbiota-brain axis. *Brain Behav Immun.* (2021) 95:330–43. doi: 10.1016/j.bbi.2021.04.005

167. Xin Y, Diling C, Jian Y, Ting L, Guoyan H, Hualun L, et al. Effects of oligosaccharides from morinda officinalis on gut microbiota and metabolome of APP/PS1 transgenic mice. *Front Neurol.* (2018) 9:412. doi: 10.3389/fneur.2018.00412

168. Pujari R, Banerjee G. Impact of prebiotics on immune response: from the bench to the clinic. *Immunol Cell Biol.* (2021) 99:255–73. doi: 10.1111/imcb.12409

169. Nishikawa M, Brickman AM, Manly JJ, Schupf N, Mayeux RP, Gu Y. Association of dietary prebiotic consumption with reduced risk of alzheimer's disease in a multiethnic population. *Curr Alzheimer Res.* (2021) 18:984–92. doi: 10.2174/1567205019666211222115142

170. Gibson GR, Roberfroid MB. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J Nutr.* (1995) 125:1401–12. doi: 10.1093/jn/125.6.1401

171. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, Verbeke K, et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastroenterol Hepatol.* (2020) 17:687–701. doi: 10.1038/s41575-020-0344-2

172. Haghighat N, Mohammadshahi M, Shayanpour S, Haghighizadeh MH, Rahmdel S, Rajaei M. The effect of synbiotic and probiotic supplementation on mental health parameters in patients undergoing hemodialysis: A double-blind, randomized, placebo-controlled trial. *Indian J Nephrol.* (2021) 31:149–56. doi: 10.4103/ijn.IJN_341_19

173. Li C, Zhao X, Xu H, Liu X, He Y, Gu J. NMN synbiotics: A multifaceted therapeutic approach for alzheimer's disease. *Neurochem Res.* (2024) 49:2888–96. doi: 10.1007/s11064-024-04210-z

174. 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:e0214985. doi: 10.1371/journal.pone.0214985

175. 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) 74:748–53. doi: 10.1002/iub.2589

176. Tamtaji OR, Heidari-Soureshjani R, Mirhosseini N, Kouchaki E, Bahmani F, Aghadavod E, et al. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: A randomized, double-blind, controlled trial. *Clin Nutr.* (2019) 38:2569–75. doi: 10.1016/j.clnu.2018.11.034

177. Ton AMM, Campagnaro BP, Alves GA, Aires R, Côco LZ, Arpini CM, et al. Oxidative stress and dementia in alzheimer's patients: effects of synbiotic supplementation. *Oxid Med Cell Longev.* (2020) 2020:2638703. doi: 10.1155/2020/2638703

178. Kiousi DE, Karapetsas A, Karolidou K, Panayiotidis MI, Pappa A, Galanis A. Probiotics in extraintestinal diseases: current trends and new directions. *Nutrients.* (2019) 11:788. doi: 10.3390/nu11040788

179. Mccarville JL, Chen GY, Cuevas VD, Troha K, Ayres JS. Microbiota metabolites in health and disease. *Annu Rev Immunol.* (2020) 38:147–70. doi: 10.1146/annurev-immunol-071219-125715

180. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol.* (2020) 17:223–37. doi: 10.1038/s41575-019-0258-z

181. Hays KE, Pfaffinger JM, Ryznar R. The interplay between gut microbiota, short-chain fatty acids, and implications for host health and disease. *Gut Microbes.* (2024) 16:2393270. doi: 10.1080/19490976.2024.2393270

182. Yao Y, Cai X, Fei W, Ye Y, Zhao M, Zheng C. The role of short-chain fatty acids in immunity, inflammation and metabolism. *Crit Rev Food Sci Nutr.* (2022) 62:1–12. doi: 10.1080/10408398.2020.1854675

183. Yao C, Sakata D, Esaki Y, Li Y, Matsuoka T, Kuroiwa K, et al. Prostaglandin E2-EP4 signaling promotes immune inflammation through Th1 cell differentiation and Th17 cell expansion. *Nat Med.* (2009) 15:633–40. doi: 10.1038/nm.1968

184. Davie JR. Inhibition of histone deacetylase activity by butyrate. *J Nutr.* (2003) 133:2485s–93s. doi: 10.1093/jn/133.7.2485S

185. Dicks LMT. How important are fatty acids in human health and can they be used in treating diseases? *Gut Microbes.* (2024) 16:2420765. doi: 10.1080/19490976.2024.2420765

186. Galland L. The gut microbiome and the brain. *J Med Food.* (2014) 17:1261–72. doi: 10.1089/jmf.2014.7000

187. Modoux M, Rolhion N, Lefevre JH, Oeuvray C, Nádvorník P, Illes P, et al. Butyrate acts through HDAC inhibition to enhance aryl hydrocarbon receptor activation by gut microbiota-derived ligands. *Gut Microbes.* (2022) 14:2105637. doi: 10.1080/19490976.2022.2105637

188. Korecka A, Dona A, Lahiri S, Tett AJ, Al-Asmakh M, Braniste V, et al. Bidirectional communication between the Aryl hydrocarbon Receptor (AhR) and the microbiome tunes host metabolism. *NPJ Biofilms Microbiom.* (2016) 2:16014. doi: 10.1038/npjbiofilms.2016.14

189. Fernando W, Martins IJ, Morici M, Bharadwaj P, Rainey-Smith SR, Lim WLF, et al. Sodium butyrate reduces brain amyloid-β Levels and improves cognitive memory performance in an alzheimer's disease transgenic mouse model at an early disease stage. *J Alzheimers Dis.* (2020) 74:91–9. doi: 10.3233/jad-190120

190. Li Y, Liu A, Chen K, Li L, Zhang X, Zou F, et al. Sodium butyrate alleviates lead-induced neuroinflammation and improves cognitive and memory impairment through the ACSS2/H3K9ac/BDNF pathway. *Environ Int.* (2024) 184:108479. doi: 10.1016/j.envint.2024.108479

191. Corrêa-Oliveira R, Fachi JL, Vieira A, Sato FT, Vinolo MA. Regulation of immune cell function by short-chain fatty acids. *Clin Transl Immunol.* (2016) 5:e73. doi: 10.1038/cti.2016.17

192. Gill PA, Van Zelm MC, Muir JG, Gibson PR. Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. *Aliment Pharmacol Ther.* (2018) 48:15–34. doi: 10.1111/apt.14689

193. Rodrigues HG, Takeo Sato F, Curi R, Vinolo M. Fatty acids as modulators of neutrophil recruitment, function and survival. *Eur J Pharmacol.* (2016) 785:50–8. doi: 10.1016/j.ejphar.2015.03.098

194. Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med.* (2014) 6:263ra158. doi: 10.1126/scitranslmed.3009759

195. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. *Cell Host Microbe.* (2015) 17:565–76. doi: 10.1016/j.chom.2015.04.011

196. Ferreira TM, Leonel AJ, Melo MA, Santos RR, Cara DC, Cardoso VN, et al. Oral supplementation of butyrate reduces mucositis and intestinal permeability associated with 5-Fluorouracil administration. *Lipids.* (2012) 47:669–78. doi: 10.1007/s11745-012-3680-3

197. Korsten S, Vromans H, Garssen J, Willemsen LEM. Butyrate protects barrier integrity and suppresses immune activation in a caco-2/PBMC co-Culture model while HDAC inhibition mimics butyrate in restoring cytokine-Induced barrier disruption. *Nutrients.* (2023) 15:2760. doi: 10.3390/nu15122760

198. Andersen JV, Skotte NH, Christensen SK, Polli FS, Shabani M, Markussen KH, et al. Hippocampal disruptions of synaptic and astrocyte metabolism are primary events of early amyloid pathology in the 5xFAD mouse model of Alzheimer's disease. *Cell Death Dis.* (2021) 12:954. doi: 10.1038/s41419-021-04237-y

199. Parolisi S, Montanari C, Borghi E, Cazzorla C, Zuvadelli J, Tosi M, et al. Possible role of tryptophan metabolism along the microbiota-gut-brain axis on cognitive & behavioral aspects in Phenylketonuria. *Pharmacol Res.* (2023) 197:106952. doi: 10.1016/j.phrs.2023.106952

200. Stone TW, Williams RO. Modulation of T cells by tryptophan metabolites in the kynurenine pathway. *Trends Pharmacol Sci.* (2023) 44:442–56. doi: 10.1016/j.tips.2023.04.006

201. Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters-key factors in neurological and neurodegenerative disorders of the central nervous system. *Int J Mol Sci.* (2022) 23:5954. doi: 10.3390/ijms23115954

202. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol.* (2021) 17:157–72. doi: 10.1038/s41582-020-00435-y

203. Molska M, Mruczyk K, Cisek-Woźniak A, Prokopowicz W, Szydełko P, Jakuszewska Z, et al. The influence of intestinal microbiota on BDNF levels. *Nutrients.* (2024) 16:2891. doi: 10.3390/nu16172891

204. Allegretti JR, Kassam Z, Osman M, Budree S, Fischer M, Kelly CR. The 5D framework: a clinical primer for fecal microbiota transplantation to treat Clostridium difficile infection. *Gastrointest Endosc.* (2018) 87:18–29. doi: 10.1016/j.gie.2017.05.036

205. Allegretti JR, Mullish BH, Kelly C, Fischer M. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *Lancet.* (2019) 394:420–31. doi: 10.1016/s0140-6736(19)31266-8

206. Shen H, Guan Q, Zhang X, Yuan C, Tan Z, Zhai L, et al. New mechanism of neuroinflammation in Alzheimer's disease: The activation of NLRP3 inflammasome mediated by gut microbiota. *Prog Neuropsychopharmacol Biol Psychiatry.* (2020) 100:109884. doi: 10.1016/j.pnpbp.2020.109884

207. Kim MS, Kim Y, Choi H, Kim W, Park S, Lee D, et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut.* (2020) 69:283–94. doi: 10.1136/gutjnl-2018-317431

208. Kim DK, Park J, Han D, Yang J, Kim A, Woo J, et al. Molecular and functional signatures in a novel Alzheimer's disease mouse model assessed by quantitative proteomics. *Mol Neurodegener.* (2018) 13:2. doi: 10.1186/s13024-017-0234-4

209. Kim N, Jeon SH, Ju IG, Gee MS, Do J, Oh MS, et al. Transplantation of gut microbiota derived from Alzheimer's disease mouse model impairs memory function and neurogenesis in C57BL/6 mice. *Brain Behav Immun.* (2021) 98:357–65. doi: 10.1016/j.bbi.2021.09.002

210. Elangovan S, Borody TJ, Holsinger RMD. Fecal microbiota transplantation reduces pathology and improves cognition in a mouse model of alzheimer's disease. *Cells.* (2022) 12:119. doi: 10.3390/cells12010119

211. Hazan S. Rapid improvement in Alzheimer's disease symptoms following fecal microbiota transplantation: a case report. *J Int Med Res.* (2020) 48:300060520925930. doi: 10.1177/0300060520925930

212. Park SH, Lee JH, Shin J, Kim JS, Cha B, Lee S, et al. Cognitive function improvement after fecal microbiota transplantation in Alzheimer's dementia patient: a case report. *Curr Med Res Opin.* (2021) 37:1739–44. doi: 10.1080/03007995.2021.1957807

213. De Bruyne T, Steenput B, Roth L, De Meyer GRY, Santos CND, Valentová K, et al. Dietary polyphenols targeting arterial stiffness: interplay of contributing mechanisms and gut microbiome-related metabolism. *Nutrients.* (2019) 11:578. doi: 10.3390/nu11030578

214. Godos J, Currenti W, Angelino D, Mena P, Castellano S, Caraci F, et al. Diet and mental health: review of the recent updates on molecular mechanisms. *Antioxid (Basel)*. (2020) 9:346. doi: 10.3390/antiox9040346

215. Luo Y, Jian Y, Liu Y, Jiang S, Muhammad D, Wang W. Flavanols from nature: A phytochemistry and biological activity review. *Molecules*. (2022) 27:719. doi: 10.3390/molecules27030719

216. Wang D, Ho L, Faith J, Ono K, Janle EM, Lachcik PJ, et al. Role of intestinal microbiota in the generation of polyphenol-derived phenolic acid mediated attenuation of Alzheimer's disease β-amyloid oligomerization. *Mol Nutr Food Res*. (2015) 59:1025–40. doi: 10.1002/mnfr.201400544

217. Flanagan E, Müller M, Hornberger M, Vauzour D. Impact of flavonoids on cellular and molecular mechanisms underlying age-related cognitive decline and neurodegeneration. *Curr Nutr Rep*. (2018) 7:49–57. doi: 10.1007/s13668-018-0226-1

218. Martínez-Coria H, Arrieta-Cruz I, Gutiérrez-Juárez R, López-Valdés HE. Anti-inflammatory effects of flavonoids in common neurological disorders associated with aging. *Int J Mol Sci*. (2023) 24:4297. doi: 10.3390/ijms24054297

219. Banji OJF, Banji D, Makeen HA, Alqahtani SS, Alshahrani S. Neuroinflammation: the role of anthocyanins as neuroprotectants. *Curr Neuropharmacol*. (2022) 20:2156–74. doi: 10.2174/1570159x20666220119140835

220. Tran PHL, Tran TTD. Blueberry supplementation in neuronal health and protective technologies for efficient delivery of blueberry anthocyanins. *Biomolecules*. (2021) 11:102. doi: 10.3390/biom11010102

221. Karlsen A, Retterstøl L, Laake P, Paur I, Bøhn SK, Sandvik L, et al. Anthocyanins inhibit nuclear factor-kappaB activation in monocytes and reduce plasma concentrations of pro-inflammatory mediators in healthy adults. *J Nutr*. (2007) 137:1951–4. doi: 10.1093/jn/137.8.1951