

Review

Microbiota-Gut-Brain Axis Dysregulation in Alzheimer's Disease: Multi-Pathway Effects and Therapeutic Potential

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ABSTRACT: An essential regulator of neurodegenerative conditions like Alzheimer's disease (AD) is the gut microbiota. Alterations in intestinal permeability brought on by gut microbiota dysregulation encourage neuroinflammation, central immune dysregulation, and peripheral immunological dysregulation in AD, as well as hasten aberrant protein aggregation and neuronal death in the brain. However, it is unclear how the gut microbiota transmits information to the brain and how it influences brain cognition and function. In this review, we summarized the multiple pathways involved in the gut microbiome in AD and provided detailed treatment strategies based on the gut microbiome. Based on these observations, this review also discusses the problems, challenges, and strategies to address current therapeutic strategies.

Key words: Alzheimer's disease, gut microbiota, nervous system, immune system, neurotransmitter

1. Introduction

Alzheimer's disease (AD), a prevalent and progressive neurodegenerative disorder of the central nervous system (CNS), significantly impacts the psychological and social functioning of patients, leading to a decline in their overall quality of life. It is the most common form of dementia observed in older individuals [1]. AD patients frequently exhibit a gradual loss of brain cells and cognitive decline, accompanied by the abnormal accumulation of amyloid β (A β) plaques around or outside neurons, as well as the buildup of microtubule-associated protein Tau in cortical neuronal dendrites and axons [2–4]. The accumulation and aberrant aggregation of Tau proteins in neurons lead

to reduced microtubule stability, synaptic failure, and disturbance of Ca²⁺ homeostasis, ultimately resulting in apoptosis in neuronal cells [5, 6]. Currently, there are approximately 57.4 million individuals worldwide affected by dementia, and this number is projected to exceed 152.8 million by the year 2050 [7]. Given the escalating prevalence of AD and the substantial treatment burden it imposes, the analysis of AD pathogenesis and the pursuit of effective treatment have emerged as paramount imperatives for researchers. Despite extensive investigations into the etiology of AD, the underlying mechanisms remain incompletely elucidated. Numerous risk factors, including genetics, cerebrovascular disease, hypertension, type 2 diabetes, obesity, dyslipidemia,

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physical activity, and diet, have been identified, all of which converge on a pivotal element: the gut microbiota [8].

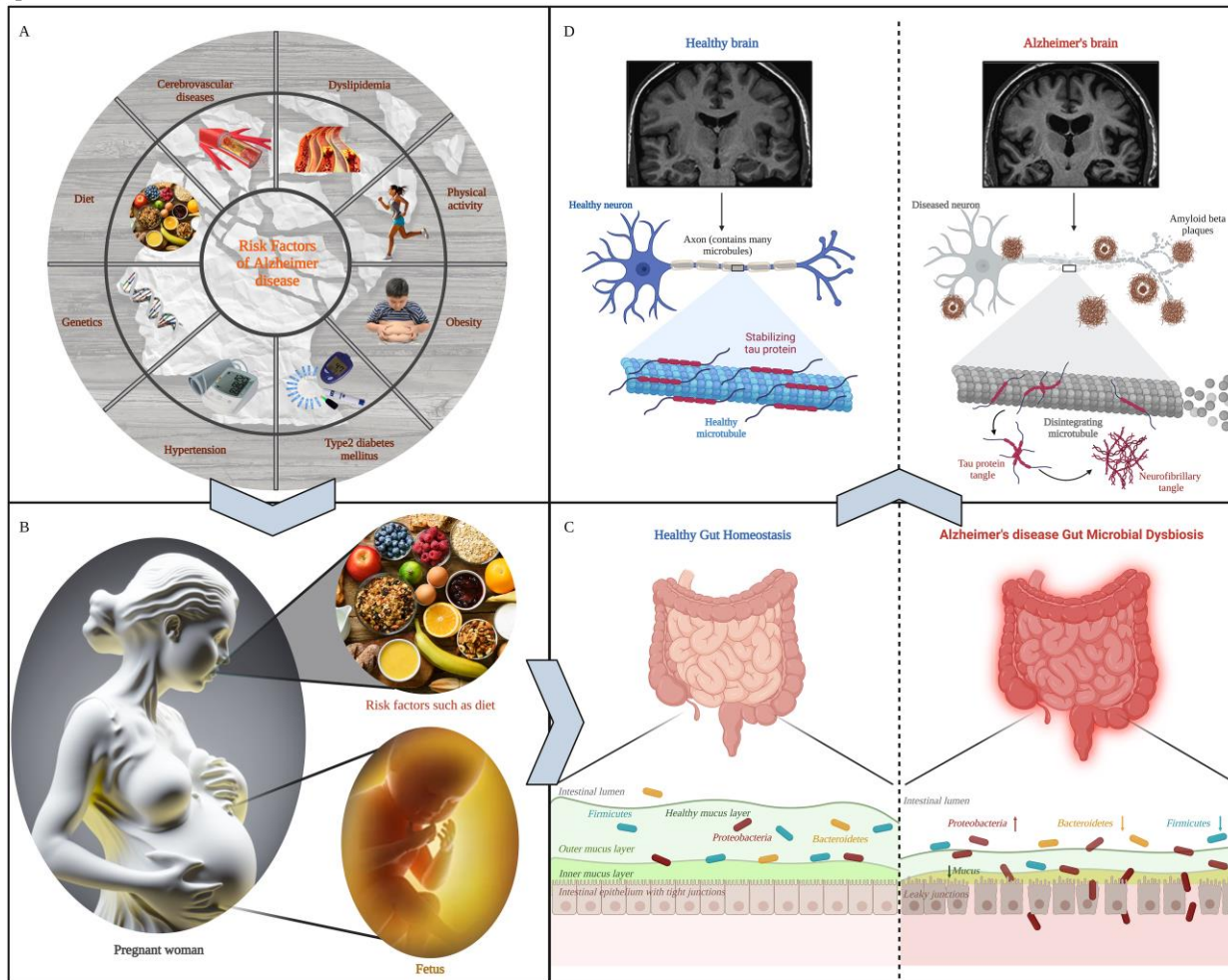


Figure 1. Multiple risk factors lead to AD by regulating gut microbiota. (A) Multiple risk factors for AD. AD has many risk factors, including heredity, diet and obesity, which greatly increase the incidence and pathological progress of AD. (B) The formation of gut microbiota. The fetal gut microbiota is influenced by the maternal microbiota during its initial formation and is differentially influenced by the postnatal environment, breast milk and maternal infections, obesity and other factors on the fetal microbiota. (C) Gut composition in healthy and Alzheimer's patients. In patients with AD, the abundance of intestinal beneficial bacteria decreased, the abundance of harmful bacteria increased, the thickness of mucosal layer decreased, and intestinal permeability increased, which led to the entry of pathogenic bacteria and harmful metabolites into the body through intestinal cells and induced inflammation. (D) Brain characteristics of healthy and AD patients. The imbalance of gut microbiota accelerated the pathological development of AD, promoted the dissociation of microtubule-associated proteins, the deposition of A β protein and neuronal apoptosis.

The presence of an imbalance in intestinal microflora, a reduction in the abundance and number of beneficial bacteria, is frequently observed in patients with AD. This observation suggests that the intestinal flora plays an indispensable role in the pathological progression of AD [9]. This condition gives rise to enduring inflammation and intestinal metabolic issues, alongside the deterioration of the intestinal barrier. Concurrently, bacteria and their byproducts exploit this opportunity to exacerbate insulin resistance (IR), glucose metabolism dysfunction, and neuronal demise, thereby inflicting

damage upon the brain and other organs, ultimately fostering the onset of AD and other disorders [10]. Consequently, the microbiota gut-brain axis (MGBA) has been posited as a prospective target for the treatment of neurodegenerative disorders such as AD and has emerged as an innovative therapeutic approach [11].

The establishment of the microbial community within the human body commences during birth, wherein the fetus is exposed to the maternal gut microbiota while in utero [12, 13]. Research has demonstrated that the mode of delivery, whether natural birth or cesarean section,

exerts an influence on the microbial community of neonates, leading to notable disparities in the composition of the microbiome [14, 15]. Furthermore, apart from the mode of delivery, a multitude of factors during the initial phases of life, such as prematurity, feeding regimen, host genetics, environmental conditions, maternal inheritance, infections, obesity, stress, and exposures to both antibiotics and non-antibiotic substances, exert diverse levels of impact on the microbiota composition of neonates [12]. Therefore, the microbiota is distinct and uniform for each individual, primarily localized in the gastrointestinal tract, and plays a crucial role in preserving host homeostasis and overall well-being. The intricate communication pathways linking the gastrointestinal tract and the brain involve the CNS, the enteric nervous system (ENS), and the intestinal microflora, collectively known as the MGBA [16]. The gut microbiota communicates bidirectionally with the brain through the neural, humoral, immune, and endocrine systems and influences the brain's physiology, cognition and behavior (Fig. 1).

This paper aims to examine the multi-pathway role of intestinal flora in AD, encompassing its impact on both the immune and nervous systems, as well as the intricate small molecular metabolic system that exists between microorganisms and the brain. Additionally, this study systematically summarizes the various approaches to directly or indirectly intervene in gut flora, thereby potentially influencing the development and progression of AD. Furthermore, this paper thoroughly examines the complexities associated with interventions targeting gut flora in the context of AD. It also puts forth potential remedies, highlighting the significance of investigating the role and therapeutic efficacy of gut flora in AD research. This study anticipates that further exploration in this area will yield substantial evidence to enhance and address the treatment of AD.

2. Multi-pathway effect of intestinal flora on AD

There are multiple pathways, encompass intricate neural interactions and meticulously regulated neuronal pathways, as well as a subtle and challenging to detect small molecular information transmission system, that can facilitate the transfer of information and interactions between the brain and the gut microbiota. This relationship has emerged as a highly relevant factor in the context of AD.

2.1 Nervous system pathway

There are two neuroanatomical pathways that facilitate communication between the gut and brain. The first pathway involves the direct communication between the gut and brain through the vagus nerve (VN) in the spinal

cord and the autonomic nervous system (ANS). The second pathway involves bidirectional communication between the gut and brain can communicate in both directions through the ENS in the intestinal tract, ANS and VN in the spinal cord [17]. The integration and monitoring of gut function, as well as the connection between the brain's affective and cognitive regions with peripheral gut processes such as immunostimulation, gut permeability, responses, and gut endocrine signaling, are facilitated by the interplay of immunological and neuroendocrine mediators. Furthermore, the stimulation of the VN has been found to have several beneficial effects on the gut microbiota and exhibit anti-inflammatory properties [17]. The brain plays a significant role in regulating various aspects of the communication network, including the microbiota, intestinal motility, sensory, and secretory functions. Conversely, signals originating from the gut and bacteria also exert an influence on brain function [18]. Imbalances in the gut microflora and associated dysfunction in the MGBA have been implicated in the development of numerous neurodevelopmental, cognitive, and neurodegenerative disorders. These abiotic factors have been identified as contributors to brain defects such as behavioral and neuronal dysfunction, leading to the development of AD and other related mental disorders. Moreover, they are closely associated with inappropriate systemic inflammatory responses. In addition to the neurological system's signaling, there exist various communication pathways between the gut microbiota and the brain, including immunological pathways, inflammation-promoting cytokines, short chain fatty acids (SCFAs), and neurotransmitters (NT) produced by the gut microbiota (Fig. 2).

2.2 Immune system pathway

The immune system is regulated by the presence of intestinal microflora, which accounts for over 70% of the total immune capacity. The dysregulation of gut microbiota has a profound impact on human homeostasis and overall health due to its influence on intestinal permeability [20]. An overabundance of unfavorable flora or a decrease in microbial diversity can significantly alter intestinal permeability. Consequently, invasive microorganisms, lipopolysaccharides (LPS), and specific metabolites can breach the colon barrier and enter the bloodstream, triggering the release of various inflammatory cytokines by the immune system. The intestinal mucosa's chronic or persistent inflammatory response can potentially overpower the immune system, leading to a chronic, hyperactive yet inefficient immune response. This phenomenon occurs despite the crucial and highly efficient nature of this immune system strategy

during emergency situations [21]. Chronic translocation of microorganisms not only elicits an inflammatory response, but also inflicts and exerts an influence on distant organs. Moreover, the integrity of the blood-brain barrier (BBB) integrity was significantly compromised due to bacterial translocation and the release of proinflammatory cytokines, thereby instigating a cascade of neuroinflammatory reactions [22–24]. Microorganisms originating from the periphery possess the capability to infiltrate the brain or reactivate dormant microorganisms within the brain tissue, thereby inducing detrimental chronic inflammation and facilitating the manifestation of AD pathological characteristics, such as the excessive

deposition of A β . Consequently, this expedites the progression of AD pathology. Furthermore, neuroinflammation can be triggered by the entry of LPS and microbial metabolites that into the brain [25, 26]. Hence, the dysbiosis of gut microbiota not only detrimentally effects the digestive tract, but also significantly disrupts the equilibrium between microflora and immune cells. Consequently, a reciprocal relationship between the intestinal tract and the brain leads to various neurological modifications. A growing body of research suggests that neuroinflammation plays a pivotal role in the initiation of A β deposition, tau protein phosphorylation, and eventual neuronal demise [27, 28].

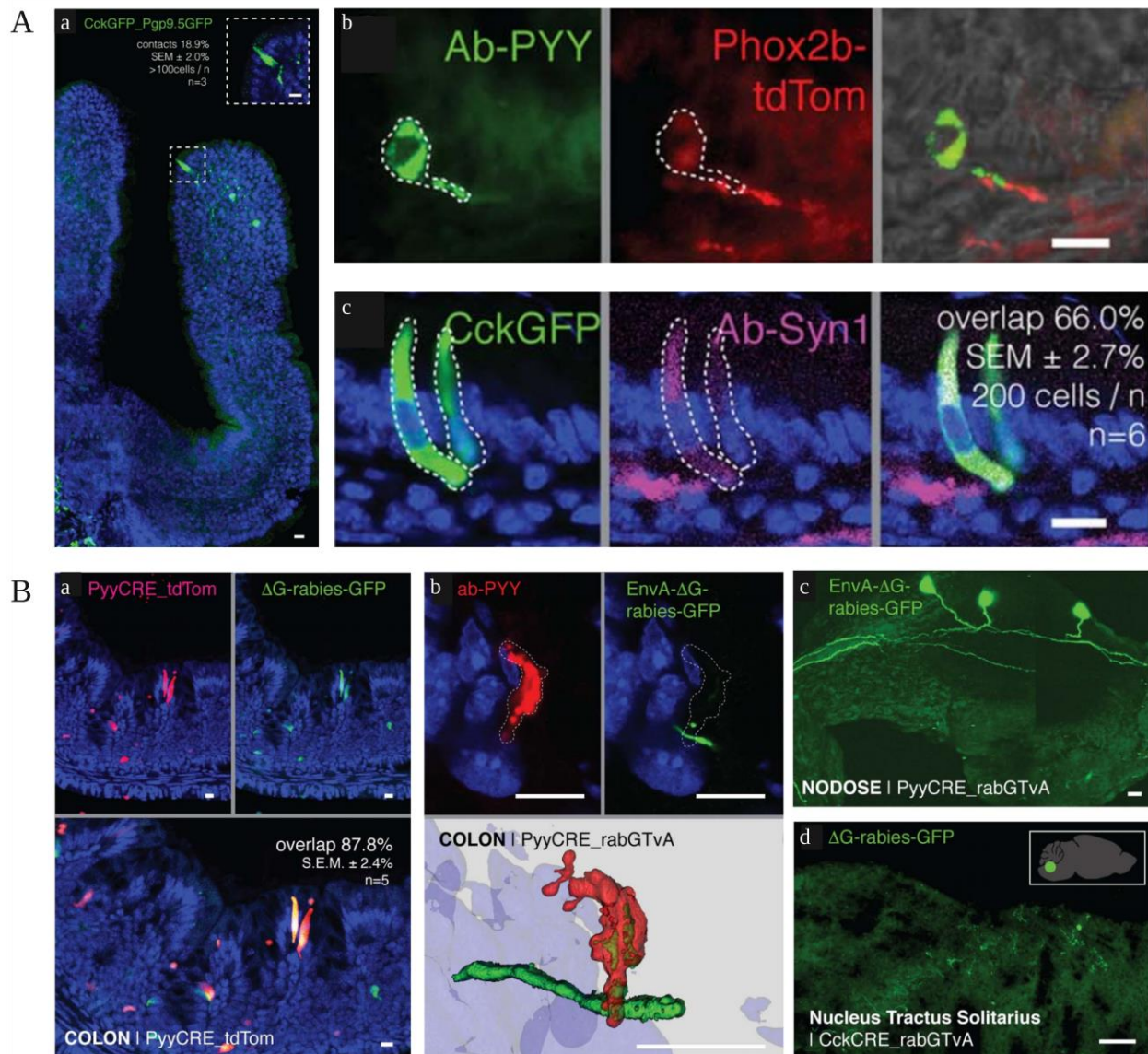


Figure 2. Enterocerebral neural pathways of the intestine and brain. (A) Enterocendocrine cells contact sensory nerve fibers. **(B)** Enterocendocrine cells of the colon and small intestine synapse interact with vagal tubercle neurons. Copyright © 2018, American Association for the Advancement of Science Publishing Group. Replicated with permission from Ref. [19].

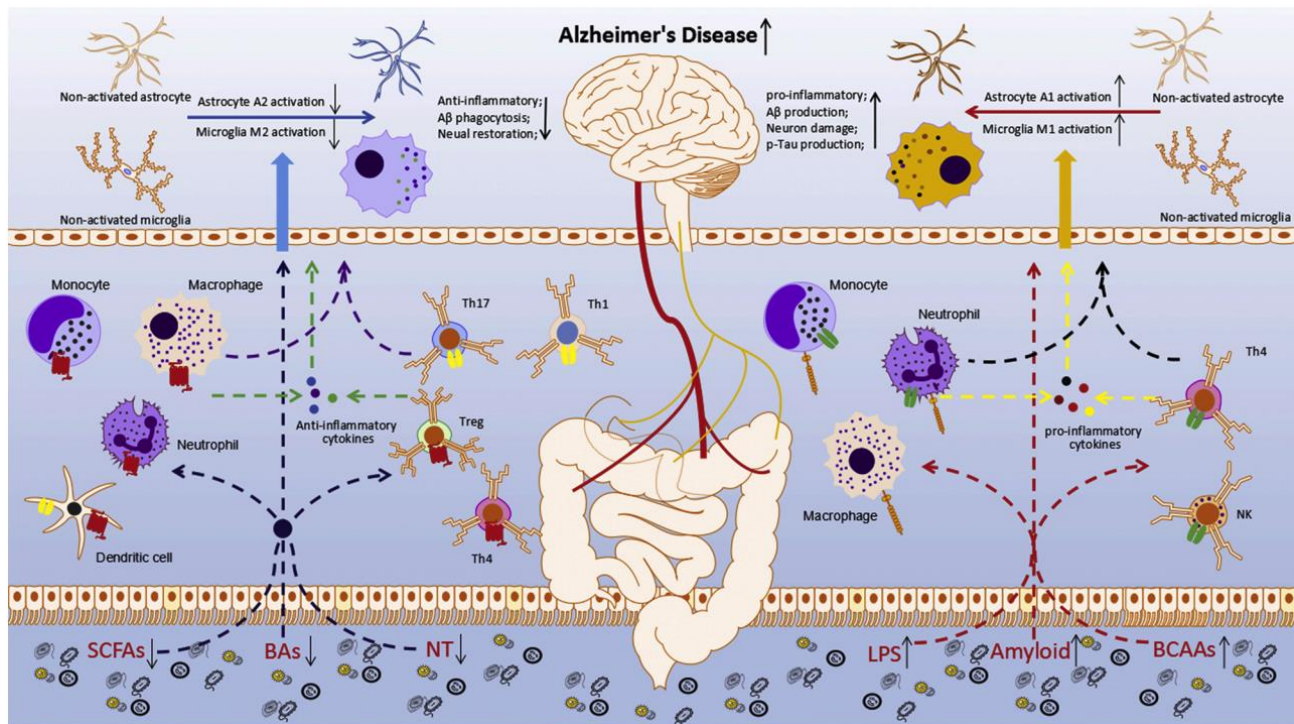


Figure 3. Gut microbiota accelerates the development of AD through the immune system. The decrease in anti-inflammatory and increase in pro-inflammatory bacteria in the intestinal flora of AD patients leads to an increase in harmful metabolites and a decrease in beneficial metabolites in the gut. These changes accelerate neuroinflammatory and systemic inflammatory responses in AD patients and reduce A β protein clearance and repair of nerve damage, accelerate Tau protein phosphorylation, and A β protein deposition, thus accelerating the development of AD. Copyright © 2018, Elsevier Publishing Group. Replicated with permission from Ref. [33].

Over time, pro-inflammatory cytokines, which are initially considered protective agents of the nervous system, undergo a transformation and become implicated as the causative factors of neuropathy[28, 29]. Consequently, the extent of neuropathic damage induced by inflammation is contingent upon the host's degree of activation, stage of pathology, environmental factors, and other variables. SCFAs, which are produced by intestinal microorganisms, during digestion, have the capacity to modulate microglial overactivation by crossing the BBB and triggering the release of numerous inflammatory mediators. These excessive inflammatory reactions serve as the catalyst for the initiation of neurodegenerative processes, subsequently perpetuating and intensifying the ongoing neuroinflammatory cycle [30, 31]. Furthermore, in the presence of an imbalance in the intestinal microecology, certain substances discharged by intestinal microorganisms, including interleukin-6 (IL-6), IL-8, and other inflammatory factors produced by specific *Proteus bacteria*, stimulate the activation of triggering receptors expressed on myeloid (TREM) found on macrophages. This leads to an exaggerated pro-inflammatory reaction and subsequent nerve injury through the modulation of the MGBA [32]. The imbalance of gut microbiota is directly associated with intestinal barrier failure and heightened intestinal permeability. It has been postulated that the

pathological progression of the disease is influenced by chronic intestinal inflammation in conjunction with risk factors for AD (Fig. 3).

2.3 Pathway of small molecule metabolite delivery system

2.3.1 SCFAs

Evidence from numerous studies suggests that the physiology and behavior of the CNS is influenced by SCFAs, which include propionic acid, butyric acid, and succinic acid, are produced by the fermentation of dietary fiber and sugars by gut microbiota and affect the regulation of fat and glucose metabolism in the body. Research has demonstrated a strong correlation between alterations in the concentrations of SCFAs and the abundance of SCFA-producing bacteria within the gastrointestinal tract, and the onset and progression of neurological disorders, notably AD. SCFAs exert their influence on brain function and behavior through diverse molecular mechanisms, including amelioration of cognitive impairment, modulation of AD-associated marker deposition, regulation of BBB permeability, and provision of anti-inflammatory and anti-apoptotic effects.

In relation to cognitive processes, SCFAs have been shown to enhance the expression of proteins associated with synaptic plasticity. Research has indicated a significant association between histone acetylation and neurodegenerative disorders such as AD. Histone acetylation is jointly regulated by histone acetyltransferases (HATS) and histone deacetylases (HDAC), with HDAC inhibiting histone acetylation and inducing chromatin compaction. Consequently, gene promoters experience reduced accessibility for transcription factors, leading to inducing chromatin compaction. Consequently, gene promoters experience reduced accessibility [35, 36]. The utilization of HDAC inhibitors to regulate HDAC in AD appears to be a promising approach for enhancing gene expression and mitigating AD-associated pathology in affected individuals. SCFAs, being a broad-spectrum HDAC inhibitor, hold significant significance in the inhibition of HDAC [37]. In their study, Govindarajan et al. observed an augmentation in the acetylation of H3K14, H4K5 and H4K12 sites within the hippocampus of APPPS1 double transgenic AD model subsequent to enhanced after sodium butyrate administration. Furthermore, the researchers detected an elevation in the expression of genes associated with synaptic plasticity subsequent to sodium butyrate treatment, thereby implying that sodium butyrate may alleviate cognitive impairment in APPPS1 mice by upregulating the expression of synaptic plasticity-related proteins [38]. Furthermore, Barichello et al. discovered that the administration of sodium butyrate resulted in an augmentation of neurotrophic factor (NF) expression, as well as glial cell line-derived NF, to hereby ameliorating memory impairment caused by experimental pneumococcal meningitis. These findings underscore the pivotal role of NFs in safeguarding neurons and enhancing memory function [39]. The potential mechanism by which sodium butyrate enhances cognitive impairment was investigated. Sodium butyrate mitigates radiation-induced cognitive impairment by mitigates inhibiting hippocampal phosphorylation of cAMP response element binding proteins or promoting the expression of brain derived neurotrophic factor (BDNF) [40]. Additionally, it was observed that sodium butyrate enhances synaptic plasticity through long-term potentiation and depotentiation [41]. In microglia, the augmentation of long-term potentiation and synaptic plasticity is facilitated by sodium butyrate through the up-regulation of the phosphoinositide 3 kinase (PI3K)/protein kinase B (AKT)/cAMP response element binding (CREB)/BDNF signaling pathway [42]. It is noteworthy to mention that acetate also assumes a significant role in AD. Acetyl-CoA, derived from acetate, serves as an acetyl donor to facilitate histone acetylation and modulate the inflammatory response triggered by microglial

activation in the brain, thereby mitigating neuroinflammation in individuals affected by AD [43, 44]. Furthermore, SCFAs exert their influence on the pathological effects of A β and Tau through diverse mechanisms. Notably, in a study involving 5 \times FAD rats treated with sodium butyrate, a dose-dependent decrease in brain A β levels was observed in the initial phases of the disease, with the extent of reduction correlating with the dosage of sodium butyrate [38]. However, it should be noted that the administration of sodium butyrate through the lateral ventricles did not result in a decrease in A β levels during the advanced stages of the illness [45]. This might be connected to both A β 's qualities and the sodium butyrate treatment's dosage and duration. A β is monomeric in the brain during the early stages of the illness, but as the illness worsens, monomeric A β spontaneously aggregates into more toxic and challenging to remove A β oligomers or A β neural fiber tangles [45]. Sun et al. discovered that sodium butyrate has an impact on mitochondrial function and cell proliferation. This effect is mediated through the regulation of the G protein-coupled receptor (GPR) 109A receptor, inhibition of amyloid precursor protein (APP), promotion of neprilysin (NEP) and BDNF gene expression, and reduction of A β damage to cells [46]. Similarly, Filippone et al. observed that sodium butyrate inhibits nitric oxide (NO) synthase and cyclooxygenase-2 (COX-2), thereby mitigating A β -induced damage to nerves and the spinal cord [47]. Furthermore, sodium butyrate has been observed to regulate the hyperphosphorylation of Tau and the expression of inflammatory glial fibrin acidic protein in cDKO mice, in addition to its impact on A β [48].

In terms of inflammation, SCFAs can alleviate the inflammatory response and diminish the levels of pro-inflammatory cytokines. In there in vivo experiments, Soliman et al. observed that acetate led to an augmentation in the acetylation of brain acetyl coenzyme A and histones, while concurrently reducing the activation of glial cells induced by LPS and the expression of IL-1 β [44]. Liu et al. discovered that the administration of acetate to APP/PS1 mice resulted in a reduction in G protein expression through the activation of GPR41 and inhibition of the ERK/JNK/NF- κ B pathway. Additionally, acetate treatment led to decreased levels of COX-2 and IL-1 β , thereby mitigating the neuroinflammatory consequences associated with AD [49]. Moreover, in order to examine the influence of SCFAs on microglial activity, Wenzel et al. utilized differentiated HL-60 monocytes and human THP-1 monocytes as surrogate models for human microglia. In the presence of SCFAs, the levels of inflammatory mediators such as tumor necrosis factor- α (TNF- α) and IL-1 β were diminished, and the generation of reactive oxygen species (ROS) was suppressed reduced by

inhibiting the respiratory chain triggered by N-formyl-methionine-leucyl-phenylalanine [50]. A comparable finding was reached whereby, following a 4-week treatment involving the administration of water infused with a mixture of SCFAs, a significant restoration in the quantity, functionality, and maturation of microglia within the murine brain was observed [51]. Additionally, Li et al. discovered that SCFAs exhibited a partial reversal of hippocampal neuronal inflammation and damage induced by a high fructose diet, accomplished through the repair of intestinal epithelial barrier impairment and the

restoration of NOD-like receptor family pyrin domain-containing 6 (NLRP6) inflammatory body dysfunction in mice [52]. Sodium propionate has been observed to enhance cell survival following antibody stimulation through the reduction of nuclear factor levels in the kappa light peptide gene enhancer of B-cell inhibitory factor alpha, as well as decrease levels of nitrite, NO, and COX-2. These findings suggest an additional molecular mechanism by which SCFAs may contribute to the protection against neuronal injury [47].

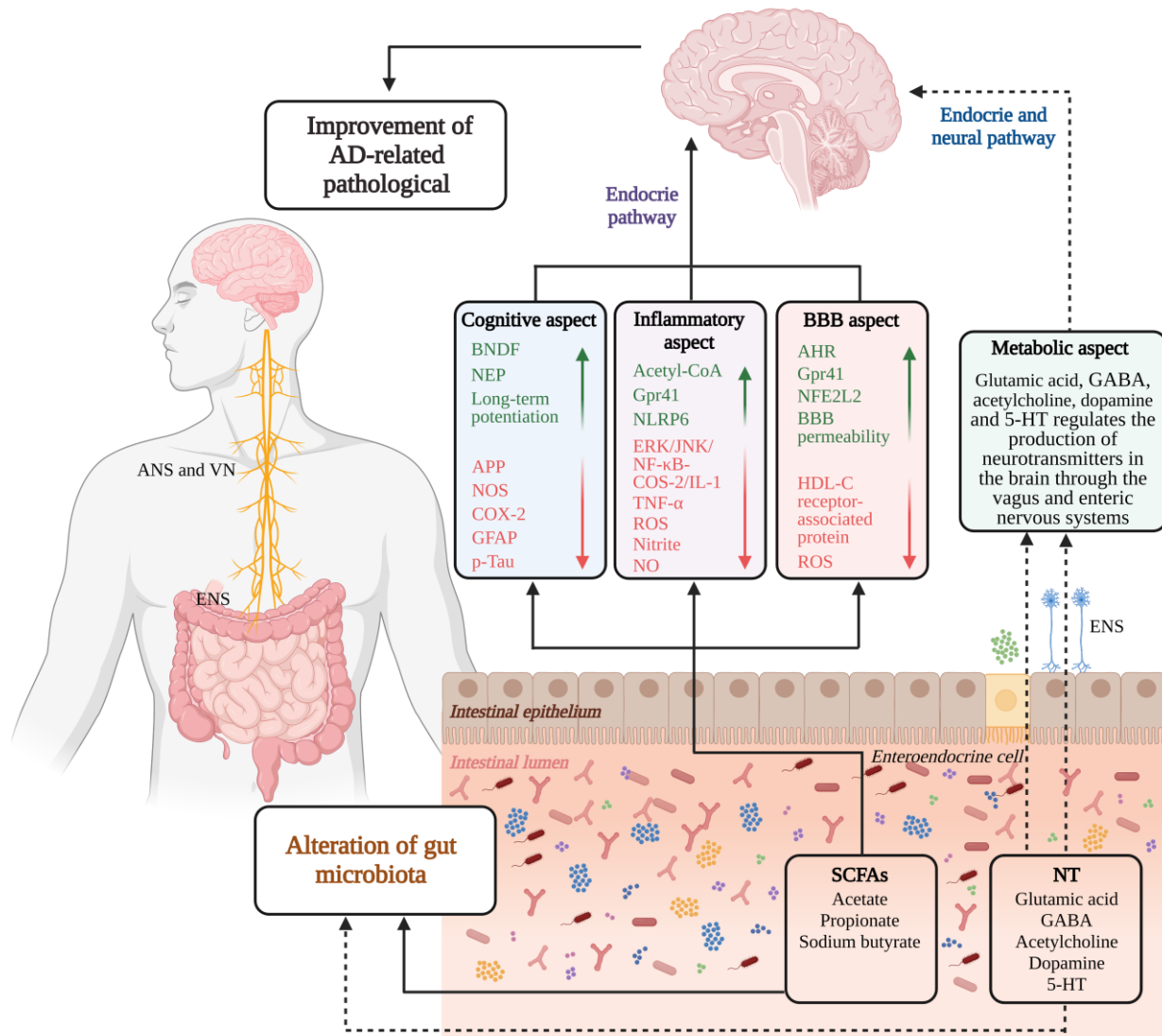


Figure 4. Gut microbiota accelerates the development of AD through small molecule metabolite delivery system. In patients with AD, the exchange of information between the intestine and the brain decreases, and due to the decrease of the content of SCFAs and NT produced by the intestine, these beneficial metabolites can not positively stimulate and regulate brain metabolism, accelerating the development of AD. Appropriate supplementation of SCFAs and NT can regulate brain metabolism, slow down the pathological process of AD, and improve cognitive impairment, neuroinflammation and BBB integrity in patients with AD.

In terms of the BBB, SCFAs exhibit a safeguarding and restorative effect on the BBB's functionality and architecture. The presence of sodium butyrate leads to an

increased expression of tight junction proteins in the mouse brain. Furthermore, the administration of butyrate-, acetate-, and propionate-producing microbiota to germ-

free (GF) mice resulted in a noteworthy enhancement of BBB permeability [53–55]. Furthermore, the aromatic hydrocarbon receptor (AHR), responsible for regulating the metabolic and immunological functions of the gastrointestinal tract, can also be modulated by SCFAs, exhibiting AHR-like properties that mitigate intestinal inflammation and further improve BBB permeability [56, 57]. In addition, exhibits a comparable impact by serving as an activator for GPR41 within the BBB and diminishing the expression of the transporter linked to low-density lipoprotein receptor 1. The oxidative stress (OS) -induced impairment of the BBB is mitigated through the signaling of nuclear factor (erythroid-derived) 2-like 2 [58]. These aforementioned discoveries indicate that the dysregulation of SCFAs resulting from an imbalance in the gut microbiota significantly contributes to the pathophysiology of AD (Fig. 4).

2.3.2 NT

In addition to SCFAs, intestinal bacteria have the capacity to synthesize various NT, including glutamate, γ -aminobutyric acid (GABA), acetylcholine, dopamine and 5-hydroxytryptamine (5-HT) [59–61]. These NT play a crucial role in the neurological and psychological aspects of diverse brain functions, encompassing motor skills, emotional states, cognitive processes, and memory formation [62–64].

Glutamate, an excitatory neurotransmitter, is highly prevalent in the brain and serves a vital function in facilitating the transmission of information among neurons [65, 66]. Research has indicated that, apart from the brain's production of glutamate, certain intestinal endocrine cells within the gastrointestinal tract are also capable of generating glutamate and transmitting stimulation signals to the brain via the VN [19]. This study highlights the role of intestinal endocrine cells in transmitting signals to the VN and promoting the transcription of vesicular glutamate transporter 1 (VGLUT1), leading to the release of glutamate. This rapid transmission of information from the intestine to the brain has been observed. Notably, Frost et al. conducted an experiment involving mice that were administered ¹³C-labeled inulin orally. The results showed that ¹³C acetate accumulated in the BBB in the hypothalamus and was involved in the production of glutamate through the neuronal-glial cycle, which is associated with hypothalamic glutamate-glutamine metabolism [67].

GABA plays a crucial role in various physiological processes and brain metabolism, functioning as an inhibitory neurotransmitter that facilitates communication between the gut and brain [68, 69]. Within GABAergic neurons, the enzyme glutamate decarboxylase converts the primary precursor of GABA, glutamate, into GABA

[70]. Furthermore, research has revealed that GABA can be synthesized by gut microbiota, stimulating the ENS. In their search for essential growth factors for bacterial life, Strandwitz et al. identified that *Bacteroides fragilis* as a significant producer of GABA, serving as its primary growth factor source [71]. The authors have additionally ascertained that *Bifidobacteria*, *Parabacteria*, and *Eubacteria* can possess the ability to synthesize GABA. It is noteworthy that GABA does not traverse the BBB, and the GABA synthesized by the gut microbiota exerts its effects primarily within the VN or ENS [72]. Importantly, certain metabolites produced by the gut microbiota, such as acetate, can permeate the BBB and accumulate in the hypothalamus, thereby participating in the GABA metabolic cycle [67].

Acetylcholine, a prototypical cholinergic neurotransmitter, is involved in local mediation role by transmitting excitatory signals between neurons in both the central and peripheral nervous systems in vertebrates [73]. The expression and functioning of acetylcholine are closely associated with neurodegenerative disorders such as AD [74]. Acetylcholine is a commonly occurring metabolite in bacteria, specifically in *Lactobacillus plantarum*, *Bacillus subtilis*, *Escherichia coli*, and *Staphylococcus aureus* [75, 76]. Nevertheless, acetylcholine is unable to traverse the BBB; however, its precursor choline can be transported to the brain through a carrier present on the capillary endothelial cells. Once in the brain, choline can contribute to the biosynthesis of acetylcholine [77].

Dopamine, a catecholamine neurotransmitter, is highly prevalent in the brain and exerts regulatory control over various within the CNS. Dysregulation of the dopamine system significantly contributes to the pathological progression of AD and Parkinson's disease (PD) [78, 79]. Williams et al. found that staphylococcus bacteria residing in the human gut produce substantial quantities of dopamine via the enzymatic activity of aromatic amino acid decarboxylase (SADA) [80]. Further studies by Eisenhofer et al. has demonstrated that the mesenteric organs within the gastrointestinal tract, which are under the influence of the gut microbiota, exhibit substantial dopamine production, constituting approximately 50% of the overall dopamine levels in the body [81]. The disruption of the dopamine system due to alterations in the gut microbiota has the potential to expedite the pathological progression of CNS disorders, including AD and PD.

5-HT, an indole derivative, is predominantly synthesized by intestinal chromophores located in the mucosa of the gastrointestinal tract, constituting 90 percent of the total 5-HT within the body. It serves as a stimulant in the modulation of mood, memory, and overall bodily functions, exerting a positive influence on

emotional well-being. Within the intestinal environment, the activity of intestinal chromophores is regulated by the bacterial kynurenine synthesis pathway, facilitating the conversion of tryptophan derived from dietary proteins into 5-HT. Furthermore, it has been observed that bacteria, specifically bacteriophage forming bacteria such as *Clostridium perfringens* in the intestinal tract, can enhance the expression of tryptophan hydroxylase 1 (TPH1), which is the rate-limiting enzyme responsible for the synthesis of 5-HT. This ultimately leads to an accelerated biosynthesis of 5-HT [82, 83]. Luqman et al. have discovered that certain species within the *Staphylococcus* genus possess the capability to decarboxylate the precursor of 5-HT, known as 5-hydroxytryptophan (5-HTP), into 5-HT through the activity of *Staphylococcus* SADA[84]. Furthermore, the metabolites derived from the microbiota, particularly acetate and butyrate, stimulate the upregulation of TPH1, thereby enhancing the synthesis of 5-HT by intestinal chromaffin cells. Consequently, the and microbial modulation of intestinal homeostasis could be profoundly influenced by the production of 5-HT, , particularly with regards to especially on intestinal motility and platelet function [85–87]. Consequently, disruptions in 5-HT metabolism resulting from imbalances in the intestinal microbiota may expedite the progression of neurodegenerative disorders.

In addition to the aforementioned NT, the brain also harbors a limited quantity of NT, including tyramine and tryptamine among others. Despite their relatively low prevalence in the brain, a significant population of staphylococci capable of synthesizing these trace NT is present in the human intestinal tract [84]. Collectively, these NT play a pivotal role in governing neuronal function and facilitating interneuronal communication within the brain (Fig. 4). In summary, these results demonstrate the irreplaceable role of gut microbiota in regulating host NT and neural signal transduction.

3. Treatment strategy of AD based on gut microbiota

The acceleration of the pathophysiological progression of neurodegenerative disorders, such as AD, is facilitated by the gut microbiota. Alterations in the composition and functionality of the intestinal flora have been identified as risk factors for neurodegenerative diseases, both in healthy individuals and patients. Consequently, the investigation of gut microbiota is imperative in order to identify novel therapeutic targets and methodologies for AD. An increasing body of evidence indicates that directing interventions towards the modulation of gut microbiota may present a promising avenue for prevention and treatment of AD. Currently, a diverse range variety of therapeutic interventions has been

employed to address gut microbiota disorders, reinstate gut microbiota equilibrium, and enhance the clinical results of diseases such as AD. These interventions encompass the utilization of probiotics, prebiotics and fecal microbiota transplantation (FMT).

3.1 Probiotics

According to the definition published in 1956, probiotics are live microorganisms that exhibit minimal or no pathogenicity and exert beneficial effects on the health of the host[88]. These microorganisms regulate the activity of intestinal cells by modulating specific intracellular signaling pathways, stimulating the production of SCFAs, regulating cell function, enhancing the immune system's defensive capabilities, and reducing the production of inflammatory cytokines. Consequently, probiotics contribute to thereby enhancing the maintenance of gut barrier function integrity and influence the dynamic ecological equilibrium of the gut microbiota (Fig. 5) [89–97]. Additionally, as previously mentioned, the administration of probiotics has been shown to modulate various cognitive, affective, learning, and memory functions within the CNS through the production of SCFAs and NT. Specifically, when the probiotic mixture VSL#3 was administered to animal models with AD, it resulted in an increase in Actinobacteria and Bacteroides within the gut microbiota, a decrease in the expression of markers associated with microglia activation, and an enhancement in the expression of BDNF and synaptic proteins [98]. Moreover, as previously stated, probiotics have the ability to regulate cognitive, emotional, learning and memory processes within the CNS by producing various SCFAs and NTs. In studies involving animal models of AD, the administration of the probiotic mixture VSL#3 resulted in increased levels of *Actinobacteria* and *Bacteroidetes* in the gut microbiota, as well as elevated expression of BDNF and synaptophysin, while reducing indicators of microglia activation indicators [99]. In terms of modulation of intestinal flora metabolites, O'Hagan et al. discovered that the probiotics preparation Lab4, consisting of *Lactobacillus* and *Bifidobacterium*, exerted an influence on the modulation of intestinal flora metabolites. This impact extended to metabolites like GABA and glutamate in the brain, which were altered through multiple pathways. Consequently, the probiotics preparation exhibited the ability to enhance both long-term and short-term memory behavior in rats [100]. The pathological progression of AD is influenced by both mitochondrial dysfunction and an excessive occurrence of OS. A study conducted on transgenic AD mice demonstrated that SLAB51, a combination of *Lactobacillus* and *Bifidobacterium*, activated SIRT1-dependent pathways, resulting in a significant reduction

of OS in the brain of 3xTg-AD mice [101]. Moreover, SLAB51 exhibited various beneficial effects such as enhancing the production of anti-inflammatory metabolites in the intestine, increasing plasma levels of

neuroprotective gut hormones, improving glucose absorption and metabolism, reducing amyloid deposition and brain damage, and ameliorating cognitive impairment [102].

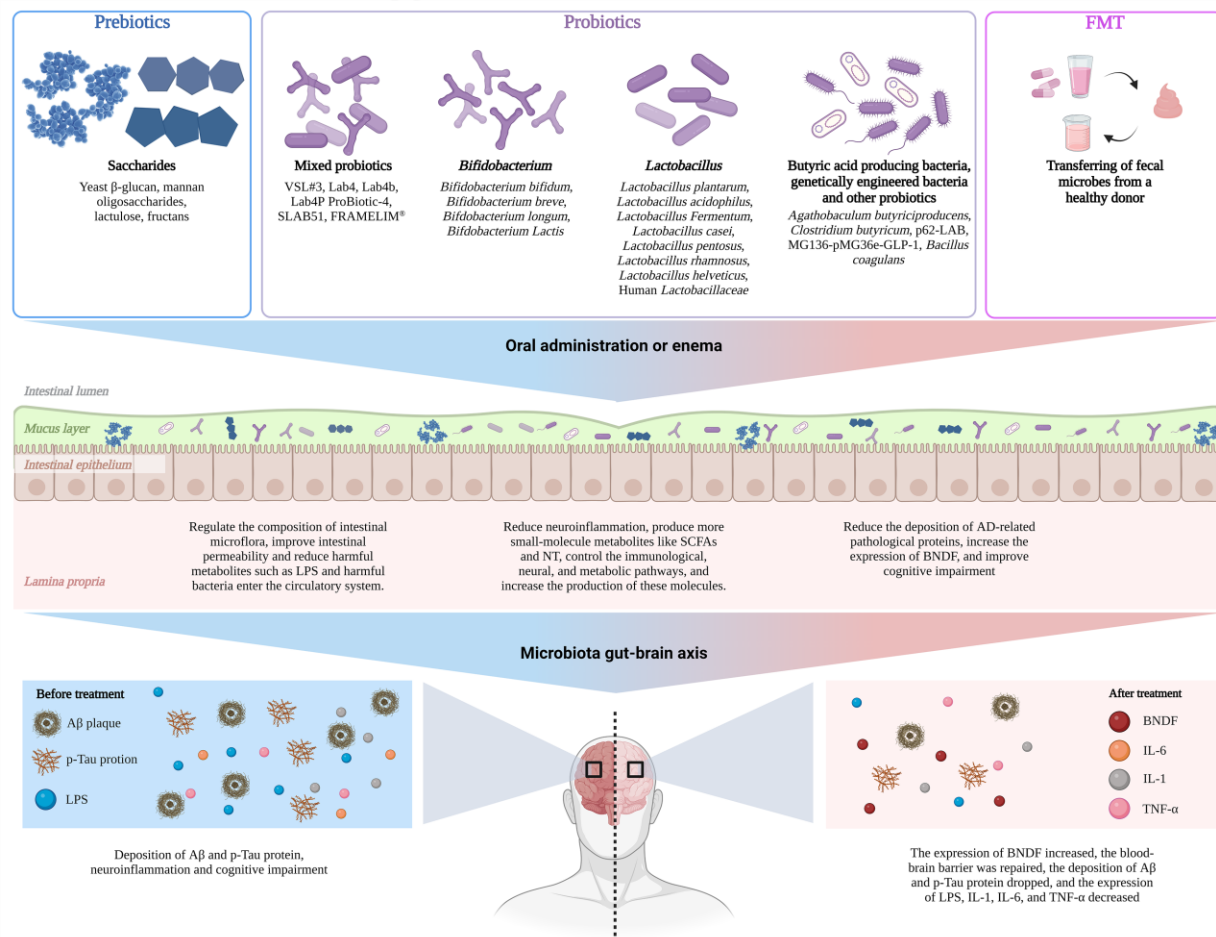


Figure 5. Improvement effect of probiotics, prebiotics and FMT on patients with AD. Probiotics, prebiotics and FMT can regulate the composition of intestinal flora, improve intestinal permeability, and increase beneficial metabolites in patients with AD. And reduce neuroinflammation, reduce the deposition of ad-related pathological proteins and improve cognitive impairment in patients with AD through neural, immune, and small molecular delivery systems.

Azm et al. found similar conclusions in their study. They observed a decrease in levels of OS biomarkers and a significant improvement in spatial memory skills in AD mice treated with a combination consisting of *Lactobacillus acidophilus*, *Lactobacillus fermentum*, *Bifidobacterium lactis*, and *Bifidobacterium longum* [103]. *Bifidobacterium* A1 was found to reduce memory behavior and cognitive impairment in AD mice by regulating neuroinflammation and A β formation. This was achieved through the inhibition of inflammatory and immunoreactive gene expression in the hippocampus induced by A β , either directly by *Bifidobacterium* A1 or its metabolite acetate [104]. Moreover, the *Bifidobacterium* family member, *Bifidobacterium breve* MCC1274, has been found to exhibit a comparable impact on the hippocampus by decreasing the levels of presenilin

1 protein and phosphorylated tau protein [105]. *Bifidobacterium Lactis* Probio-M8 has demonstrated the ability to diminish the accumulation of A β plaque throughout the entire brain, mitigate gut microbiota imbalance, and alleviate cognitive impairment in APP/PS1 mice [106]. Additionally, the study revealed that the administration of *Clostridium butyricum* effectively inhibited the synthesis of A β and mitigated neuroinflammation. In the context of rats with AD, the introduction of *Clostridium butyricum* successfully prevented cognitive decline, A β accumulation, activation of microglia, and the production of TNF- α and IL-1 β . Moreover, it demonstrated a reduction in aberrant expression of gut microbiota and levels of butyric acid [107]. *Akkermansia muciniphila* (*A. muciniphila*) exhibited comparable functionalities, as evidenced by its

significant amelioration of A β protein deposition and intestinal barrier dysfunction in the brains of APP/PS1 mice, and neurobehavioral assessments demonstrated notable enhancements in memory function and mitigation of obesity induced by a high-fat diet [108, 109]. Subsequent investigations unveiled that pasteurized *A. muciniphila* yielded significantly superior outcomes in memory, anxiety, aggression, and social preference compared to untreated *A. muciniphila* [110]. By modulating gut microbiota, the authors also discovered that pasteurized *A. muciniphila* enhanced systemic metabolism and A protein deposition in the brain [110]. SLAB51 exhibited comparable efficacy to *A. muciniphila* in reducing blood glucose and lipids. The administration of SLAB51 resulted in enhanced glucose levels in the brain through the restoration of GLUT3 and GLUT1 expression along with insulin-like growth factor receptor expression. Consequently, this led to dephosphorylation of protein kinase B and adenosine monophosphate-activated protein kinase. At the same time, the treated mice demonstrated a significant decrease of 108% in phosphorylated tau aggregates [111]. As previously stated, the acceleration of the AD pathological process is facilitated by the heightened intestinal permeability caused by dysbiosis of the intestinal flora. In light of this, investigations into the treatment of old and AD mice with probiotics have demonstrated that *Bifidobacterium longum* modifies the composition of the intestinal microbiota, diminishes the presence of LPS in both stool and blood, inhibits the activation of NF- κ B, suppresses the expression of TNF- α , and enhances the expression of intestinal tight junction proteins. These findings suggest that *Bifidobacterium longum* mitigates cognitive decline, reduces A β protein aggregation and improves intestinal permeability through the modulation of the microbiota [112]. Yang et al. also reached the same conclusion. The researchers observed a significant reduction in intestinal barrier dysfunction and BBB dysfunction in aged mice treated with probiotic-4. Additionally, the levels of IL-6 and TNF- α mRNA and protein were decreased. These effects were specifically observed in SAMP8 animals that received probiotic treatment. Furthermore, the study revealed a decrease in NF- κ B translocation, toll-like receptor 4 (TLR4) expression, as well as a reduction in decreased plasma and brain LPS concentration [113]. In addition to natural probiotics, genetically engineered bacteria have also played a role in improving and alleviating the pathological process of AD. The AD mice's brain A β levels, as well as neuronal oxidative and inflammatory processes, were considerably enhanced by the engineered probiotics *Lactobacillus lactis*, which carries an encoded human p62 protein [114].

Probiotics have been discovered to have therapeutic effects when mixed with medications in addition to their

effects when taken alone. Intestinal flora can be recovered using *Lactobacillus plantarum* and AD together. *Lactobacillus plantarum* prevents the synthesis of trimethylamine-N-oxide (TMAO). The digestive tract produces the microbial metabolite TMAO, which has the ability to accelerate the clinical traits of AD mice and speed up the disease progression [115]. In addition to drug combination, probiotics are also used in combination with other beneficial stimuli. In this regard, the combination of probiotics FRAMELIM[®] and exercise has been shown to regulate intestinal flora, and the deposition of A β in the hippocampus of AD mice is decreased, and memory function is significantly improved [116]. Moreover, the synergistic effect of selenium and probiotics supplements has been uncovered, as they effectively ameliorate cognitive impairment associated with AD by addressing metabolic dysfunctions, mitigating inflammation, and reducing OS [117].

In addition to animal models, clinical studies have yielded similar results. In comparison to the placebo group, AD patients treated for 12 weeks with a probiotics mixture containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and *Lactobacillus fermentum* showed improved levels of plasma malondialdehyde, serum C-reactive protein, beta cell function, serum triglyceride levels, and there were significant differences in the Mini-Mental State Exam (MMSE) [118]. *Bifidobacterium breve* A1 exhibited a comparable function. The participants' scores on the Repeatable Battery for the Assessment of Neuropsychological Status significantly improved after a 16-week intervention with *Bifidobacterium breve* A1 compared to the placebo group. Additionally, the subjects' scores in the domains of immediate memory, visual space, and memory were significantly enhanced [119]. This finding aligns with the conclusion reached by Asaoka et al [120]. The MMSE and categorical verbal fluency test scores were much higher after a 12-week course of treatment with *Bifidobacterium longum* R0175 and *Lactobacillus rhamnosus* HA-114, and AD-related symptoms were dramatically reduced in AD patients [121]. Furthermore, the administration of combined probiotics, namely *Bifidobacterium longum* BORI BGN4 and *Bifidobacterium bifidum*, effectively mitigated the psychological stress in elderly individuals and substantially elevated the expression levels of BDNF. It is worth emphasizing that BDNF plays a pivotal role in safeguarding neurons, enhancing memory, and reducing neuronal degeneration in the elderly population [122]. Additionally, it has been observed that a number of probiotics exhibit advantageous preventive and enhancing effects on individuals who do not suffer from cognitive impairments. Following a continuous 16 weeks administration of *Bifidobacterium longum* BB68S

probiotics, the RBANS scores of the subjects, as well as relative abundance of probiotics such as *Lachnospira*, *Bifidobacterium*, *Dorea*, and *Cellulosilyticum* in the gastrointestinal tract, were found to be significantly higher [123]. Besides, the therapeutic effects of AD have been demonstrated. Ton et al. conducted a study which revealed that the consumption of milk fermented with mixed probiotics led to a significant reduction in inflammation and OS biomarkers in AD patients. Additionally, this intervention improved mitochondrial function, DNA damage or repair, and reduced apoptosis

[124]. In addition, a meta-analysis demonstrated that individuals who consumed probiotics experienced enhanced cognitive function and a notable decrease in inflammation and OS-related biomarkers when compared to control group [125, 126]. Table 1 summarizes in detail the application and treatment outcomes of various probiotics in different animal models and clinical settings.

In summary, it has become possible to use probiotics to prevent or improve neurodegenerative diseases such as AD. However, some of its mechanisms remain to be explored.

Table 1. Application and therapeutic effect of multiple probiotics in different animal models and clinical environments.

Probiotics	Species	Methods of Administration and Disposal	Probiotics dosage	Experimental Cycle	Study Cohort/Sample Size	Results	Ref.
VSL#3	<i>Streptococcus</i> , <i>Bifidobacterium</i> , <i>Lactobacillus</i>	Mixed in maple syrup	12.86 billion living bacteria/kg/day	6 weeks	3-months and 20-22-months old Wistar rat (n=5)	Age-related deficits were reduced in Wistar rats treated with VSL#3, activation indicators of microglia were moderately reduced, expression of BDNF and synaptophysin was up, and <i>Actinobacteria</i> and <i>Bacteroides</i> were increased in the intestinal microbiota.	[98]
	<i>Streptococcus</i> , <i>Bifidobacterium</i> , <i>Lactobacillus</i>	Mixed in MediGel®	0.32×10^9 CFU bacteria/25 g mice	2 months	6-8-months old female C57BL/6 wild-type and <i>App^{NL-G-F}</i> mice (n=15)	Both genotypes' serum concentrations of the SCFAs acetate, butyric acid, and lactic acid rose following treatment with VSL#3, and the c-Fos staining in the hippocampus of <i>App^{NL-G-F}</i> animals rose as well.	[99]
Lab4	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Sprinkled on standard laboratory food pellets	1×10^8 CFU/capsule per rat	2 months	15-months-old male Lister Hooded rats (N=14/13)	Lab4 improved the changes of metabolites such as GABA and glutamate in rats' brain and improved the long-term and short-term memory behavior of rats.	[100]
Lab4b	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Dissolved in forage	5×10^8 CFU/mouse/day	12 weeks	12-weeks old male 3xTg-AD mice (n=10)	The Lab4b group performed better in new object recognition tests, significantly improved the spinal density of hippocampal neurons, reduced brain and systemic inflammatory response, and regulated intestinal flora.	[127]
Lab4P	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Lyophilized powder	5×10^8 CFU/mouse/day	14 weeks	Male 3xTg-AD and C57BL/6 mice (n=18)	Probiotics had an anti-inflammatory impact, as shown by Lab4P, which significantly reduced the density of spinous process in hippocampal neurons and the disease-related decline in mRNA expression in hippocampal tissue. Lab4P metabolites also had a protective effect on nerve cells.	[128]
SLAB51	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Dissolved in water	200 billion bacteria/Kg/day	16 weeks	8-weeks old male 3xTg-AD mice (n=32)	SLAB51 significantly reduces OS in the brains of AD mice through activation of SIRT1-dependent mechanisms.	[101]
	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Dissolved in water	2×10^{11} CFU bacteria/kg/day	2 and 12 months	8-weeks old male 3xTg-AD mouse (n=24)	SLAB51 enhanced cognitive impairment, glucose absorption and metabolism, decreased Aβ build up and brain damage in 3xTg-AD mouse, and elevated plasma levels of neuroprotective intestinal hormones.	[102]
	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Dissolved in water	200 billion bacteria/kg/day	16 and 48 weeks	8-weeks old male 3xTg-AD and wild-type B6129SF2 mice (n=24)	SLAB51 boosted glucose absorption in 3xTg-AD mice by improving phosphorylated tau aggregates and memory function in the brain, and by restoring the expression levels of critical glucose transporters (GLUT3, GLUT1) and insulin-like growth factor receptor in the brain.	[111]
<i>Akkermansia muciniphila</i>	<i>Akkermansia</i>	Dissolved in PBS	200μL 5×10^9 CFU/mL/day	6 months	3-months old APP/PS1 mice (n=6/10)	<i>A. muciniphila</i> can effectively reduce the levels of fasting blood glucose and serum diamine oxidase in APP/PS1 mice, reduce the decrease of colonic mucous cells, improve the level of blood lipids and liver steatosis, promote the decrease of Aβ level in cerebral cortex and improve memory function.	[108]
	<i>Akkermansia</i>	Dissolved in PBS and 30 min at 70 °C	10μL 5×10^9 CFU/mL/day	6-7 months	6-7 months old wild-type zebrafish (n=100)	Pasteurized <i>A. muciniphila</i> significantly improved and prevented glycemic, body mass index and diabetic indicators in zebrafish with diabetes combined with AD and alleviated AD-related indicators and significantly improved memory, anxiety, aggression and socially preferred behaviors.	[110]
<i>Bifidobacterium breve</i> MCC1274	<i>Bifidobacterium</i>	Dissolved in normal saline	1×10^9 CFU/6.25 mg/200 μL saline/mouse/day	4 months	2-month-old C57BL/6J-AD mice (n=20)	<i>Bifidobacterium breve</i> MCC1274 alleviates AD-like pathology in WT mice by reducing the level of presenilin1 protein and phosphorylated tau protein, reducing the level of soluble Aβ 42 in hippocampus,	[105]

	<i>Bifidobacterium</i>	Dissolved in normal saline	0.2mL 1 × 10 ⁹ CFU/mouse/day	4 months	6-months old <i>App^{NL-G-F}</i> mice (n=26)	alleviating neuroinflammation and improving the level of synaptic protein. By raising the levels of a-disintegrin and metalloproteinase 10, <i>Bifidobacterium breve</i> MCC1274 can prevent cognitive decline and decrease Aβ deposition in the hippocampus. Additionally, it weakens the activation of microglia and stimulates the ERK/HIF-1 signal pathway, which lowers the mRNA expression of pro-inflammatory cytokines in brain tissue.	[129]
<i>Bifidobacterium breve</i> HNX26M4	<i>Bifidobacterium</i>	Dissolved in skimmed milk	1 × 10 ⁹ CFU/mouse/day	12weeks	16-weeks old male APPswe/PS1dE 9 mice (n=8)	<i>Bifidobacterium breve</i> HNX26M4 improved the function of the intestinal barrier, reduced neuroinflammation and synaptic dysfunction, improved the composition of the intestinal flora, and lessened the cognitive impairment in APP/PS1 mice.	[130]
<i>Bifidobacterium breve</i> A1	<i>Bifidobacterium</i>	Lyophilized capsule	2 × 10 ¹⁰ CFU/human/day	16 weeks	Mild cognition impairment patient (n=40)	The total score of RBANS in the <i>Bifidobacterium breve</i> A1 group was significantly higher than that in the placebo group, especially in the areas of immediate memory, visual space/structure and delayed memory.	[119]
	<i>Bifidobacterium</i>	Lyophilized powder containing cornstarch	2 × 10 ¹⁰ CFU/human/day	24 weeks	65-88-years old mild cognition impairment patient (n=55/60)	The MMSE's "orientation in time" and "writing" subscales significantly improved for the <i>Bifidobacterium breve</i> A1 group, and <i>Bifidobacterium breve</i> A1 also prevented the patient's brain from growing in an unfavorable way.	[120]
<i>Bifidobacterium breve</i> strain A1, non-viable components of the bacterium or its metabolite acetate	<i>Bifidobacterium</i>	Dissolved in normal saline, 30 min at 60 °C and sonicate treatment	0.2mL 1 × 10 ⁹ CFU/mL/day	6 days	10-week-old male ddY mice (n=11/12)	<i>Bifidobacterium breve</i> strain A1 reversed the impairment of alternating behavior in the Y-maze test and the reduction of delay time in the passive avoidance test, and the non-living component of the bacteria or its metabolite acetate partially ameliorated the cognitive decline in AD mice.	[104]
<i>Bifidobacterium breve</i> CCFM1025 and <i>Bifidobacterium breve</i> JSWX22M4	<i>Bifidobacterium</i>	Dissolved in skimmed milk	6 × 10 ⁸ CFU/mouse/day	6 weeks	8-weeks old male C57BL/6J mice (n=8)	<i>Bifidobacterium breve</i> CCFM1025 and <i>Bifidobacterium breve</i> JSWX22M4 treatment significantly improved synaptic plasticity and increased BDNF and fibronectin type III domain-containing protein 5, and postsynaptic density protein 95, thus delaying the pathological development of AD.	[131]
<i>Bifidobacterium longum</i>	<i>Bifidobacterium</i>	Dissolved in PBS	1 × 10 ⁹ CFU/mouse/day	4 and 8 weeks	6-months, 18-months old male C57BL/6 and 5×FAD-Tg mice (n=6)	<i>Bifidobacterium longum</i> changed the gut microbiota of 5×FAD-Tg and aged mice, decreased the level of LPS in feces and blood, inhibited the activation of NF-κB and the expression of TNF-α, increased the expression of tight junction protein in colon, and inhibited the expression of Aβ, β/γ-secretase, caspase-3 and Aβ accumulation in hippocampus.	[112]
<i>Bifidobacterium longum</i> BB68S	<i>Bifidobacterium</i>	Freeze-dried powder	1 × 10 ¹¹ CFU/human/day	8 weeks	healthy elder (n=30)	<i>Bifidobacterium longum</i> BB68S intervention increased the relative abundance of the beneficial bacteria <i>Lachnospira</i> , <i>Bifidobacterium</i> , <i>Dorea</i> , and <i>Cellulosilyticum</i> and decreased the relative abundance of bacteria associated with cognitive impairment such as <i>Collinsella</i> , <i>Tyzerella</i> and <i>Parabacteroides</i> .	[123]
<i>Bifidobacterium bifidum</i> BGN4 and <i>Bifidobacterium longum</i> BORI	<i>Bifidobacterium</i>	Dissolved in sterile water	1 × 10 ⁹ CFU/mouse/day	30 days	3-months old C57BL/6 and 5×FAD mice (n=10)	<i>Bifidobacterium bifidum</i> BGN4 and <i>Bifidobacterium longum</i> BORI effectively inhibited amyloidosis and apoptotic processes by improving neuroinflammatory responses and BDNF expression and ameliorated cognitive and memory deficits in AD mice.	[132]
	<i>Bifidobacterium</i>	Probiotics capsules containing soybean oil	1 × 10 ⁹ CFU/human/day	12 weeks	63-years old healthy elder (n=31)	The serum BDNF level was significantly higher in the <i>Bifidobacterium bifidum</i> BGN4 and <i>Bifidobacterium longum</i> BORI group compared to the placebo group, and both the psychological flexibility test and stress score improved.	[122]
<i>Bifidobacterium bifidum</i> , <i>Lactobacillus plantarum</i> and exercise	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Dissolved in water	2 × 10 ⁹ CFU/mouse/day	8 weeks	8-weeks old male Wistar rat (n=5)	The combination of <i>Bifidobacterium bifidum</i> , <i>Lactobacillus plantarum</i> and exercise significantly improved Aβ plaque deposition and reduced brain cell death in the brains of AD mice.	[133]
FRAMELIM® and exercise	<i>Bifidobacterium</i> , <i>Lactobacillus</i>	Direct feeding	120 mg/mouse/day	20 weeks	3-months old male APP/PS1 transgenic mice (n=32)	Exercise and FRAMELIM® supplementation significantly reduced the amount of Aβ in the hippocampus of APP/PS1 mice, improved cognitive level, and regulated intestinal flora imbalance.	[116]
<i>Bifidobacterium Lactis</i> Probio-M8	<i>Bifidobacterium</i>	Dissolved in normal saline	1 × 10 ⁹ CFU/mL Probio-M8 at the dose of 0.2 mL/10 g	45 days	4-months old APP/PS1 mice (n=11/12)	<i>Bifidobacterium Lactis</i> Probio-M8 can reduce the deposition of Aβ plaque in the whole brain, prevent the imbalance of intestinal flora, and alleviate the cognitive impairment of APP/PS1 mice.	[106]

			body weight				
<i>Bacillus coagulans</i> JA845	<i>Bacillus</i>	Dissolved in normal saline	1 × 10 ⁹ CFU/mouse/day	10 weeks	Male ICR mice (n=8)	By regulating NRF2/HO-1 and MyD88/TRAF6/NF-κB, <i>Bacillus coagulans</i> JA845 pretreatment can prevent cognitive decline, reduce hippocampal neuronal damage, protect neuronal integrity, reduce the deposition of A and excessive phosphorus of tau in the hippocampus of AD model mice, as well as OS and serum inflammatory cytokines.	[134]
<i>Lactobacillus acidophilus</i> , <i>Lactobacillus Fermentum</i> , <i>Bifidobacterium lactis</i> , and <i>Bifidobacterium longum</i>	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Dissolved in water	2g(1×10 ¹⁰ c fu/g)/day	8 weeks	8-weeks old male Wistar rat (n=12)	By changing the flora, probiotics reduce the levels of OS indicators in Male Wistar rats and significantly enhance behaviors like spatial memory.	[103]
<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium longum</i> and selenium	<i>Bifidobacterium</i>	Dissolved in water	2 × 10 ⁹ CFU/human/day	12 weeks	AD patient (n=26/27)	Patients in the probiotics supplemented selenium group by altered flora had significantly lower insulin, steady-state IR model, LDL and total/HDL-cholesterol, significantly higher total glutathione and quantitative insulin sensitivity assay indices, and total serum antioxidant capacity and glutathione levels were again increased in the probiotics plus selenium group compared to patients in the selenium supplemented group alone. Modulation of OS biomarker levels in Male Wistar rats and significant improvement in behaviors such as spatial memory were observed.	[117]
<i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Bifidobacterium bifidum</i> , and <i>Lactobacillus fermentum</i>	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Dissolved in milk	2 × 10 ⁹ CFU/g/200 mL/human/day	12 weeks	AD patient (n=30)	Plasma malondialdehyde, serum high-sensitivity C-reactive protein, beta-cell function, and serum triglyceride levels were significantly improved in patients treated with multiple probiotics, and there were significant differences in MMSE score results.	[118]
<i>Lactobacillus plantarum</i> DP189	<i>Lactobacillus</i>	Dissolved in normal saline	1 × 10 ⁹ CFU/mouse/day	10 weeks	8-weeks old male and female ICR mice (n=10)	By raising levels of 5-HT, dopamine, and GABA, <i>Lactobacillus plantarum</i> DP189 reduces Aβ deposition and neuronal damage, suppresses tau hyperphosphorylation by controlling the PI3K/AKT/GSK-3β pathway, and controls issues with intestinal microbiota.	[135]
<i>Lactobacillus plantarum</i> and memantine	<i>Lactobacillus</i>	Dissolved in PBS comprising 15% glycerol	5 × 10 ⁹ CFU/mL/mouse/day	12 weeks	8-weeks old male C57BL/6J, 6-months old male wild type and PrP-hAβPPswe/PS1 ^{E9} transgenic mice (n=15/30)	<i>Lactobacillus plantarum</i> and memantine treatment can improve cognitive deterioration, reduce the level of ββ in the hippocampus, protect the integrity and plasticity of neurons, and inhibit the synthesis of TMAO.	[115]
<i>Lactobacillus plantarum</i> MA2	<i>Lactobacillus</i>	Dissolved in normal saline	1 × 10 ⁸ and 1 × 10 ⁹ CFU/kg/day	12 weeks	6-weeks old SPF grade Wistar male rats (n=8)	<i>Lactobacillus plantarum</i> MA2 can improve the cognitive impairment and anxiety-like behavior of AD rats induced by D-Galactose/AIC3, reduce neuronal degeneration and Aβ accumulation in the brain, regulate gut microbiota imbalance, alleviate intestinal mucosal injury through TLR4/MYD88/NLRP3 signal pathway, and inhibit microglial activation and neuroinflammation.	[136]
<i>Lactobacillus plantarum</i> NK151 and <i>Bifidobacterium longum</i> NK173	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Supernatant after centrifugation	1 × 10 ⁹ CFU/mouse/day	5 days	6-weeks old male C57BL/6 mice (n=7)	The behavioral and cognitive damage brought on by <i>Escherichia coli</i> K1 can be considerably reduced by <i>Lactobacillus plantarum</i> NK151 and <i>Bifidobacterium longum</i> NK173, and the amount of neuroinflammatory markers in the hippocampus can also be decreased.	[137]
<i>Lactobacillus plantarum</i> , <i>Bifidobacterium bifidum</i> and interval training		Dissolved in water	1mL 1 × 10 ⁹ CFU/mouse/day	8 weeks	Male Wistar rat (n=8)	<i>Lactobacillus plantarum</i> , <i>Bifidobacterium bifidum</i> and interval training groups of mice showed significantly improved hippocampal cell destruction, neuronal degeneration and short-term memory, and significantly higher BDNF mRNA levels.	[138]
<i>Lactobacillus pentosus</i> var. <i>plantarum</i> C29	<i>Lactobacillus</i>	50 mM sodium bicarbonate buffer containing 1% glucose	1 × 10 ¹⁰ CFU/mouse/day	5 weeks	20-weeks old male C57BL/6J mice	<i>Lactobacillus pentosus</i> var. <i>plantarum</i> C29 ameliorated D-galactose-induced memory impairment, reversed the inhibition of BDNF and doublecortin expression and cAMP response element-binding protein activation, and reduced the inhibition of aging p16 and inflammatory markers p-p65, p-FOXO3a, cyclooxygenase (COX)-2 and inducible NO synthase (iNOS).	[139]

<i>Lactobacillus rhamnosus</i> HA-114 or <i>Bifidobacterium longum</i> R0175	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Probiotics capsule	1×10^{15} CFU/human/day	12 weeks	AD patient (n=45)	<i>Lactobacillus rhamnosus</i> HA-114 or <i>Bifidobacterium longum</i> R0175 significantly improved the MMSE score of patients.	[121]
<i>Lactobacillus rhamnosus</i> UBLR-58 and curcumin	<i>Lactobacillus</i>	Supernatant after centrifugation	1×10^6 CFU/mouse/day	10 days	Scopolamine-induced albino female mice (n=6)	as combined with <i>Lactobacillus rhamnosus</i> UBLR-58, curcumin considerably boosted the amount of antioxidant enzymes, reduced neuronal damage, and significantly enhanced memory and cognitive skills as compared to the curcumin group alone.	[140]
<i>Lactobacillus fermentum</i> LAB9 or <i>Lactobacillus fermentum</i> LABPC	<i>Lactobacillus</i>	Dissolved in normal saline	0.2mL 1×10^9 CFU/mouse/day	28 days	2-months old male ICR mice (n=6)	<i>Lactobacillus fermentum</i> LAB9 or <i>Lactobacillus fermentum</i> LABPC attenuated LPS-induced memory impairment in mice, increased the level of antioxidants and decreased the levels of MDA, AChE and proinflammatory cytokines.	[141]
<i>Lactobacillus helveticus</i> R0052 and <i>Bifidobacterium longum</i> R0175	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Dissolved in normal saline or distilled water	1×10^9 CFU/mouse/day	14 days	Male Wistar rat (n=10)	<i>Lactobacillus helveticus</i> R0052 and <i>Bifidobacterium longum</i> R0175 significantly improved the level of pro-inflammatory cytokines in hippocampus induced by LPS and alleviated the memory damage induced by LPS by up-regulating the expression of BDNF.	[142]
<i>Agathobaculum butyriciproducens</i>	<i>Agathobaculum</i>	Dissolved in PBS	2×10^8 CFU/mouse/day	10 weeks	8-weeks old Tg-APPswe/PS1dE9 and C57BL/6J mice	A β deposition and microglia activation in the parietal cortex and hippocampus of APP/PS1 mice were significantly reduced after treatment with <i>Agathobaculum butyriciproducens</i> , and IL-1 and C1QB gene expression levels in the cerebral cortex were decreased while the gene expression levels of downstream signal pathways were up-regulated. Controlling neuroinflammation and the IGF-1 signal in the animal model enhanced cognitive function.	[143]
<i>Clostridium butyricum</i> or butyrate	<i>Clostridium</i>	Dissolved in phosphate-buffered saline (PBS)	200 μ L 1×10^9 CFU/mL/day	4 weeks	6-months old APPswe/PS1dE9 mice (n=10)	Treatment with <i>Clostridium butyricum</i> could stop TNF- α , A β deposition, microglial activation, and cognitive impairment in the brains of APP/PS1 mice. In BV-2 microglia that had been activated by A, butyrate therapy reduced CD11b and COX-2 levels and prevented the phosphorylation of NF- κ B p65.	[107]
ProBiotic-4	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Direct feeding	2×10^9 CFU/mouse/day	12 weeks	9-months old male SAMP8 mice (n=12)	ProBiotic-4 significantly improved memory deficits, brain neuronal and synaptic damage, glial activation, and microbiota composition in feces and brain in aged SAMP8 mice, and significantly attenuated aging-related disruption of the intestinal and BBB, reduced IL-6 and TNF- α mRNA and protein levels, and decreased plasma and brain LPS concentrations, TLR4 expression, and brain NF- κ B nuclear translocation.	[113]
Human <i>Lactobacillaceae</i>	<i>Lactobacillus</i>	Lyophilized powder	1×10^9 CFU/mouse/day	12 weeks	APPswe/PS1dE9 mice (n=12)	Human <i>Lactobacillaceae</i> significantly reduced the expression of A β plaques, tau phosphorylation and neuroinflammation in the hippocampal region of the mouse brain, increased GSH-PX activity in the brain, decreased the expression levels of IL-6 and MDA, as well as increased the abundance of beneficial bacteria in the gut, inhibited pathogenic bacteria and improved cognitive function in mice.	[144]
p62 (SQSTM1)-engineered lactic acid Bacteria (p62-LAB)	<i>Lactobacillus</i>	Genetic engineering treatment and dissolved in pasteurized skimmed milk	1×10^9 CFU live p62-LAB/mouse/day	2 months	8-weeks old 3xTg-AD mice (n=8)	P62-LAB improved the memory function of 3xTg-AD mice, showing the regulation of ubiquitin-proteasome system and autophagy, the decrease of amyloid peptide level, and the decrease of neuronal oxidation and inflammation.	[114]
MG136-pMG36e-GLP-1	<i>Lactobacillus</i>	Genetic engineering treatment and dissolved in water	1×10^9 CFU/mouse/day	7 days	Male C57BL/6 mice (n=12)	Through TLR4/NF κ B and AKT/ glycogen synthase kinase 3 β (GSK-3 β) signal pathways, MG136-pMG36eGLP-1 could significantly reduce the memory impairment induced by LPS and motor dysfunction induced by LPS. It also decreased the abundance of pathogens <i>Enterococcus</i> and <i>Proteus</i> and increased the abundance of probiotics <i>A. muciniphila</i> .	[145]

3.2 Prebiotics

According to the International Scientific Association for Probiotics and Prebiotics, prebiotics are defined as food ingredients that are capable of being utilized by the host microbiota and exert positive effects on human health

[146]. Prebiotics, on the other hand, have been employed as supplementary treatments for neurological and psychiatric disorders, including depression, PD, and autism, due to their demonstrated ability to substantially enhance the abundance of beneficial bacteria, such as *Bifidobacteria* and *Lactobacilli*, within the gut microbiota

(Fig. 5) [147, 148]. A recent study suggests that prebiotics may have a comparable impact on the prevention and treatment of AD. The study on prebiotics therapy in AD mice found that yeast beta-glucan effectively enhanced the abundance of both pro- and anti-inflammatory bacteria in the gut microbiota, elevated the production of SCFAs, and mitigated neuroinflammation and brain IR [149]. Mannan oligosaccharides have been observed to exhibit comparable effects, including the regulation of intestinal microbiota, enhanced synthesis of SCFAs, improved cognitive abilities, memory function and spatial memory, reduced accumulation of A β in the cerebral cortex, hippocampus, and amygdala, as well as substantial mitigation of neuroinflammatory responses and notable adjustment of brain redox equilibrium [150]. Moreover, it has been demonstrated that lactulose enhances cognitive function in AD mice via autophagic and anti-inflammatory pathways [151]. In rat and mouse models of AD, oligosaccharides from *Morinda officinalis* have been shown to have similar efficacy with improved memory and learning functions and reduced A β plaque formation, OS, and overall inflammation levels [152, 153]. In human studies, a study of 1837 healthy older persons without signs of neurodegeneration revealed that daily use of fructans dramatically decreased the risk of acquiring AD [154]. The data supporting the use of prebiotics in clinical practice, even if this study was standardized for subject age, sex, race, daily calorie consumption, education, and ApoE genes, nevertheless lacks validity [155].

In conclusion, although probiotics have demonstrated in mice that they may help in the treatment and prevention of AD, clinical trial data and standardized implementation strategies are still lacking.

3.3 FMT

The administration of a treated solution of healthy human feces, known as FMT, is a method employed to restore the gut microbiota and treat illnesses. Currently, FMT has proven effective in treating *Clostridium difficile* infections [156]. However, trials investigating the potential benefits of FMT in neurodegenerative, inflammatory bowel, and metabolic disorders are still in the preclinical stage and lack clinical trial data. Although these preliminary findings are promising, further research is required to draw definitive conclusions (Fig. 5).

Following the introduction of FMT from healthy mice to AD mice, a decline in neurogenesis and expression of BDNF in the adult hippocampus was observed, accompanied by an increase in p21 expression, deposition of A β plaques, and the onset of memory impairment. Furthermore, activation of hippocampal microglia and heightened expression of pro-inflammatory cytokines observed in the mice [157, 158]. Sterile APP transgenic

mice exhibited significantly lower levels of A β protein in their brains compared to non-aseptic APP transgenic mice within the aseptic animal model [159]. Similarly, after treatment of GF mice with SAMR1 from anti-aging mice versus SAMP8 FMT from non-aging mice, mice in the SAMR1-treated group exhibited improved behavior and indices of gut microbial α -diversity and β -diversity [160]. In human FMT trials, GF mice were transplanted with FMT from both healthy volunteers and patients with cognitive impairments, leading to notably inferior performance in object localization and object recognition tests, as well as had significantly reduced levels of GABA, taurine, and valine in their fecal samples compared to the donors [161]. The results of the study on the treatment of AD mice with FMT demonstrate the significance of gut microbiota in the pathogenesis process and progression of neurodegenerative diseases such as AD. The administration of FMT resulted in improvements in A β deposition, neurogenic fiber tangles, neuroglial cell reactivity, and cognitive deficits in the brains of AD mice. Additionally, FMT reversed abnormal intestinal macrophage activity and abnormal expression of circulating blood inflammatory monocyte-related genes in the colon [162]. Another study conducted on mice with AD that were treated with FMT observed a reversal in the alterations of gut microbiota and SCFAs, as well as a decrease in COX-2 and CD11b levels. Furthermore, there was a reduction in the accumulation of A β and Tau proteins in the brain, an increase in synaptic plasticity, and a reversal of the changes in gut microbiota and SCFAs [163]. Similarly, Dodiya et al. reached a comparable conclusion and identified changes in the functionality of microglia due to FMT [164]. Furthermore, clinical studies have yielded noteworthy findings alongside animal models. Notably, patients diagnosed with AD exhibited a notable amelioration in gut microbiota and a substantial enhancement in SCFAs levels subsequent to undergoing FMT treatment [165]. These outcomes suggest a significant potential for the application of FMT in the therapeutic management of AD. In conclusion, despite the evidence provided by FMT regarding the significant involvement of gut microbiota in the initiation and progression of neurodegenerative diseases like AD in mice, the current body of clinical experimental data and standardized implementation procedures remains insufficient.

4. Conclusion and perspectives

In the context of treating AD, probiotics, prebiotics and FMT exhibit fewer adverse effects, relatively higher safety profiles, and non-addictive properties compared to alternative therapies. These interventions have the potential to enhance composition of intestinal

microorganisms, augment the abundance of beneficial microflora, diminish the presence of detrimental bacteria, mitigate intestinal inflammation, and enhance the functionality of the intestinal mucosal barrier. Nevertheless, drug therapy fails to attain this outcome due to its numerous adverse reactions, high addictive potential, and inadequate safety. Conversely, probiotics, prebiotics, and FMT can effectively modulate the levels of SCFAs and NT within the intestinal tract. Consequently, these interventions alleviate the cognitive impairment associated with AD and enhance brain pathology through diverse mechanisms.

The augmentation of intestinal microbiota diversity and abundance through the administration of probiotics therapy or supplements has the potential to improve intestinal health, thereby exerting a therapeutic influence on various diseases, such as AD. There are still certain flaws and drawbacks, though: (I) The lack of adequate, high-quality, multicenter clinical research evidence demonstrating the efficacy of probiotics therapy or supplements in the treatment of AD. (II) The optimal type and dosage of probiotics for treating AD remain uncertain, as do the specific symptoms and pathological stages exhibited by different AD patients. Furthermore, the absence of a standardized implementation strategy further complicates the identification of the most suitable probiotic strain or combination for effective treatment of Alzheimer's. (III) Although probiotics therapy and supplements have been shown to potentially benefit individuals with AD, the precise mechanism underlying their efficacy remains uncertain, necessitating further investigation to elucidate this phenomenon. (IV) Patient survival time and survival rate. There is no concrete proof that probiotics therapy or supplements can increase the survival time of patients with AD or lower their mortality, despite the fact that numerous studies have shown that intestinal flora and pathological traits of AD patients are significantly improved after probiotics treatment. (v) It is imperative to prioritize the monitoring of side effects and safety concerns, particularly individuals with AD concurrently experiencing other disorders. The administration of probiotic therapy or supplements may potentially yield diverse adverse effects, including but not limited to diarrhea, abdominal pain, and flatulence. (VI) Acid-base intolerance. Probiotics often develop in the digestive system. In order to effectively survive and carry out their intended functions within the intestinal system, probiotics necessitate a specific degree of tolerance towards both acidic and alkaline conditions. This is imperative as they undergo digestion by stomach acid and bile upon entry into the gastrointestinal tract. Furthermore, prebiotics pose similar challenges as probiotics in terms of their impact on drug absorption, as they have the potential to alter intestinal pH and disrupt

intestinal barrier function. Consequently, this can diminish the effectiveness of certain medications or result in unfavorable reactions. Hence, it is imperative to undertake meticulous multicenter clinical research, investigate the precise mechanisms underlying probiotics and prebiotics, and consider long-term biocompatibility. Moreover, the utilization of appropriate technical approaches or drug delivery systems is necessary to enhance the bioavailability and efficacy of prebiotics. To enhance the acid and alkali resistance of prebiotics supplements, researchers employed various technical approaches, including microencapsulation and coating to envelop probiotics within a protective layer. This technique effectively augments the strain's survival rate in gastric acid and bile, thereby enhancing its bioavailability and efficacy. Nevertheless, the utilization of these methods in prebiotics therapy for patients with AD remains scarcely documented.

Intestinal illnesses are treated using FMT, which has been the subject of extensive research. FMT has drawn attention in recent years as a potential treatment for AD, although there is currently little research being done in this area and many flaws and shortcomings. The selection of donors and the composition of intestinal flora of donors are very important to the effect of FMT. The diversity and individual variations of gut flora, however, it is not easy to select a suitable donor, which may affect the efficacy of FMT. The safety concerns associated with FMT encompass infectious diseases and immune-related reactions, patients with AD commonly present with comorbidities and diverse pharmacological interventions, which can potentially give rise to severe adverse reactions. Consequently, a more comprehensive assessment and surveillance of FMT's safety profile is imperative. The absence of established protocols for FMT poses challenges in replicating findings from previous studies and comparing results across different clinical investigations. The lack of a standardized FMT methodology for AD may lead to variations in procedures and dosages employed, potentially influencing the efficacy and safety of FMT interventions. FMT also involves the topic of allogeneic and xenogeneic transplantation. Allogeneic transplantation can lead to intestinal immune rejection, graft failure, or adverse reactions due to inter-individual variations in gut microbial communities. Consequently, allogeneic transplantation exhibits a superior success rate compared to xenogeneic transplantation.

To sum up, probiotics, prebiotics and FMT are relatively safe, effective, with few side effects, and can regulate systemic and brain metabolism from bottom to top to improve the pathology of AD. Probiotics and FMT are both utilized in varying degrees, with probiotics being more prevalent. Furthermore, the therapeutic efficacy of

probiotics appears to be superior. Considering the potential involvement of intestinal flora in AD progression and its potential influence on AD treatment, forthcoming research endeavors will ascertain the modulation of gut microbiota and its integration with other therapeutic interventions for AD patients, aiming to enhance the overall therapeutic outcome.

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Author contributions

Conceptualization, D.S., Q.Y. and W.W.; writing-original draft preparation, L.Q., Y.L., F.L., Y.F. and J.H.; writing-review and editing, J.M., T.X., L.W., P.L. and H.D.; visualization, L.J. and L.Q.; supervision, D.S. and Q.Y.; funding acquisition, D.S. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

References

- [1] Wimo A, Guerchet M, Ali G, Wu Y, Prina AM, Winblad B, et al. (2017). The worldwide costs of dementia 2015 and comparisons with 2010. *Alzheimer's & Dementia*, 13:1–7.
- [2] Braak H, Braak E (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*, 82:239–259.
- [3] Alzheimer's Association (2019). 2019 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 15:321–387.
- [4] Hampel H, Blennow K, Shaw LM, Hoessler YC, Zetterberg H, Trojanowski JQ (2010). Total and phosphorylated tau protein as biological markers of Alzheimer's disease. *Experimental Gerontology*, 45:30–40.
- [5] Reitz C (2012). Alzheimer's Disease and the Amyloid Cascade Hypothesis: A Critical Review. *International Journal of Alzheimer's Disease*, 2012:1–11.
- [6] Mucke L, Selkoe DJ (2012). Neurotoxicity of Amyloid -Protein: Synaptic and Network Dysfunction. *Cold Spring Harbor Perspectives in Medicine*, 2:a006338–a006338.
- [7] Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health*, 7:e105–e125.
- [8] Silva MVF, Loures C de MG, Alves LCV, de Souza LC, Borges KBG, Carvalho M das G (2019). Alzheimer's disease: risk factors and potentially protective measures. *J Biomed Sci*, 26:33.
- [9] Doifode T, Giridharan VV, Generoso JS, Bhatti G, Collodel A, Schulz PE, et al. (2021). The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. *Pharmacological Research*, 164:105314.
- [10] Stolfi C, Maresca C, Monteleone G, Laudisi F (2022). Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases. *Biomedicine*, 10:289.
- [11] Angelucci F, Cechova K, Amlerova J, Hort J (2019). Antibiotics, gut microbiota, and Alzheimer's disease. *J Neuroinflammation*, 16:108.
- [12] Stiemsma LT, Michels KB (2018). The Role of the Microbiome in the Developmental Origins of Health and Disease. *Pediatrics*, 141:e20172437.
- [13] Schoenmakers S, Steegers-Theunissen R, Faas M (2019). The matter of the reproductive microbiome. *Obstet Med*, 12:107–115.
- [14] Dunn AB, Jordan S, Baker BJ, Carlson NS (2017). The Maternal Infant Microbiome: Considerations for Labor and Birth. doi: 10.1097/NMC.0000000000000373.
- [15] Tribe RM, Taylor PD, Kelly NM, Rees D, Sandall J, Kennedy HP (2018). Parturition and the perinatal period: can mode of delivery impact on the future health of the neonate?: Mode of delivery and future health. *J Physiol*, 596:5709–5722.
- [16] Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaansen TFS, Boehme M, et al. (2019). The Microbiota-Gut-Brain Axis. *Physiological Reviews*, 99:1877–2013.
- [17] Wang H-X, Wang Y-P (2016). Gut Microbiota-brain Axis. *Chinese Medical Journal*, 129:2373–2380.
- [18] Lynch SV, Pedersen O (2016). The Human Intestinal Microbiome in Health and Disease. *N Engl J Med*, 375:2369–2379.
- [19] Kaelberer MM, Buchanan KL, Klein ME, Barth BB, Montoya MM, Shen X, et al. (2018). A gut-brain neural circuit for nutrient sensory transduction. *Science*, 361:eaat5236.
- [20] Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F (2008). Allergy and the gastrointestinal system. *Clinical and Experimental Immunology*, 153:3–6.
- [21] Al Bander Z, Nitert MD, Mousa A, Naderpoor N (2020). The Gut Microbiota and Inflammation: An Overview. *IJERPH*, 17:7618.
- [22] Sampson TR, Mazmanian SK (2015). Control of Brain Development, Function, and Behavior by the Microbiome. *Cell Host & Microbe*, 17:565–576.
- [23] Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S (2017). Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. *Cell Mol Life Sci*, 74:3769–3787.
- [24] de J.R. De-Paula V, Forlenza AS, Forlenza OV (2018). Relevance of gutmicrobiota in cognition, behaviour and Alzheimer's disease. *Pharmacological Research*, 136:29–34.

- [25] Wang J, Gu BJ, Masters CL, Wang Y-J (2017). A systemic view of Alzheimer disease — insights from amyloid- β metabolism beyond the brain. *Nat Rev Neurol*, 13:612–623.
- [26] Schoeler M, Caesar R (2019). Dietary lipids, gut microbiota and lipid metabolism. *Rev Endocr Metab Disord*, 20:461–472.
- [27] Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. (2021). The Amyloid- β Pathway in Alzheimer's Disease. *Mol Psychiatry*, 26:5481–5503.
- [28] Laurent C, Buée L, Blum D (2018). Tau and neuroinflammation: What impact for Alzheimer's Disease and Tauopathies? *Biomedical Journal*, 41:21–33.
- [29] Bronzuoli MR, Iacomino A, Steardo L, Scuderi C (2016). Targeting neuroinflammation in Alzheimer's disease. *JIR*, Volume 9:199–208.
- [30] Hickman S, Izzy S, Sen P, Morsett L, El Khoury J (2018). Microglia in neurodegeneration. *Nat Neurosci*, 21:1359–1369.
- [31] Kwon HS (2020). Neuroinflammation in neurodegenerative disorders: the roles of microglia and astrocytes. .
- [32] Natale G, Biagioni F, Busceti CL, Gambardella S, Limanaqi F, Fornai F (2019). TREM Receptors Connecting Bowel Inflammation to Neurodegenerative Disorders. *Cells*, 8:1124.
- [33] Qian X (2021). Inflammatory pathways in Alzheimer's disease mediated by gut microbiota. *Ageing Research Reviews*.
- [34] Fischer A (2014). Targeting histone-modifications in Alzheimer's disease. What is the evidence that this is a promising therapeutic avenue? *Neuropharmacology*, 80:95–102.
- [35] Haberland M, Montgomery RL, Olson EN (2009). The many roles of histone deacetylases in development and physiology: implications for disease and therapy. *Nat Rev Genet*, 10:32–42.
- [36] Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L (2014). The Role of Short-Chain Fatty Acids in Health and Disease. *Advances in Immunology*. Elsevier, 91–119.
- [37] Govindarajan N, Agis-Balboa RC, Walter J, Sananbenesi F, Fischer A (2011). Sodium Butyrate Improves Memory Function in an Alzheimer's Disease Mouse Model When Administered at an Advanced Stage of Disease Progression. *JAD*, 26:187–197.
- [38] Barichello T, Generoso JS, Simões LR, Faller CJ, Ceretta RA, Petronilho F, et al. (2015). Sodium Butyrate Prevents Memory Impairment by Re-establishing BDNF and GDNF Expression in Experimental Pneumococcal Meningitis. *Mol Neurobiol*, 52:734–740.
- [39] Lee H, Son Y, Lee M, Moon C, Kim S, Shin I, et al. (2019). Sodium butyrate prevents radiation-induced cognitive impairment by restoring pCREB/BDNF expression. *Neural Regen Res*, 14:1530.
- [40] Jiang Y, Li K, Li X, Xu L, Yang Z (2021). Sodium butyrate ameliorates the impairment of synaptic plasticity by inhibiting the neuroinflammation in 5XFAD mice. *Chemico-Biological Interactions*, 341:109452.
- [41] Saw G, Krishna K, Gupta N, Soong TW, Mallilankaraman K, Sajikumar S, et al. (2020). Epigenetic regulation of microglial phosphatidylinositol 3-kinase pathway involved in long-term potentiation and synaptic plasticity in rats. *Glia*, 68:656–669.
- [42] Shi L, Tu BP (2015). Acetyl-CoA and the regulation of metabolism: mechanisms and consequences. *Current Opinion in Cell Biology*, 33:125–131.
- [43] Soliman ML, Puig KL, Combs CK, Rosenberger TA (2012). Acetate reduces microglia inflammatory signaling *in vitro*. *J Neurochem*, 123:555–567.
- [44] Fernando WMADB, Martins IJ, Morici M, Bharadwaj P, Rainey-Smith SR, Lim WLF, et al. (2020). 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. *JAD*, 74:91–99.
- [45] Zhang H, Wei W, Zhao M, Ma L, Jiang X, Pei H, et al. (2021). Interaction between A β and Tau in the Pathogenesis of Alzheimer's Disease. *Int J Biol Sci*, 17:2181–2192.
- [46] Sun J, Yuan B, Wu Y, Gong Y, Guo W, Fu S, et al. (2020). Sodium Butyrate Protects N2a Cells against A β Toxicity In Vitro. *Mediators of Inflammation*, 2020:1–9.
- [47] Filippone A, Lanza M, Campolo M, Casili G, Paterniti I, Cuzzocrea S, et al. (2020). Protective effect of sodium propionate in A β 1-42 -induced neurotoxicity and spinal cord trauma. *Neuropharmacology*, 166:107977.
- [48] Cao T, Zhou X, Zheng X, Cui Y, Tsien JZ, Li C, et al. (2018). Histone Deacetylase Inhibitor Alleviates the Neurodegenerative Phenotypes and Histone Dysregulation in Presenilins-Deficient Mice. *Front Aging Neurosci*, 10:137.
- [49] Liu J, Li H, Gong T, Chen W, Mao S, Kong Y, et al. (2020). Anti-neuroinflammatory Effect of Short-Chain Fatty Acid Acetate against Alzheimer's Disease via Upregulating GPR41 and Inhibiting ERK/JNK/NF- κ B. *J Agric Food Chem*, 68:7152–7161.
- [50] Wenzel TJ, Gates EJ, Ranger AL, Klegeris A (2020). Short-chain fatty acids (SCFAs) alone or in combination regulate select immune functions of microglia-like cells. *Molecular and Cellular Neuroscience*, 105:103493.
- [51] Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. (2015). Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci*, 18:965–977.
- [52] Li J-M, Yu R, Zhang L-P, Wen S-Y, Wang S-J, Zhang X-Y, et al. (2019). Dietary fructose-induced gut dysbiosis promotes mouse hippocampal neuroinflammation: a benefit of short-chain fatty acids. *Microbiome*, 7:98.
- [53] Braniste V, Al-Asmakh M, Kowal C, Anuar F, Abbaspour A, Tóth M, et al. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med*. doi: 10.1126/scitranslmed.3009759.

- [54] Li H, Sun J, Wang F, Ding G, Chen W, Fang R, et al. (2016). Sodium butyrate exerts neuroprotective effects by restoring the blood-brain barrier in traumatic brain injury mice. *Brain Research*, 1642:70–78.
- [55] Wen J, Ding Y, Wang L, Xiao Y (2020). Gut microbiome improves postoperative cognitive function by decreasing permeability of the blood-brain barrier in aged mice. *Brain Research Bulletin*, 164:249–256.
- [56] Yang W, Yu T, Huang X, Bilotta AJ, Xu L, Lu Y, et al. (2020). Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. *Nat Commun*, 11:4457.
- [57] Rosser EC, Piper CJM, Matei DE, Blair PA, Rendeiro AF, Orford M, et al. (2020). Microbiota-Derived Metabolites Suppress Arthritis by Amplifying Aryl-Hydrocarbon Receptor Activation in Regulatory B Cells. *Cell Metabolism*, 31:837–851.e10.
- [58] Engdahl E, van Schijndel MDM, Voulgaris D, Di Criscio M, Ramsbottom KA, Rigden DJ, et al. (2021). Bisphenol A Inhibits the Transporter Function of the Blood-Brain Barrier by Directly Interacting with the ABC Transporter Breast Cancer Resistance Protein (BCRP). *IJMS*, 22:5534.
- [59] Koopman N, Katsavelis D, Ten Hove A, Brul S, de Jonge W, Seppen J (2021). The Multifaceted Role of Serotonin in Intestinal Homeostasis. *IJMS*, 22:9487.
- [60] Strandwitz P (2018). Neurotransmitter modulation by the gut microbiota. *Brain Research*, 1693:128–133.
- [61] D'Alessandro G, Lauro C, Quaglio D, Ghirga F, Botta B, Trettel F, et al. (2021). Neuro-Signals from Gut Microbiota: Perspectives for Brain Glioma. *Cancers*, 13:2810.
- [62] Singh D, Singh P, Srivastava P, Kakkar D, Pathak M, Tiwari AK (2023). Development and challenges in the discovery of 5-HT1A and 5-HT7 receptor ligands. *Bioorganic Chemistry*, 131:106254.
- [63] Akagbosu CO, Evans GC, Gulick D, Suckow RF, Bucci DJ (2012). Exposure to Kynurenic Acid During Adolescence Produces Memory Deficits in Adulthood. *Schizophrenia Bulletin*, 38:769–778.
- [64] Prévot T, Sibille E (2021). Altered GABA-mediated information processing and cognitive dysfunctions in depression and other brain disorders. *Mol Psychiatry*, 26:151–167.
- [65] Piermartiri T, Pan H, Figueiredo T, Marini A (2015). α -Linolenic Acid, A Nutraceutical with Pleiotropic Properties That Targets Endogenous Neuroprotective Pathways to Protect against Organophosphate Nerve Agent-Induced Neuropathology. *Molecules*, 20:20355–20380.
- [66] Omeragic A, Kayode O, Hoque MT, Bendayan R (2020). Potential pharmacological approaches for the treatment of HIV-1 associated neurocognitive disorders. *Fluids Barriers CNS*, 17:42.
- [67] Frost G, Sleeth ML, Sahuri-Arisoylu M, Lizarbe B, Cerdan S, Brody L, et al. (2014). The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat Commun*, 5:3611.
- [68] Han H, Yi B, Zhong R, Wang M, Zhang S, Ma J, et al. (2021). From gut microbiota to host appetite: gut microbiota-derived metabolites as key regulators. *Microbiome*, 9:162.
- [69] Schmidt MJ, Mirnics K (2015). Neurodevelopment, GABA System Dysfunction, and Schizophrenia. *Neuropsychopharmacol*, 40:190–206.
- [70] Hnilicová P, Štrbák O, Kolisek M, Kurča E, Zelenák K, Sivák Š, et al. (2020). Current Methods of Magnetic Resonance for Noninvasive Assessment of Molecular Aspects of Pathoetiology in Multiple Sclerosis. *IJMS*, 21:6117.
- [71] Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, Levering J, et al. (2018). GABA-modulating bacteria of the human gut microbiota. *Nat Microbiol*, 4:396–403.
- [72] Ekundayo TC, Olasehinde TA, Okaiyeto K, Okoh AI (2021). Microbial Pathogenesis and Pathophysiology of Alzheimer's Disease: A Systematic Assessment of Microorganisms' Implications in the Neurodegenerative Disease. *Front Neurosci*, 15:648484.
- [73] Picciotto MR, Higley MJ, Mineur YS (2012). Acetylcholine as a Neuromodulator: Cholinergic Signaling Shapes Nervous System Function and Behavior. *Neuron*, 76:116–129.
- [74] Roy J, Tsui KC, Ng J, Fung M-L, Lim LW (2021). Regulation of Melatonin and Neurotransmission in Alzheimer's Disease. *IJMS*, 22:6841.
- [75] Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG (2014). Minireview: Gut Microbiota: The Neglected Endocrine Organ. *Molecular Endocrinology*, 28:1221–1238.
- [76] Horiuchi Y, Kimura R, Kato N, Fujii T, Seki M, Endo T, et al. (2003). Evolutional study on acetylcholine expression. *Life Sciences*, 72:1745–1756.
- [77] Inazu M (2019). Functional Expression of Choline Transporters in the Blood-Brain Barrier. *Nutrients*, 11:2265.
- [78] Liu C, Goel P, Kaeser PS (2021). Spatial and temporal scales of dopamine transmission. *Nat Rev Neurosci*, 22:345–358.
- [79] González-Arancibia C, Urrutia-Piñones J, Illanes-González J, Martínez-Pinto J, Sotomayor-Zárate R, Julio-Pieper M, et al. (2019). Do your gut microbes affect your brain dopamine? *Psychopharmacology*, 236:1611–1622.
- [80] Williams BB, Van Benschoten AH, Cimerancic P, Donia MS, Zimmermann M, Taketani M, et al. (2014). Discovery and Characterization of Gut Microbiota Decarboxylases that Can Produce the Neurotransmitter Tryptamine. *Cell Host & Microbe*, 16:495–503.
- [81] Eisenhofer G, Åneman A, Friberg P, Hooper D, Fändriks L, Lonroth H, et al. (1997). Substantial Production of Dopamine in the Human Gastrointestinal Tract. 82:.
- [82] Camilleri M (2013). Pharmacological agents currently in clinical trials for disorders in neurogastroenterology. *J Clin Invest*, 123:4111–4120.
- [83] Crispino M, Volpicelli F, Perrone-Capano C (2020). Role of the Serotonin Receptor 7 in Brain Plasticity: From Development to Disease. *IJMS*, 21:505.

- [84] Luqman A, Nega M, Nguyen M-T, Ebner P, Götz F (2018). SadA-Expressing Staphylococci in the Human Gut Show Increased Cell Adherence and Internalization. *Cell Reports*, 22:535–545.
- [85] Jayasimhan A, Mariño E (2019). Dietary SCFAs, IL-22, and GFAP: The Three Musketeers in the Gut–Neuro–Immune Network in Type 1 Diabetes. *Front Immunol*, 10:2429.
- [86] Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al. (2015). Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. *Cell*, 161:264–276.
- [87] Reigstad CS, Salmonson CE, Iii JFR, Szurszewski JH, Linden DR, Sonnenburg JL, et al. (2015). Gut microbes promote colonic serotonin production through an effect of short-chain fatty acids on enterochromaffin cells. *FASEB j*, 29:1395–1403.
- [88] Lilly DM, Stillwell RH (1965). Probiotics: Growth-Promoting Factors Produced by Microorganisms. *Science*, 147:747–748.
- [89] Lu Y, Yuan X, Wang M, He Z, Li H, Wang J, et al. (2022). Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. *J Hematol Oncol*, 15:47.
- [90] de Vos WM, Tilg H, Van Hul M, Cani PD (2022). Gut microbiome and health: mechanistic insights. *Gut*, 71:1020–1032.
- [91] Fang Z, Li L, Zhang H, Zhao J, Lu W, Chen W (2021). Gut Microbiota, Probiotics, and Their Interactions in Prevention and Treatment of Atopic Dermatitis: A Review. *Front Immunol*, 12:720393.
- [92] Park DH, Kim JW, Park H-J, Hahn D-H (2021). Comparative Analysis of the Microbiome across the Gut–Skin Axis in Atopic Dermatitis. *IJMS*, 22:4228.
- [93] Carranza-Naval MJ, Vargas-Soria M, Hierro-Bujalance C, Baena-Nieto G, Garcia-Alloza M, Infante-Garcia C, et al. (2021). Alzheimer’s Disease and Diabetes: Role of Diet, Microbiota and Inflammation in Preclinical Models. *Biomolecules*, 11:262.
- [94] Zhou B, Yuan Y, Zhang S, Guo C, Li X, Li G, et al. (2020). Intestinal Flora and Disease Mutually Shape the Regional Immune System in the Intestinal Tract. *Front Immunol*, 11:575.
- [95] Dimidi E, Christodoulides S, Scott SM, Whelan K (2017). Mechanisms of Action of Probiotics and the Gastrointestinal Microbiota on Gut Motility and Constipation. *Advances in Nutrition*, 8:484–494.
- [96] Kumar Bajaj B, J.J. Claes I, Lebeer S (2015). FUNCTIONAL MECHANISMS OF PROBIOTICS. *J microb biotech food sci*, 4:321–327.
- [97] Thomas CM, Versalovic J (2010). Probiotics-host communication: Modulation of signaling pathways in the intestine. *Gut Microbes*, 1:148–163.
- [98] Distrutti E, O’Reilly J-A, McDonald C, Cipriani S, Renga B, Lynch MA, et al. (2014). Modulation of Intestinal Microbiota by the Probiotic VSL#3 Resets Brain Gene Expression and Ameliorates the Age-Related Deficit in LTP. *PLoS ONE*, 9:e106503.
- [99] Kaur H, Golovko S, Golovko MY, Singh S, Darland DC, Combs CK (2020). Effects of Probiotic Supplementation on Short Chain Fatty Acids in the AppNL-G-F Mouse Model of Alzheimer’s Disease. *JAD*, 76:1083–1102.
- [100] O’Hagan C, Li JV, Marchesi JR, Plummer S, Garaiova I, Good MA (2017). Long-term multi-species *Lactobacillus* and *Bifidobacterium* dietary supplement enhances memory and changes regional brain metabolites in middle-aged rats. *Neurobiology of Learning and Memory*, 144:36–47.
- [101] Bonfili L, Cecarini V, Cuccioloni M, Angeletti M, Berardi S, Scarpona S, et al. (2018). SLAB51 Probiotic Formulation Activates SIRT1 Pathway Promoting Antioxidant and Neuroprotective Effects in an AD Mouse Model. *Mol Neurobiol*, 55:7987–8000.
- [102] Bonfili L, Cuccioloni M, Gong C, Cecarini V, Spina M, Zheng Y, et al. (2022). Gut microbiota modulation in Alzheimer’s disease: Focus on lipid metabolism. *Clinical Nutrition*, 41:698–708.
- [103] Athari Nik Azm S, Djazayeri A, Safa M, Azami K, Ahmadvand B, Sabbaghziarani F, et al. (2018). Lactobacilli and bifidobacteria ameliorate memory and learning deficits and oxidative stress in β -amyloid (1–42) injected rats. *Appl Physiol Nutr Metab*, 43:718–726.
- [104] Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A, et al. (2017). Therapeutic potential of *Bifidobacterium breve* strain A1 for preventing cognitive impairment in Alzheimer’s disease. *Sci Rep*, 7:13510.
- [105] Abdelhamid M, Zhou C, Jung C-G, Michikawa M (2022). Probiotic *Bifidobacterium breve* MCC1274 Mitigates Alzheimer’s Disease-Related Pathologies in Wild-Type Mice. *Nutrients*, 14:2543.
- [106] Cao J, Amakye WK, Qi C, Liu X, Ma J, Ren J (2021). *Bifidobacterium Lactis* Probio-M8 regulates gut microbiota to alleviate Alzheimer’s disease in the APP/PS1 mouse model. *Eur J Nutr*, 60:3757–3769.
- [107] Sun J, Xu J, Yang B, Chen K, Kong Y, Fang N, et al. (2020). Effect of *Clostridium butyricum* against Microglia-Mediated Neuroinflammation in Alzheimer’s Disease via Regulating Gut Microbiota and Metabolites Butyrate. *Mol Nutr Food Res*, 64:1900636.
- [108] Ou Z, Deng L, Lu Z, Wu F, Liu W, Huang D, et al. (2020). Protective effects of *Akkermansia muciniphila* on cognitive deficits and amyloid pathology in a mouse model of Alzheimer’s disease. *Nutr Diabetes*, 10:12.
- [109] Xu R, Zhang Y, Chen S, Zeng Y, Fu X, Chen T, et al. (2023). The role of the probiotic *Akkermansia muciniphila* in brain functions: insights underpinning therapeutic potential. *Critical Reviews in Microbiology*, 49:151–176.
- [110] Qu L, Liu F, Fang Y, Wang L, Chen H, Yang Q, et al. (2023). Improvement in Zebrafish with Diabetes and Alzheimer’s Disease Treated with Pasteurized *Akkermansia muciniphila*. *Microbiol Spectr*, e00849-23.
- [111] Bonfili L, Cecarini V, Gogoi O, Berardi S, Scarpona S, Angeletti M, et al. (2020). Gut microbiota manipulation through probiotics oral administration restores glucose

- homeostasis in a mouse model of Alzheimer's disease. *Neurobiology of Aging*, 87:35–43.
- [112] Lee H-J, Lee K-E, Kim J-K, Kim D-H (2019). Suppression of gut dysbiosis by *Bifidobacterium longum* alleviates cognitive decline in 5XFAD transgenic and aged mice. *Sci Rep*, 9:11814.
- [113] Yang X, Yu D, Xue L, Li H, Du J (2020). Probiotics modulate the microbiota–gut–brain axis and improve memory deficits in aged SAMP8 mice. *Acta Pharmaceutica Sinica B*, 10:475–487.
- [114] Cecarini V, Bonfili L, Gogoi O, Lawrence S, Venanzi FM, Azevedo V, et al. (2020). Neuroprotective effects of p62(SQSTM1)-engineered lactic acid bacteria in Alzheimer's disease: a pre-clinical study. *Aging*, 12:15995–16020.
- [115] Wang Q-J, Shen Y-E, Wang X, Fu S, Zhang X, Zhang Y-N, et al. (2020). Concomitant memantine and *Lactobacillus plantarum* treatment attenuates cognitive impairments in APP/PS1 mice. *Aging*, 12:628–649.
- [116] Abraham D, Feher J, Scuderi GL, Szabo D, Dobolyi A, Cservenak M, et al. (2019). Exercise and probiotics attenuate the development of Alzheimer's disease in transgenic mice: Role of microbiome. *Experimental Gerontology*, 115:122–131.
- [117] Tamtaji OR, Heidari-soureshjani R, Mirhosseini N, Kouchaki E, Bahmani F, Aghadavod E, et al. (2019). Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: A randomized, double-blind, controlled trial. *Clinical Nutrition*, 38:2569–2575.
- [118] Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, et al. (2016). Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial. *Front Aging Neurosci*. doi: 10.3389/fnagi.2016.00256.
- [119] Xiao J, Katsumata N, Bernier F, Ohno K, Yamauchi Y, Odamaki T, et al. (2020). Probiotic *Bifidobacterium breve* in Improving Cognitive Functions of Older Adults with Suspected Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled Trial. *JAD*, 77:139–147.
- [120] Asaoka D, Xiao J, Takeda T, Yanagisawa N, Yamazaki T, Matsubara Y, et al. (2022). Effect of Probiotic *Bifidobacterium breve* in Improving Cognitive Function and Preventing Brain Atrophy in Older Patients with Suspected Mild Cognitive Impairment: Results of a 24-Week Randomized, Double-Blind, Placebo-Controlled Trial. *JAD*, 88:75–95.
- [121] Akhgarjand C, Vahabi Z, Shab-Bidar S, Etesam F, Djafarian K (2022). Effects of probiotic supplements on cognition, anxiety, and physical activity in subjects with mild and moderate Alzheimer's disease: A randomized, double-blind, and placebo-controlled study. *Front Aging Neurosci*, 14:1032494.
- [122] Kim C-S, Cha L, Sim M, Jung S, Chun WY, Baik HW, et al. (2021). 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. *The Journals of Gerontology: Series A*, 76:32–40.
- [123] Shi S, Zhang Q, Sang Y, Ge S, Wang Q, Wang R, et al. (2022). Probiotic *Bifidobacterium longum* BB68S Improves Cognitive Functions in Healthy Older Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients*, 15:51.
- [124] Ton AMM, Campagnaro BP, Alves GA, Aires R, Côco LZ, Arpini CM, et al. (2020). Oxidative Stress and Dementia in Alzheimer's Patients: Effects of Synbiotic Supplementation. *Oxidative Medicine and Cellular Longevity*, 2020:1–14.
- [125] Den H, Dong X, Chen M, Zou Z (2020). Efficacy of probiotics on cognition, and biomarkers of inflammation and oxidative stress in adults with Alzheimer's disease or mild cognitive impairment — a meta-analysis of randomized controlled trials. *Aging*, 12:4010–4039.
- [126] Liu C, Guo X, Chang X (2022). Intestinal Flora Balance Therapy Based on Probiotic Support Improves Cognitive Function and Symptoms in Patients with Alzheimer's Disease: A Systematic Review and Meta-analysis. *BioMed Research International*, 2022:1–9.
- [127] Webberley TS, Masetti G, Bevan RJ, Kerry-Smith J, Jack AA, Michael DR, et al. (2022). The Impact of Probiotic Supplementation on Cognitive, Pathological and Metabolic Markers in a Transgenic Mouse Model of Alzheimer's Disease. *Front Neurosci*, 16:843105.
- [128] Webberley TS, Bevan RJ, Kerry-Smith J, Dally J, Michael DR, Thomas S, et al. (2023). Assessment of Lab4P Probiotic Effects on Cognition in 3xTg-AD Alzheimer's Disease Model Mice and the SH-SY5Y Neuronal Cell Line. *IJMS*, 24:4683.
- [129] Abdelhamid M, Zhou C, Ohno K, Kuhara T, Taslima F, Abdullah M, et al. Probiotic *Bifidobacterium breve* Prevents Memory Impairment Through the Reduction of Both Amyloid- β Production and Microglia Activation in APP Knock-In Mouse. .
- [130] Zhu G, Zhao J, Wang G, Chen W (2023). *Bifidobacterium breve* HNX26M4 Attenuates Cognitive Deficits and Neuroinflammation by Regulating the Gut–Brain Axis in APP/PS1 Mice. *J Agric Food Chem*, 71:4646–4655.
- [131] Zhu G, Zhao J, Zhang H, Chen W, Wang G (2021). Administration of *Bifidobacterium breve* Improves the Brain Function of A β 1-42-Treated Mice via the Modulation of the Gut Microbiome. *Nutrients*, 13:1602.
- [132] Kim H, Kim S, Park S, Park G, Shin H, Park MS, et al. (2021). Administration of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI Improves Cognitive and Memory Function in the Mouse Model of Alzheimer's Disease. *Front Aging Neurosci*, 13:709091.
- [133] Shamsipour S, Sharifi G, Taghian F (2021). An 8-Week Administration of *Bifidobacterium bifidum* and *Lactobacillus plantarum* Combined with Exercise Training Alleviates Neurotoxicity of A β and Spatial Learning via Acetylcholine in Alzheimer Rat Model. *J Mol Neurosci*, 71:1495–1505.

- [134] Song X, Zhao Z, Zhao Y, Jin Q, Li S (2022). Protective Effects of *Bacillus coagulans* JA845 against D-Galactose/ AlCl_3 -Induced Cognitive Decline, Oxidative Stress and Neuroinflammation. *J Microbiol Biotechnol*, 32:212–219.
- [135] Song X, Zhao Z, Zhao Y, Wang Z, Wang C, Yang G, et al. (2022). *Lactobacillus plantarum* DP189 prevents cognitive dysfunction in D-galactose/ AlCl_3 induced mouse model of Alzheimer's disease via modulating gut microbiota and PI3K/Akt/GSK-3 β signaling pathway. *Nutritional Neuroscience*, 25:2588–2600.
- [136] Wang Y, Wang D, Lv H, Dong Q, Li J, Geng W, et al. (2022). Modulation of the Gut Microbiota and Glycometabolism by a Probiotic to Alleviate Amyloid Accumulation and Cognitive Impairments in AD Rats. *Molecular Nutrition Food Res*, 66:2200265.
- [137] Lee D-Y, Shin Y-J, Kim J-K, Jang H-M, Joo M-K, Kim D-H (2021). Alleviation of cognitive impairment by gut microbiota lipopolysaccharide production-suppressing *Lactobacillus plantarum* and *Bifidobacterium longum* in mice. *Food Funct*, 12:10750–10763.
- [138] Shamsipour S, Sharifi G, Taghian F (2021). Impact of interval training with probiotic (*L. plantarum* / *Bifidobacterium bifidum*) on passive avoidance test, ChAT and BDNF in the hippocampus of rats with Alzheimer's disease. *Neuroscience Letters*, 756:135949.
- [139] Woo J-Y, Gu W, Kim K-A, Jang S-E, Han MJ, Kim D-H (2014). *Lactobacillus pentosus* var. *plantarum* C29 ameliorates memory impairment and inflammaging in a d-galactose-induced accelerated aging mouse model. *Anaerobe*, 27:22–26.
- [140] Patel C, Pande S, Acharya S (2020). Potentiation of anti-Alzheimer activity of curcumin by probiotic *Lactobacillus rhamnosus* UBLR-58 against scopolamine-induced memory impairment in mice. *Naunyn-Schmiedeberg's Arch Pharmacol*, 393:1955–1962.
- [141] Musa NH, Mani V, Lim SM, Vidyadaran S, Abdul Majeed AB, Ramasamy K (2017). Lactobacilli-fermented cow's milk attenuated lipopolysaccharide-induced neuroinflammation and memory impairment in vitro and in vivo. *Journal of Dairy Research*, 84:488–495.
- [142] Mohammadi G, Dargahi L, Peymani A, Mirzanejad Y, Alizadeh SA, Naserpour T, et al. (2019). The Effects of Probiotic Formulation Pretreatment (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) on a Lipopolysaccharide Rat Model. *Journal of the American College of Nutrition*, 38:209–217.
- [143] Go J, Chang D-H, Ryu Y-K, Park H-Y, Lee I-B, Noh J-R, et al. (2021). Human gut microbiota *Agathobaculum butyriciproducens* improves cognitive impairment in LPS-induced and APP/PS1 mouse models of Alzheimer's disease. *Nutrition Research*, 86:96–108.
- [144] Wu Y, Niu X, Li P, Tong T, Wang Q, Zhang M, et al. (2023). Lactobacillaceae improve cognitive dysfunction via regulating gut microbiota and suppressing A β deposits and neuroinflammation in APP/PS1 mice. *Arch Microbiol*, 205:118.
- [145] Fang X, Zhou X, Miao Y, Han Y, Wei J, Chen T (2020). Therapeutic effect of GLP-1 engineered strain on mice model of Alzheimer's disease and Parkinson's disease. *AMB Expr*, 10:80.
- [146] Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. (2014). The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*, 11:506–514.
- [147] Rajanala K, Kumar N, Chamallamudi MR (2021). Modulation of Gut-Brain Axis by Probiotics: A Promising Anti-depressant Approach. *CN*, 19:990–1006.
- [148] Fukui H (2017). Gut Microbiome-based Therapeutics in Liver Cirrhosis: Basic Consideration for the Next Step. *JCTH*. doi: 10.14218/JCTH.2017.00008.
- [149] Xu M, Mo X, Huang H, Chen X, Liu H, Peng Z, et al. (2020). Yeast β -glucan alleviates cognitive deficit by regulating gut microbiota and metabolites in A β 1–42-induced AD-like mice. *International Journal of Biological Macromolecules*, 161:258–270.
- [150] Liu Q, Xi Y, Wang Q, Liu J, Li P, Meng X, et al. (2021). Mannan oligosaccharide attenuates cognitive and behavioral disorders in the 5xFAD Alzheimer's disease mouse model via regulating the gut microbiota-brain axis. *Brain, Behavior, and Immunity*, 95:330–343.
- [151] Lee Y-S, Lai D-M, Huang H-J, Lee-Chen G-J, Chang C-H, Hsieh-Li HM, et al. (2021). Prebiotic Lactulose Ameliorates the Cognitive Deficit in Alzheimer's Disease Mouse Model through Macroautophagy and Chaperone-Mediated Autophagy Pathways. *J Agric Food Chem*, 69:2422–2437.
- [152] Chen D, Yang X, Yang J, Lai G, Yong T, Tang X, et al. (2017). Prebiotic Effect of Fructooligosaccharides from *Morinda officinalis* on Alzheimer's Disease in Rodent Models by Targeting the Microbiota-Gut-Brain Axis. *Front Aging Neurosci*, 9:403.
- [153] Xin Y, Diling C, Jian Y, Ting L, Guoyan H, Hualun L, et al. (2018). Effects of Oligosaccharides From *Morinda officinalis* on Gut Microbiota and Metabolome of APP/PS1 Transgenic Mice. *Front Neurol*, 9:412.
- [154] Nishikawa M, Brickman AM, Manly JJ, Schupf N, Mayeux RP, Gu Y (2021). Association of Dietary Prebiotic Consumption with Reduced Risk of Alzheimer's Disease in a Multiethnic Population. *CAR*, 18:984–992.
- [155] Barbosa RSD, Vieira-Coelho MA (2020). Probiotics and prebiotics: focus on psychiatric disorders – a systematic review. *Nutrition Reviews*, 78:437–450.
- [156] Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. (2013). Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections. *American Journal of Gastroenterology*, 108:478–498.
- [157] Kim N, Jeon SH, Ju IG, Gee MS, Do J, Oh MS, et al. (2021). Transplantation of gut microbiota derived from Alzheimer's disease mouse model impairs memory function and neurogenesis in C57BL/6 mice. *Brain, Behavior, and Immunity*, 98:357–365.

- [158] Wang M, Cao J, Gong C, Amakye WK, Yao M, Ren J (2021). Exploring the microbiota-Alzheimer's disease linkage using short-term antibiotic treatment followed by fecal microbiota transplantation. *Brain, Behavior, and Immunity*, 96:227–238.
- [159] Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, et al. (2017). Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. *Sci Rep*, 7:41802.
- [160] Zhan G, Yang N, Li S, Huang N, Fang X, Zhang J, et al. (2018). Abnormal gut microbiota composition contributes to cognitive dysfunction in SAMP8 mice. *Aging*, 10:1257–1267.
- [161] Fujii Y, Nguyen TTT, Fujimura Y, Kameya N, Nakamura S, Arakawa K, et al. (2019). Fecal metabolite of a gnotobiotic mouse transplanted with gut microbiota from a patient with Alzheimer's disease. *Bioscience, Biotechnology, and Biochemistry*, 83:2144–2152.
- [162] Kim M-S, Kim Y, Choi H, Kim W, Park S, Lee D, et al. (2020). Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut*, 69:283–294.
- [163] Sun J, Xu J, Ling Y, Wang F, Gong T, Yang C, et al. (2019). Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. *Transl Psychiatry*, 9:189.
- [164] Dodiya HB, Kuntz T, Shaik SM, Baufeld C, Leibowitz J, Zhang X, et al. (2019). Sex-specific effects of microbiome perturbations on cerebral A β amyloidosis and microglia phenotypes. *Journal of Experimental Medicine*, 216:1542–1560.
- [165] Park S-H, Lee JH, Shin J, Kim J-S, Cha B, Lee S, et al. (2021). Cognitive function improvement after fecal microbiota transplantation in Alzheimer's dementia patient: a case report. *Current Medical Research and Opinion*, 37:1739–1744.