Chapter 6

Probiotics for Preventing Cognitive Impairment in Alzheimer's Disease

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Additional information is available at the end of the chapter

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Abstract

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease that results in gradual cognitive impairment and eventually leads to dementia. However, despite AD being one of the most prevalent neurodegenerative diseases in aging societies, no clinically successful therapeutic strategies for its treatment or prevention have been reported to date. Studies have indicated that gut microbial alterations are linked to AD. Probiotics are living microorganisms that are known to confer health benefits to the host when ingested in adequate amounts. Certain strains of probiotics appear to influence the central nervous system (CNS) and behavior via the microbiota-gut-brain axis. Increasing evidence from preclinical and clinical studies has demonstrated that probiotics possess preventive as well as therapeutic potential for AD. It is speculated that probiotics could ameliorate the progression of AD by modulating the inflammatory process, counteracting oxidative stress, and other possible mechanisms, although further studies are needed to understand the details. In this chapter, we will highlight the current understandings of the effects as well as the possible mechanisms of action of probiotics for preventing cognitive impairment in AD.

Keywords: Alzheimer's disease, probiotics, microbiota, gut-brain axis

1. Introduction

Alzheimer's disease (AD) is the most common form of neurodegenerative disease and the leading cause of dementia in the elderly, accounting for an estimated 60–80% of dementia cases worldwide [1]. It is a highly incapacitating disorder, progressing from gradual deterioration of memory and cognitive functions to a complete incapacity, which consequently leads

to death of patients within 3–9 years after diagnosis [2]. Aging is recognized as the major risk factor of all AD cases, and the aging of world population will lead to a steep increase in the prevalence of AD [1]. Despite much effort has been made in AD research in the past few decades, the pathophysiology of AD remains unclear, and to date, there is no effective therapeutic treatment for the disease. Hence, new therapeutic solutions that can effectively combat the disease are of utmost importance.

Recent studies have shown that the gut microbiota is involved in the neurodegenerative disorders and diverse cognitive functions through regulating the gut-brain axis [3, 4]. The concept of microbiota-gut-brain axis is emerging and its dysregulation has now been linked to the progression of AD [5]. In light of this, it is suggested that modulation of the gut microbiota through the use of probiotics might possibly prevent or ameliorate AD symptoms.

In this chapter, we discuss the roles of the gut microbiota in the development of AD, highlighting the specific contribution of probiotics intervention to the amelioration of AD progression. We examine recent scientific literature addressing the beneficial effects of probiotics for the prevention and treatment of AD and point out the possible mechanisms of action of probiotics for preventing cognitive impairments in AD.

2. Clinical features and pathogenesis of Alzheimer's disease

AD is a chronic progressive neurodegenerative disorder characterized by three clinical phases in which the patients exhibit different symptoms over time [6]. The first stage (early stage; mild AD) includes memory loss, language difficulties, and executive dysfunction. The second stage (middle stage; moderate AD) comprises psychiatric symptoms and behavioral disturbances such as depression, hallucinations, delusions, and agitation. The third stage (late stage; severe AD) comprises severe impairment of almost all cognitive functions and difficulties to perform activities of daily living. The symptoms of AD worsen gradually, and the disease may begin to develop decades before the manifestation of the earliest clinical symptoms [7].

Despite the massive worldwide research efforts that have been made in the past few decades, the exact cause and pathogenesis of AD are not fully understood. It is widely believed that the pathogenesis of AD is primarily driven by the abnormal deposition of extracellular β-amyloid peptide (Aβ) plaques in various areas of brain, although such hypothesis may not be the sole explanation [8, 9]. Aβ is a peptide consists of 37–43 amino acids, in which $A\beta_{42}$ is a more prevalent isoform and is considered to be the most neurotoxic in nature [10]. Aβ is derived from the sequential proteolytic enzymatic cleavage of amyloid precursor protein (APP) by two membrane-bound proteases, β- and γ-secretase [11, 12]. In the amyloid cascade hypothesis of AD, the disease is characterized as a series of abnormalities in the process and secretion of the amyloid precursor protein (APP), where an imbalance between production and clearance of Aβ is the triggering event that leads to the accumulation of Aβ in the brain parenchyma [13]. As a consequence, Aβ spontaneously aggregates into soluble oligomers that are eventually deposited in diffuse senile plaques [14]. The Aβ deposition and diffused senile plaques

formation eventually lead to local microglia activation and production of pro-inflammatory cytokines [15, 16]. In turn, these cytokines stimulate reactive astrocytes to produce further amounts of $A\beta_{42}$ oligomers, thus activating more amyloid plaque formation [17]. In addition, Aβ oligomer aggregations induce oxidative damage, which, in turn, seem to provoke inflammation and facilitate tau hyperphosphorylation, resulting in adverse effects on neuronal synapses and mitochondria [18].

Neurofibrillary tangles (NFTs), which are filamentous inclusions that accumulate in selective neurons of AD brains, are another major pathological hallmark of AD. The major component of NFTs is the microtubule-associated protein tau [19, 20]. The tau protein is a highly soluble protein that promotes microtubule assembly and stabilization for axonal transport and neuronal growth under normal conditions [21]. In AD, the tau protein exhibits altered solubility properties, becomes abnormally hyperphosphorylated, and forms filamentous structures [22]. Hyperphosphorylation of tau is known to induce a lower grade of interaction of tau proteins with microtubules that leads to greater self-aggregation of tau proteins and consequently induces malfunction of axonal transport [23], mis-stabilization of actin [24], synaptic impairment [25], and defects in mitochondrial integrity [26].

Nevertheless, NFTs seem not to be the main toxic entities leading to AD. Recent studies show that the intermediate tau oligomer is likely to be the key attribute of disease onset [27, 28]. Appearing prior to NFTs formation, hyperphosphorylated tau self-assembles into oligomeric forms and insoluble materials as paired-helical filaments (PHFs), triggering neurotoxic actions that affect the normal interaction patterns of the neuronal cytoskeleton and neuronal damage [28, 29]. As a result of neuronal death, tau oligomers are released into the extracellular environment, contributing to microglia activation with overproduction of pro-inflammatory cytokines that trigger deleterious signal cascades leading to progressive neuronal degeneration in AD brains [30]. Although the exact cause on why AD onset takes decades before symptoms occur remains unclear, AD progression is likely related to a reduced ability to eliminate misfolded, oligomerized, and aggregated tau proteins that increase with advancing age. Therefore, tau protein could be another important therapeutic target in AD pathology.

3. Gut microbiota and Alzheimer's disease

3.1. Microbiota-gut-brain axis

The gut-brain axis has long been recognized as a bidirectional communication between the brain and the gut in which the brain communicates with the gastrointestinal tract by modulating permeability, motility, secretion, and immunity, and concurrently, the gut can affect brain function and behavior [31]. The complex and multifaceted network of gut-brain axis consists of the gastrointestinal tract, central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), neuroendocrine system, and immune system which drive various afferent and efferent pathways such as vagus nerve and hypothalamic-pituitary adrenal (HPA) pathway for regulation of immune and metabolic homeostasis [31]. Recently, it is

becoming increasingly evident that gut microbiota play a pivotal role in regulating the gut-brain axis, thereafter the term microbiota-gut-brain axis was introduced [32–34].

Gut microbiota is proposed as a key regulator of centrally mediated events including metabolic homeostasis, immune function, and neurological diseases [33]. Gut microbiota is a complex community composed of trillions of microorganisms, mainly bacteria, but also bacteriophage particles, viruses, fungi, and archaea [35]. A majority of the microbiota belongs to the two bacterial phyla, Bacteroidetes and Firmicutes, while Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia phyla are present in lower proportions [36]. Notably, it is increasingly evident that alterations in the gut microbiota composition may cause imbalanced gut homeostasis and detrimental effects on CNS [37]. For instance, a variety of gastrointestinal and metabolic diseases including inflammatory bowel disease (IBD), obesity, diabetes, and insulin resistance are common comorbidities in many neurological disorders [38]. More recently, metagenomics studies have revealed that gut dysbiosis is present in a variety of neurological diseases including AD. Consequently, it is inevitably important to maintain a well-balanced and healthy microbiota community in the regulation of gut-brain axis.

3.2. Gut microbiota alterations and Alzheimer's disease

Accumulating evidence suggests that gut microbiota alterations can influence the progression of neurological disease and may be a major factor in the development of AD [39, 40]. For instance, a recent preclinical study revealed a remarkable shift in the gut microbiota of APP transgenic mice as compared to healthy, wild-type mice, wherein a significant reduction in bacteria belonging to the phyla Firmicutes, Verrucomicrobia, Proteobacteria, and Actinobacteria with respect to an increase of Bacteroidetes and Tenericutes was observed in the intestine of conventionally raised transgenic APPPS1 AD mice [41]. It was strongly advocated that a distinct microbial constitution in AD mice may contribute to amyloid deposition wherein a remarkable increase in cerebral Aβ pathology was observed in APP transgenic germ-free mice colonized with microbiota from conventional APP transgenic mice, while control mice colonized with microbiota from wild-type mice was less effective in increasing cerebral Aβ levels [41]. In addition, a clinical study characterizing the gut microbiota composition of AD subjects reveals decreased microbial diversity and changes in bacterial abundance compared with controls; these changes include decreased levels of Firmicutes and *Bifidobacterium* and increased levels of Bacteroidetes [42]. Nonetheless, the exact causes and effects of gut dysbiosis on AD remain elusive.

It is plausible that microbiota alterations can lead to colonization of intrinsic pathogens and increase gut permeability that could perturb the gut-brain axis. For instance, recent study has demonstrated that enterobacteria infection exacerbated progression of AD by promoting immune hemocyte recruitment to the brain; thereby provoking tumor necrosis factor-c-Jun NH2-terminal kinase (TNF-JNK)-mediated neurodegeneration in a drosophila AD model [43]. Additionally, the intestinal opportunistic bacteria including *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia*, *Mycobacterium* spp., *Salmonella* spp., *Staphylococcus aureus*, and *Streptococcus* spp. have been found to excrete immunogenic compounds of amyloids, lipopolysaccharides (LPS),

and other microbial exudates into their circumjacent environment [44]. For instance, LPS and the *E. coli* K99 pili protein were highly detected in the brain parenchyma and blood vessels of AD patients [45]. Additionally, LPS was found to colocalize with Aβ in amyloid plaques, suggesting that bacterial components can translocate from the gut, assessing the brain and further triggering Aβ deposition in AD [45]. It has also been hypothesized that bacterial-derived amyloids may reach the systemic circulation and accumulate in the brain, thereby triggering a series of downstream events that leads to impairment of phagocytosis and contributes to $A\beta_{42}$ deposition, resulting in dysfunction of specific brain regions, such as the cerebellum and the hippocampus [46, 47].

Another clinical study involving 83 elderly subjects (40 cognitive-impaired amyloid-positive patients, 33 cognitive-impaired amyloid-negative patients, and 10 cognitively healthy amyloid-negative controls) have demonstrated that an increased abundance of a pro-inflammatory gut microbiota taxon, *Escherichia/Shigella*, and a reduced abundance of an anti-inflammatory taxon, *Enterococcus rectale*, are possibly associated with a peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis [48]. The results obtained from the study indicated the role of amyloid and related bacterial accumulation in the pathogenesis of cognitive damage [48]. A remarkable recent study using APP transgenic mice model has also demonstrated that AD pathology shifted gut microbiota composition during aging toward an inflammation-related bacterial profile and suggested that these changes could contribute to disease progression and severity [49]. Taken together, these findings highlight an intricate association between gut microbiota alterations and amyloid formation, increased systemic inflammatory responses and cognitive impairment in AD, suggesting modulation of gut microbiota with probiotics could be a promising therapy to alleviate its underlying symptoms.

4. Probiotics modulation of Alzheimer's disease

The connections between gut microbiota and AD have led to a great interest in modulation of the microbiota-gut-brain axis through probiotics. Probiotics are defined as live microorganisms that, when consumed in sufficient amounts, confer health benefits to the host [50]. The probiotics species that are most commonly studied usually belong to the genera *Lactobacillus* or *Bifidobacterium*, whereby some of the members are the natural inhabitants of the gut microbiota and generally regarded as safe. In recent years, the possibilities of probiotics exerting a positive cognitive effect in human health have emerged. A growing body of animal studies supports the idea that certain probiotics can counteract gut dysbiosis and may positively impact the pathogenesis of AD. Nonetheless, clinical data are less compelling than the animal model data.

4.1. Animal studies

Studies in rodents indicate that cognition and memory storage, particularly the hippocampal long-term potentiation, begin to decline in aging animals and these brain functions are dramatically disrupted in animal models of AD [51]. Many lines of evidence have shown that

probiotics modulation of the gut microbiota could improve age-related cognitive functions in animal models. For instance, treatment with VSL#3, a probiotics mixture containing eight different Gram-positive bacterial species, showed a significant alteration in gut microbiota, with increases in Actinobacteria and Bacteroidetes, both of which were reduced in vehicle-treated animals with a positive impact on long-term potentiation, inflammation, and neural plasticity [52]. Moreover, it was demonstrated that long-term dietary supplementation of multispecies live *Lactobacillus* and *Bifidobacterium* mixture (Lab4) to aging rats changes the brain metabolites (γ-aminobutyric acid (GABA) and glutamate) that are involved in neural signaling in the frontal cortex and hippocampus and improves task-specific memory [53]. Collectively, these findings represent proof of principle that probiotic modulation of gut microbiota can have a positive impact on cognitive functions and suggest a possible role of memory-enhancing probiotic strains in preventing cognitive impairment in AD.

A recent study has provided direct evidence for amelioration of cognitive dysfunction by probiotics treatment with the strain of *Bifidobacterium breve* strain A1 using Aβ-induced AD mice model (**Figure 1**). Administration of *B. breve* A1 to AD mice attenuated the impairment of alternation behavior in a Y maze test and reversed the reduced latency time in a passive avoidance test, indicating that *B. breve* A1 prevented cognitive dysfunction [54]. In addition to the promising effect on cognitive function, *B. breve* A1 also suppressed the immune response and neuronal inflammation induced by Aβ. Moreover, SLAB51 probiotic formulation, which consists of a mixture of lactic acid bacteria and bifidobacteria, was shown to reduce brain damage and Aβ aggregations and prevents the onset and delay progression of AD in mice in the early stage of AD [55]. Another report using $A\beta_{1\text{-}42}$-intra-hippocampal injected rats have also demonstrated that the administration of probiotics, which consisted of *L. acidophilus*, *L. fermentum*, *B. lactis*, and *B. longum*, could improve the common pathological features of AD including spatial memory and learning deficits and oxidative stress [56]. Taken together, these animal studies show that probiotics may play an important role in the bidirectional communication between the gut and the brain, and support the notion that probiotics modulation could ameliorate the development of AD; however, it clearly requires translation in humans.

4.2. Human studies

The health benefits of probiotics on numerous aspects of host health and homeostasis have been extensively studied in clinical trials. However, a detailed analysis of probiotics modulation in patients with AD is lacking and the effects of probiotics on the onset, symptoms, and pathogenesis of AD remain uncover. To date, there is only one clinical study of probiotics in subjects with AD has been carried out. The randomized, double-blind, and controlled clinical trial involved 60 patients with AD who were randomly assigned into two groups: the probiotics group (n = 30), received 200 ml/day of milk enriched with *L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum* (2×10^9 CFU/g each) for 12 weeks, and the control group (n = 30) received plain milk at the same amount [57]. All participants were introduced to the mini-mental state examination (MMSE) cognitive test for evaluation of learning and memory. After 12 weeks intervention, probiotic administration has significant improvement in the MMSE

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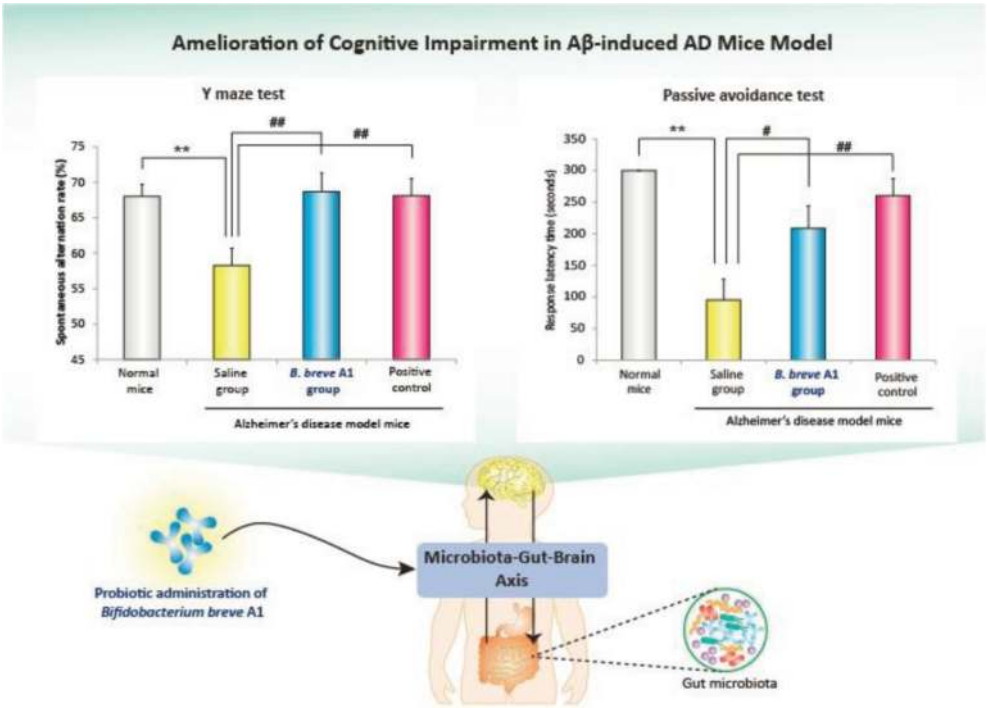

Figure 1. Probiotics intervention could potentially modulate cognitive decline in Alzheimer's disease (AD) via the microbiota-gut-brain axis. A prominent strain of probiotic, *Bifidobacterium breve* A1 ameliorated cognitive impairment in Aβ-induced AD mice model wherein administration of *B. breve* A1 to AD mice attenuated the impairment of alternation behavior in a Y maze test and reversed the reduced latency time in a passive avoidance test.

score of the subjects with AD in which the score (out of 30) was significantly increased in the probiotic group (from 8.67 ± 1.44 to 10.57 ± 1.64, +27.90 ± 8.07%) as compared to control group (from 8.47 ± 1.10 to 8.00 ± 1.08, −5.03 ± 3.00%). The probiotic treatment also has favorable effects on the levels of malondialdehyde (MDA) and high-sensitivity C-reactive protein (hs-CRP), improved insulin resistance, pancreatic beta cell secretion, and metabolic status with respect to controls; albeit the changes in other biomarkers of oxidative stress and inflammation, fasting plasma glucose (FPG) and other lipid profiles are negligible [57]. Based on the MMSE scores, the patients included in this study were having severe AD. It is generally recognized that the physiological effect of probiotics on human health is preventive but not therapeutic, thus, it is surprised to find a prominent effect of this probiotics mixture on patients with severe AD. Further investigations on the effects of probiotics on mild cognitive impairment (MCI) and moderate AD are undoubtedly needed. Collectively, the results from both animal and clinical studies offer hope for the future development of a novel probiotics-based approach to ameliorate symptoms of AD and provide a useful framework to explore the microbiota-brain axis.

5. Possible mechanisms of action of probiotics in preventing Alzheimer's disease

5.1. Modulation of immune reactions

Although many lines of evidence have shown the potential effects of probiotics in treating AD, the mechanisms of action are still speculated and unclear. One mechanism is the modulation of immune reactions. Accumulating evidence suggests that neuroinflammation has a causal role in the pathogenesis of AD wherein neuroinflammation is not a passive system activated by senile plaques and NFTs, but instead contributes as much as the plaques and tangles in AD [58]. This is substantiated by the presence of microglia cells in both AD patients and animal models of AD [59], and it is accompanied by increased levels of pro-inflammatory cytokines, such as TNF-α or interleukin (IL)-6 as found in the serum and brain tissue of AD patients [60]. In AD, aggregated Aβ as well as hyperphosphorylated tau proteins interfere with neuronal function and trigger the inflammatory activity of microglia [61]. Microglia activation leads to further accumulation of Aβ, neuronal debris, and, most probably, the sustained production of pro-inflammatory cytokines and reactive oxygen species (ROS), giving rise to a chronic, nonresolving inflammatory process [62]. Inevitably, modulation of neuroinflammation provides compelling targets for interventions in AD.

Probiotics intervention has been reported to improve the age-associated modifications of immunological features. It was demonstrated that probiotic treatments can ameliorate the immune reactions by modulating cytokine production, improving distribution and function of natural killer cells, macrophages, granulocytes, and T cells, and enhancing mucosal and systemic antibody responses [63–66]. In view of the immunomodulatory properties of probiotics, one might speculate that the probiotic bacteria may ameliorate symptoms of AD by modulating the inflammatory reactions driven by Aβ deposition and other risk factors, including inflammaging, obesity, and traumatic brain injury.

Studies have shown that probiotics could directly mitigate neuroinflammation as observed in the reductions of circulating pro-inflammatory cytokines and microglia activation. For example, chronic inflammation was suppressed after probiotic treatment with *L. pentosus var. plantarum* C29 in a D-galactose-induced accelerated aging mouse model for which the activation of transcription factor nuclear factor-kappa B (NF-κB), the pro-inflammatory cytokine TNF-α, and M1 macrophages were inhibited [67]. Moreover, administration of *B. breve* A1 ameliorated Aβ toxicity and prevented cognitive decline in AD model mice through its modulating effect on the excessive immune response and neuronal inflammation caused by Aβ injection [54]. Overall, these studies provide a mechanistic insight into the role of probiotics in modulation of inflammatory responses and amelioration of AD pathology.

5.2. Suppression of oxidative stress

In addition to the established pathology of senile plaques and NFTs, oxidative stress has emerged as an important factor contributing to the development of AD. Oxidative stress

represents the mechanism through which Aβ neurotoxic peptides and tau proteins mediate the pathological processes and cause synaptic impairment, neuroinflammation, neuronal apoptosis, and neurotransmitter dyshomeostasis in AD [68] that ultimately correlates with the typical behavioral symptoms of AD [69]. Oxidative stress is characterized as an imbalance between the production of ROS and the activities of antioxidant defense system that resulting in oxidative damage, as observed in AD patients [70]. Mounting evidence suggests that oxidative damage contributed to the onset and progression of AD wherein low antioxidant enzyme levels, high oxygen consumption, the presence of excitotoxic amino acids, and high iron content promote the production of ROS and reactive nitrogen species (RNS) in the brain [71, 72]. In addition, aberrant accumulation of Aβ can also enhance the generation of ROS through an N-methyl-D-aspartate (NMDA) receptor-dependent mechanism [73], and that oxidative stress may augment the production and deposition of Aβ as well as facilitate tau hyperphosphorylation and oligomerization, forming a viscous cycle that promotes the onset and progression of AD [74]. Therefore, it is tempting to postulate that probiotics with strong antioxidant potential may prevent and treat AD by counteracting oxidative stress and the molecular events implicated in the pathogenesis of AD.

A remarkable recent study supports the protective role of probiotics in the brain oxidative status of AD mice model and demonstrates the molecular mechanisms involved [75]. For instance, SLAB51 probiotics formulation significantly reduced oxidative damages in AD mice brain through a mechanism that involves the activation of SIRT1-related pathways [75]. SIRT1 is a deacetylase with a strong neuroprotective and antioxidant potential that regulates the expression of several antioxidant genes [76, 77]. Reduction of SIRT1 functionality and expression levels have been reported to contribute to the accumulation of Aβ and tau in the cerebral cortex of AD patients [78]. It was demonstrated that SLAB51 intervention restored the levels of SIRT1 by deactivating its nuclear receptor RARβ in AD mice [75], which, in turn, may stimulate the nonamyloidogenic pathway of APP processing and diminish Aβ production and accumulation [79]. Moreover, several studies have also reported that probiotic bacteria counteracted oxidative damage and improved cognitive impairment in AD rodent models through its antioxidant properties [56, 80]. Collectively, these findings represent the fundamental concept that probiotic ameliorates the symptomatology of AD through its antioxidative mechanism.

5.3. Modulation of CNS function mediated by bacteria-derived metabolites

Another possible mechanism of action by which probiotics can ameliorate AD is through the production of metabolites such as short-chain fatty acids (SCFAs). SCFAs, mainly acetate, butyrate, lactate, and propionate, are the main metabolites of the fermentation of dietary fibers by the gut microbiota [81]. A study using germ-free mice has revealed a substantial contribution of the gut microbiota, particularly the microbiota-derived SCFAs, to the regulation of microglia maturation and functions [82]. In addition, SCFAs have also been shown to play a role in regulation of several signaling pathways such as inhibition of NF-κB, inhibition of histone deacetylation (HDAc), and activation of G protein-coupled receptors (GPCRs), and are well known to have potent anti-inflammatory effects [83–85]. For instance, butyrate has a

direct stimulation effect on vagal afferents that have been shown in clinical trials to improve cognitive function of AD patients [86, 87]. Butyrate has also been shown to inhibit HDAc and improve memory function in a late-stage AD mouse model [88]. In addition, a study using PC12 cells demonstrated the potential neuroprotective roles of the enteric bacterial metabolites, butyrate and propionate, against AD whereby the expression of Aβ A4 protein precursor was significantly downregulated by these SCFAs [89]. Meanwhile, acetate supplementation was shown to be capable of attenuating neuroglia activation and pro-inflammatory cytokine expression in rat models of neuroinflammation [90].

Recent scientific studies indicate that probiotics modulation of gut microbiota ameliorated the inflammatory status of AD through the production of SCFAs. For example, in the study of the probiotic *B. breve* A1, the cognitive decline of Aβ-induced AD mice was also partially ameliorated by its metabolite acetate, implying that the production of SCFAs by the gut microbiota could be involved in the preventive mechanisms of Aβ-induced neuroinflammation and cognitive impairment [54]. In fact, several SCFAs produced by gut microbiota have been shown to be capable of potently inhibiting the formation of toxic soluble Aβ aggregates, *in vitro* [91]. A growing body of evidence has shown that circulating levels of SCFAs could affect CNS function [92, 93], suggesting a functional role of SCFAs in the modulation of amyloidosis, neuroinflammation, and other AD-related conditions in the brain. Moreover, in the 3xTg-AD mice model (which rapidly develops amyloid plaques and NTFs) treated with the probiotics SLAB51, the levels of the bacterial metabolites (i.e., propionate and acetate) are elevated [55]. Together with the positive interference of inflammatory cytokines, reduction of Aβ aggregates, and improvement of cognitive function by SLAB51 treatments, these data contribute to define the link between bacterial-derived metabolites and AD. Nonetheless, there is still no clear mechanistic study investigating the underlying mechanisms of SCFAs in the treatment of neurodegenerative diseases.

In addition, SCFAs were reported to be able to modulate neurotransmitter synthesis and have effect on the neurotrophic genes including brain-derived neurotrophic factor (BDNF) and nerve growth factor [92, 94]. Interestingly, a reduction in BDNF signaling was observed in both the brain and the serum of patients with AD [92], and such decline was reversed by probiotics intervention as demonstrated in rodent model [52, 95, 96]. These findings suggest that probiotic modulation may enhance the production of small ubiquitous microbiota-derived molecules like SCFAs that could act as important molecular signals between the microbiota and host, thereby improving the molecular events associated with cognitive impairment.

5.4. Amelioration of AD pathogenesis via alteration of gut microbiota composition

Another mechanism to consider is the alteration of gut microbiota composition by probiotics. Emerging evidence suggests that targeting the gut commensals through probiotics intervention could mitigate age-associated inflammation and cognitive impairment [52, 97]. It has also been reported that perturbations of gut microbiota community induced by antibiotic treatment could ameliorate Aβ deposition and inflammatory responses in an aged APP transgenic mice model of

AD [98]. Furthermore, many intervention studies in elderly subjects have also demonstrated that probiotics can augment the growth of the gut commensal, *Bifidobacterium*, while concomitantly decreasing the growth of opportunistically pathogenic enterobacteria [99].

While little is currently known regarding the role of the microbiota-gut-brain axis in AD, several scientific efforts have pointed out that probiotics can modify the gut microbiota for amelioration of AD-related pathological conditions. For instance, administration of the probiotic mixture SLAB51 induced larger shifts in the microbial communities of the 3xTg-AD mice, along with an increase in the proportions of *Bifidobacterium* spp. and a reduction in *Campylobacterales* population [55], suggesting a possible role of these bacteria in the regulation of inflammation in AD. This is substantiated by the reduced plasma concentration of pro-inflammatory cytokines in AD mice treated with SLAB51 [55]. In fact, certain strains of *Bifidobacterium* were reported to possess anti-inflammatory properties and could negatively modulate mRNA levels of pro-inflammatory cytokines produced from LPS-stimulated macrophages [100]. In contrary, *Campylobacter jejuni* and *Campylobacter coli* have been found to stimulate pro-inflammatory responses in human peripheral blood mononuclear cells [101] and chicken models [102]. Moreover, a high prevalence of *Campylobacterales* infections has been observed in patients with AD, and the parameters on cognitive function were ameliorated after *Helicobacter pylori* eradication [103]. These findings suggest that the alteration of gut microbial composition by probiotics could positively modulate the AD-related pathological conditions. Nevertheless, translational study in human subjects is undoubtedly required in order to determine whether probiotics modulation of the gut microbiota could display efficacy in mitigating the pathogenesis of AD in humans. Nonetheless, these promising findings suggest that targeting the microbiota by probiotics intervention could be a useful preventive measure for AD.

6. Conclusions and perspectives

Altogether, the results of the research summarized in this chapter suggest the potential of probiotics in preventing cognitive impairment in AD. In particular, probiotics intervention could effectively ameliorate cognitive impairment and symptomatology of AD and can be considered as an important advance in the field of AD. It is evident that the gut microbiota composition is altered in AD and the modulation of gut dysbiosis through probiotics could counteract various benchmarks of AD. Probiotics or its bioactive metabolites can improve gut microbiota homeostasis and influence the pathological factors involved in the progression of AD such as inflammatory reaction, oxidative stress, Aβ deposition, and cognitive functions (**Figure 2**). Despite still being a speculation, accumulated information from animal and human research provides fundamental proofs for the modulating effect of probiotics in AD and underlies the possible mechanisms of action involved. Further studies are definitely needed to fully elucidate the scope of probiotics for this debilitating disease, as well as to clarify the underlying mechanisms of probiotics for preventing cognitive impairment in AD.

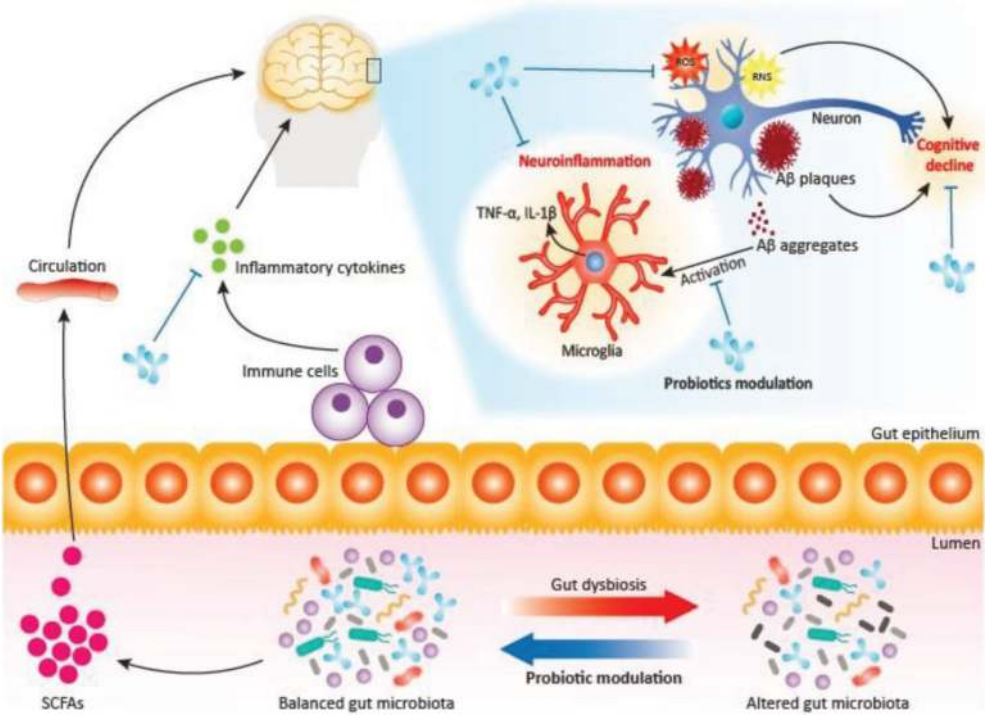

Figure 2. Schematic overview of the possible mechanisms of action of probiotics modulation for preventing cognitive impairment in Alzheimer's disease (AD). Probiotics or its bioactive metabolites such as SCFAs can improve gut microbiota homeostasis and positively influence the pathological factors involved in the progression of AD such as inflammatory reaction and oxidative stress, thereby ameliorating cognitive decline in AD.

Abbreviations

AD	Alzheimer's disease
Aβ	β-amyloid peptides
NFTs	neurofibrillary tangles

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