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Regulating the crosstalk between *Bifidobacterium* and the brain: a potential therapeutic strategy for Alzheimer's disease

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Alzheimer's disease (AD) is a common dementia in the elderly population, typically manifested through symptoms of cognitive impairment (CI) and memory loss. Pathologically, it is characterized by abnormally elevated levels of amyloid-β (Aβ) deposition and tau phosphorylation. Given the rapid rate of population aging, many scientists are investigating AD, focusing on its pathogenic mechanisms and potential treatments. Unfortunately, to date, no highly effective therapeutic strategies have emerged. Intriguingly, multiple studies have revealed alterations in the gut microbiome of individuals with AD, suggesting it may serve as a novel avenue for investigating AD pathogenesis. *Bifidobacterium*, a pivotal probiotic in the gastrointestinal tract, is crucial in upholding the equilibrium of gut flora. Notably, marked deficiencies in *Bifidobacterium* have been observed in the guts of AD patients, underscoring the potential of further inquiry into the impact of Bifidobacteria on AD via the gut-microbe-brain axis. However, current research on the mechanisms through which Bifidobacteria can alleviate AD is limited, warranting further investigation. This review examines Bifidobacterial alterations in Alzheimer's disease patients and the underlying mechanisms, with the aim of evaluating their potential as a therapeutic strategy for Alzheimer's disease.

KEYWORDS

Alzheimer's disease, *Bifidobacterium*, brain-derived neurotrophic factor, neuroinflammation, neurotransmitter, short-chain fatty acid

1 Introduction

The therapeutic landscape for AD is largely defined by strategies targeting its core neuropathological features, such as cholinesterase inhibitors for symptom management, monoclonal antibodies against amyloid-beta (Aβ) plaques and p-tau (1–6). However, the clinical efficacy of these approaches in halting or reversing disease progression remains

profoundly limited, primarily due to the multifactorial nature of AD pathogenesis and the failure of single-target therapies (7, 8). This critical gap highlights the urgent need to explore novel pathways that mediate neurodegeneration. A notable phenomenon in AD research has emerged from the growing recognition of the gut-brain axis, which positions the highly dynamic gut microbiota as a significant, modifiable influencer of brain homeostasis and neuroinflammation (9, 10).

The human gastrointestinal tract is an intricate and dense microbial ecosystem, consisting of approximately 10 to 100 trillion commensal microbial cells (9). Fascinatingly, the gut microbiota can secrete neurotransmitters, neuromodulators, and various metabolites derived from amino acids (11, 12). Within this context, mounting evidence consistently reports intestinal dysbiosis in AD patients, suggesting a strong association between altered microbial composition and neurodegenerative processes (13). The key point is that the reduction of *Bifidobacterium*, a crucial genus of probiotics in the gut, has become one of the significant microbial characteristics in AD (14, 15). This discovery is particularly important because the abundance of Bifidobacteria decreases sharply with age, which is a major non-genetic risk factor for AD (14, 16, 17). Furthermore, *Bifidobacterium* plays indispensable roles, including competitive exclusion of pathogens, fortifying the intestinal mucosal barrier, and acting as a primary producer of beneficial short-chain fatty acids (SCFAs) (18–20). The convergence of its age-related decline, its pronounced depletion in AD patients, and its crucial functions—particularly in regulating systemic inflammation and metabolic health—raises a critical and timely hypothesis: The loss of *Bifidobacterium* may not be merely a consequence of AD, but an active contributor to its pathogenesis, mediated through the gut-brain axis.

Therefore, the therapeutic potential of utilizing *Bifidobacterium* as a probiotic intervention to ameliorate AD pathology is gaining momentum (21). Current research indicates that its beneficial effects are mediated through several interconnected mechanisms: by restoring microbial stability to reduce the circulating pool of pro-inflammatory molecules (22–24); by reinforcing the gut epithelial integrity to prevent the translocation of bacterial endotoxins (e.g., Lipopolysaccharide, LPS), thereby mitigating peripheral and neuroinflammation (25–27); and by utilizing metabolites such as SCFAs to directly modulate microglia function, neurotrophic factor expression (e.g., BDNF), and neurotransmitter systems (24, 28–32). This review aims to critically synthesize the current mechanistic understanding of AD-related *Bifidobacterium* alterations and the evidence supporting *Bifidobacterium* supplementation as a novel, targeted strategy for AD intervention.

2 Bifidobacteria and AD

2.1 The decrease of *Bifidobacterium* in aging population

The gut microbiota is highly sensitive to our daily lifestyle, including diet, and sleep deprivation (33). The maintenance of gut flora homeostasis is intricately linked to overall physical well-being. Intriguingly, an expanding body of research has uncovered that the aging process significantly influences the composition of the gut microbial community (34, 35). Aging is a pivotal factor in the development of dementia, yet the complex interplay between microbes, aging, and dementia remains elusive. The connection between these three ideas remains to be fully elucidated. Understanding this relationship may enhance our comprehension of their collective influence on cognitive function and potentially inform strategies for mitigating age-related neurological decline.

The gut microbiota exhibits substantial individual variation in infants, who acquire microbial communities akin to their mothers' via multiple avenues, such as vaginal birth (36) and breastfeeding (37). The diversity of the human gut microbiota correspondingly increases with age. In a Japanese study, participants were categorized into three age cohorts-infants, adults, and the elderly-to investigate the alterations in intestinal microbiota across these distinct age groups (2). The study revealed a higher relative abundance of *Actinobacteria* in the infant cohort, an increased relative abundance of *Clostridia* in the adult group, and a significantly elevated prevalence of *Bacteroidetes*, *Betaproteobacteria*, and *Deltaproteobacteria* in the elderly group (Figure 1).

However, changes in gut microbiota cannot be ruled out by other factors, such as routine and diet. Therefore, whether age can be an independent factor influencing changes in gut flora is unclear for the time being and requires further research. Parker A et al. found that altering the gut flora can modulate biomarkers in the gut, eyes and brain (34). Transplantation of gut microbiota from young to aged mice modifies the microbial composition of the recipients, significantly increasing the relative abundance of taxa such as *Bifidobacterium animalis*, *Eubacterium* spp., *Akkermansia muciniphila*, and *Clostridium cocleatum*. At the same time, it reduces the expression of the inflammatory complement protein C3 in the retina and decreases the serum concentration of LPS-binding protein (LBP), thereby alleviating inflammation (34). Conversely, the transfer of fecal flora from older mice to young mice promotes microglia activation while exacerbating central nervous system (CNS) inflammation (34). In recent years, microglia overactivation has been denoted as an important factor in triggering neuroinflammation and an important cause of cognitive dysfunction (38). In contrast, altering the fecal flora of young mice reversed these deleterious effects. This may provide indirect evidence suggesting that the composition of the microbiota changes with age, thereby accelerating aging and cognitive decline. Therefore, the potential for using the significant decline of Bifidobacteria in the elderly gut as a novel therapeutic target for AD warrants further investigation (35).

2.2 Supplementation with *Bifidobacteria* can remodel gut microbiota in AD patients

Patients with AD exhibit clinical manifestations including CI and memory deficits, with the classic pathophysiological features characterized by Aβ deposition and hyperphosphorylation of tau protein. Nevertheless, an increasing body of evidence indicates

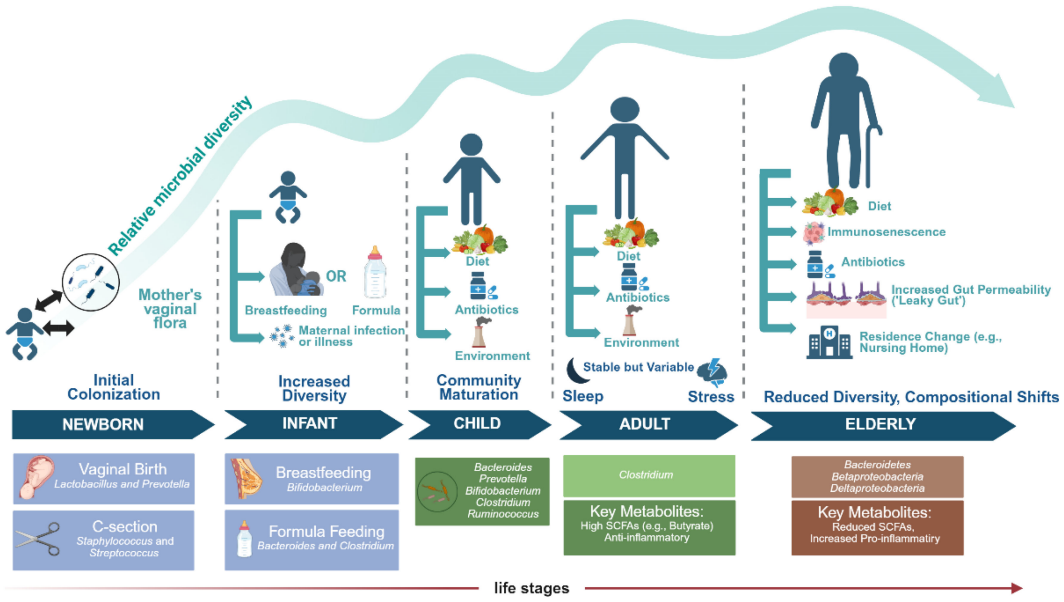

FIGURE 1
The composition of the human gut microbiota is dynamically modulated by various factors, including advancing age and alterations in lifestyle. (Image created using BioRender.com).

disturbances in the gut microbiota of individuals with AD, including an elevated relative abundance of Mycobacterium avium, as well as a reduction in the relative abundance of *Bifidobacterium* and *Firmicutes* (29, 39, 40). To date, studies have not established that specific microbiota exert therapeutic effects in Alzheimer's disease, underscoring a critical gap in the field. However, scientists are attempting to improve the imbalance of the microbiota by supplementing probiotics, ultimately alleviating AD.

This therapeutic potential of probiotics is not only limited to AD patients but also extends to the broader context of healthy aging. Shi S et al. demonstrated that oral administration of *Bifidobacterium longum* BB68S (BB68S, 5 × 10^{10} CFU/sachet)) daily for 8 weeks, markedly improved cognitive function in healthy older adults, as evidenced by an 18.89-point increase in the total RBANS score post-intervention ($p<0.0001$), with significant improvements observed in immediate memory, visuospatial/constructional skills, attention, and delayed memory (41). Concurrently, the BB68S treatment elevated the relative abundance of beneficial bacterial species, including *Lachnospira* and *Bifidobacterium*, while reducing the prevalence of taxa linked to cognitive impairment, such as *Collinsella* and *Parabacteroides* (41). The findings suggest that probiotic supplementation may mitigate cognitive deficits, but further verification is needed. The main limitations of this study include (42): a lack of analysis of the peripheral system and gut microbiota metabolites, making it unclear which metabolites were the source of therapeutic effects (43); although cognitive function significantly improved, changes in certain cognitive domains and the gut microbiota were not significant (44); an eight-week study may be insufficient to observe these outcomes, so longer-term research is needed (45); participants' diets were not strictly controlled during the intervention, so we cannot be rule out the impact of dietary changes on the gut microbiome. Future studies need more rigorously designed research, such as strict dietary control.

Furthermore, the cognitive benefits of microbiota modulation can be enhanced through synbiotic approaches, which combine probiotics with prebiotics (46). A randomized, double-blind, placebo-controlled trial showed that a synbiotic supplement containing *Bifidobacterium animalis subsp. lactis* GCL2505 and inulin significantly improved overall cognitive function, including attention, cognitive flexibility, and executive function in elderly participants over 12 weeks (47). This intervention notably increased fecal *Bifidobacterium* counts and positively modulated several inflammatory markers, suggesting that the cognitive improvements were mediated by enhancing the gut environment and alleviating inflammation (More clinically relevant experiments are presented in Table 1).

These studies provide evidence that *Bifidobacterium* supplements enhance cognition (41, 46). However, a critical question remains: How do these gut microbes exert profound effects on the brain? The mechanisms by which *Bifidobacterium* coordinates regulation of the gut-brain axis are only beginning to be elucidated. Unraveling these pathways is essential for translating probiotic therapies into targeted clinical interventions for AD.

3 Mechanisms of *Bifidobacteria* improving AD via the gut-brain axis

Increasing evidence suggests a communication between the nervous system and the gut, with the microbe-gut-brain axis emerging as a pivotal concept in the investigation of

TABLE 1 Partial Findings of Bifidobacteria Improvement in AD (Trial studies).

NO.	Disease	Intervention	CFU; Dose; Duration	linical Effects and Biological Observations of Intervention Group Compared with Placebo Group	Intestinal microorganisms	Trial ID; Reference
1	Older patients with mild cognitive impairment (MCI)	*B. animalis subsp. lactis* GCL2505	1×10^{10} CFU/day each; 12 weeks	• The treatment group showed improvements in Cognitrax (short), MMSE-J, and MoCa-J scores.	• Increased levels of fecal Bifidobacteria.	UMIN000048386; (47)
2	Healthy older adults	*B. longum* BB68S	5×10^{10} CFU/day each; 8 weeks	• Significantly improves immediate memory and attention in healthy elderly individuals.	• The relative abundance of the phyla Actinobacteria and Firmicutes increased in the BB68S group. • The relative abundance of the phylum Proteobacteria decreased.	(41)
3	AD patients	*L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum*	2×10^{9} CFU/g for each; 12 weeks	• Patients in the probiotic group showed improved MMSE scores ($P < 0.001$).		IRCT201511305623N60; (48)
4	AD patients	Selenium+*L. acidophilus*, *B. bifidum*, and *B. longum*	2×10^{9} CFU/day each; 12 weeks	• The MMSE scores showed a significant improvement ($P < 0.001$). • IL-8, TNF-α, and TGF-β levels decreased significantly.		IRCT20170612034497N5; (49)
5	AD patients	*B. longum subsp. Infantis* BLI-02, *B. breve* Bv-889, *B. animalis subsp. Lactis* CP-9, *B. bifidum* VDD088, and *Lactobacillus plantarum* PL-02	1×10^{10} CFU/day each; 12 weeks	• There were no significant differences in cognitive test scores (ADAS-Cog, MMSE, ADL, and CDR) between the active control group and the treatment group. • The treatment group exhibited a significant decrease in IL-1β, cortisol, MDA, and PCC levels, along with an increase in SOD activity ($p < 0.05$).	• The treatment group experienced an increase in the abundance of *Bifidobacterium* ($p = 0.317$), Lactobacillus ($p = 0.354$), Ruminococcus ($p = 0.286$), Clostridium ($p = 0.321$), and Akkermansia ($p = 0.934$) at the genera level. Conversely. • The presence of Megamonas ($p = 0.213$) decreased in the treatment group.	(50)
6	AD patients	*B. breve* A1	1×10^{10} CFU/day each; 24 weeks	• Patients in the treatment group showed improvement in their MMSE scores.		NCT05145881; (51)
7	Older patients with MCI	*B. breve* MCC1274	2×10^{10} CFU/day each; 16 weeks	• Patients in the treatment group showed improvement on the Assessment of Neuropsychological Status (RBANS) and the Japanese version of the MCI Screen (JMCIS) tests.		UMIN000037725; (52)
8	AD patients	*B. breve* MCC1274	2×10^{10} CFU/day each; 24 weeks	• No significant difference was found between ADAS-Jcog and MMSE.		UMIN000031507; (53)

neurodegenerative diseases. This communication is mediated primarily through immune-related, neural, endocrine, and metabolic signaling pathways (54). Thus, the maintenance of gut microbiota homeostasis is essential for ensuring optimal brain function. *Bifidobacterium*, a commonly utilized probiotic, is frequently administered alone or in concert with other probiotics to modulate the intestinal flora environment for therapeutic purposes and is currently widely employed in the management of intestinal diseases, diabetes mellitus (55), and liver diseases (56). In light of the observation that AD patients exhibit reduced levels of Bifidobacteria within their intestinal microbiota, researchers have hypothesized that Bifidobacterial supplementation, alone or in combination with other strategies, may be a potential therapeutic approach for AD.

3.1 *Bifidobacteria* improved AD by neuroinflammation inhibition

Neuroinflammation is a key pathological feature of AD, and its origin is frequently traced to the gut (57). Disruption of the symbiotic relationship between the gut microbiota and the intestinal immune system can exacerbate inflammatory processes, characterized by the release of pro-inflammatory cytokines and increased intestinal permeability, often referred to as "leaky gut" (Figure 2) (58). Critically, this inflammation extends along the gut-brain axis, leading to neuroinflammation within the brain (39). On one hand, gut dysbiosis abnormally activates microglia, causing them to release chemokines and trigger neuroinflammation (59, 60); on the other hand, it also promotes the production of LPS, leading to intestinal inflammation (61). In populations with impaired gut and blood-brain barrier (BBB), such as the elderly, LPS more easily transfers to the brain (62). Notably, plasma LPS levels in Alzheimer's disease patients are significantly higher than in healthy controls, contributing to a mild chronic inflammatory state in AD patients (63). Upon reaching the brain, LPS interacts with microglia, eliciting the activation of toll-like receptors (TLRs) and initiating potent neuroinflammatory responses (39).

Multiple studies have shown that administration of *Bifidobacterium* (as single strains or in composite formulations) significantly reduces the expression of pro-inflammatory factors like TNF-α and IL-1β in colonic tissue and decreases the infiltration of NF-κB+CD11c+ pro-inflammatory immune cells (64–66). This indicates that Bifidobacteria effectively alleviate local intestinal inflammation. Furthermore, by repairing the intestinal barrier and optimizing the microbiota composition, *Bifidobacterium* treatment leads to a significant decrease in LPS levels in both blood and feces (64, 66), signifying effective control of gut-derived systemic inflammation, or metabolic endotoxemia. This reduction in peripheral inflammatory signals subsequently extends to the CNS. Across multiple relevant models, *Bifidobacterium* intervention significantly decreased the expression of core pro-inflammatory factors—including TNF-α, IL-1β, and IL-6—in the hippocampus, a brain region critical for cognitive function, while concurrently inhibiting the activation of the NF-κB signaling pathway (64–66). This direct alleviation of the neuroinflammatory microenvironment represents a key mechanism by which Bifidobacteria may mitigate the progression of AD.

3.2 Bifidobacteria improves AD by increasing SCFAs

SCFAs are the primary metabolic products produced by the fermentation of dietary fiber by the gut microbiota. Among them, acetate, propionate, and butyrate are the most extensively studied and functionally important members. They are regarded as key "microbiota-host" communication molecules, playing a central role in neurotrophic regulation (67). As important acid-producing bacteria, *Bifidobacterium* positively influences gut-brain axis function by promoting the generation of SCFAs (68). These SCFAs can not only cross the BBB to directly act on the CNS but also indirectly regulate brain function and behavior through peripheral pathways (67). For instance, Fernando et al. found that supplementation with a composite formulation of *Bifidobacterium breve*, *Bifidobacterium longum*, and *Lactobacillus rhamnosus* significantly increased the total levels of SCFAs in the gut, highlighting the important role of *Bifidobacterium* in driving SCFA production (69).

Bifidobacterium primarily produces acetate and lactic acid through glucose metabolism, with acetate being its main end product (17). The mechanisms by which SCFAs ameliorate AD involve multiple pathways. Firstly, in maintaining the gut barrier function, acetate, as a vital energy source for colonic epithelial cells, supports their normal proliferation and function, thereby ensuring the integrity of the intestinal mucosa (70). More importantly, acetate can upregulate the expression and stability of tight junction (TJ) proteins (such as Claudin, Occludin, and ZO-1), reducing intestinal permeability (i.e., "leaky gut"). This effectively prevents harmful substances like endotoxins (e.g., LPS) from entering the bloodstream, thereby alleviating LPS-driven systemic and CNS inflammation and achieving indirect neuroprotection (71).

Secondly, SCFAs, particularly butyrate, demonstrate potent direct neuroprotective effects (72). Although *Bifidobacterium* does not produce butyrate directly, its metabolic products, acetate and lactic acid, can serve as substrates for other butyrate-producing bacteria (such as *Clostridia* and *Eubacterium*), indirectly promoting butyrate generation through a "cross-feeding" mechanism (Figure 3) (73).

This synergistic acid production process is crucial for host health. In AD mouse models, intervention with sodium butyrate (NaB) not only significantly enhanced synaptic plasticity but also directly reduced the levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) in the brain, inhibited the overactivation of microglia, and prevented the deposition of β-amyloid (Aβ) (74). Its molecular mechanism involves binding to the GPR109A receptor, which in turn upregulates PPAR-γ expression and inhibits the activation of the TLR4/NF-κB signaling pathway. This process corrects the M1/M2 polarization imbalance in microglia, ultimately potentially

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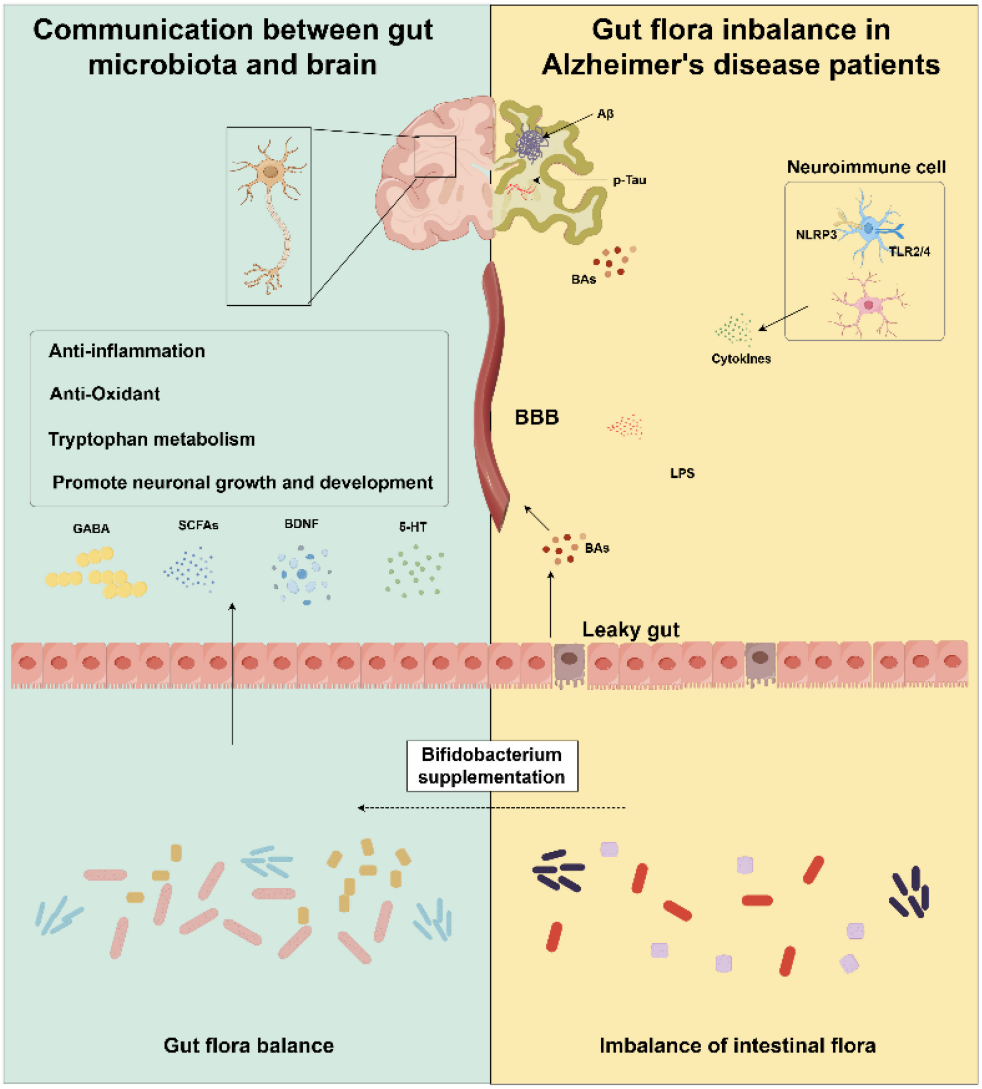

FIGURE 2
By supplementing Bifidobacteria, it can promote the production of GABA, SCFAs, BDNF and 5-HT, reduce neuroinflammation, promote the growth and development of neurons and thus improve AD. (Image created using Figdraw). GABA, gamma-aminobutyric acid; SCFAs, short-chain fatty acids; BDNF, Brain-derived neurotrophic factor; Aβ, amyloid-β; BAs, bile acids; LPS, Lipopolysaccharide; NLRP3, NOD-like receptor 3; TLR2/4, Toll like receptors 2/4.

improving cognitive deficits in mice (75). In addition to butyrate, acetate can also exert anti-neuroinflammatory effects by activating receptors such as GPR41 on microglia, thereby inhibiting pro-inflammatory signaling pathways like p38 MAPK, JNK, and NF-κB (76–78). The above studies exemplify the great potential of SCFAs and related salts, especially butyric acid and butyrate molecules, in improving AD.

In summary, current evidence strongly suggests that *Bifidobacterium* can exert its multifaceted functions by modulating the generation and composition of SCFAs. These functions include strengthening the intestinal barrier, exerting systemic anti-inflammatory effects, and providing direct neuroprotection, such as inhibiting neuroinflammation, reducing Aβ accumulation, and improving synaptic function. Therefore, targeting the *Bifidobacterium*-SCFA axis represents a highly promising therapeutic strategy for intervening in AD, and its associated molecular mechanisms provide an important theoretical foundation (79–85).

3.3 Bifidobacteria improved AD by increasing BDNF

Brain-derived neurotrophic factor (BDNF) is a critical protein essential for neuronal survival, growth, and function (86). Its promotion of neurogenesis and synaptic plasticity constitutes the biological basis of learning and memory. Substantial evidence indicates that BDNF levels in the brains of patients with AD are negatively correlated with disease severity (87, 88). In recent years, the modulation of BDNF-mediated brain function via the gut-brain

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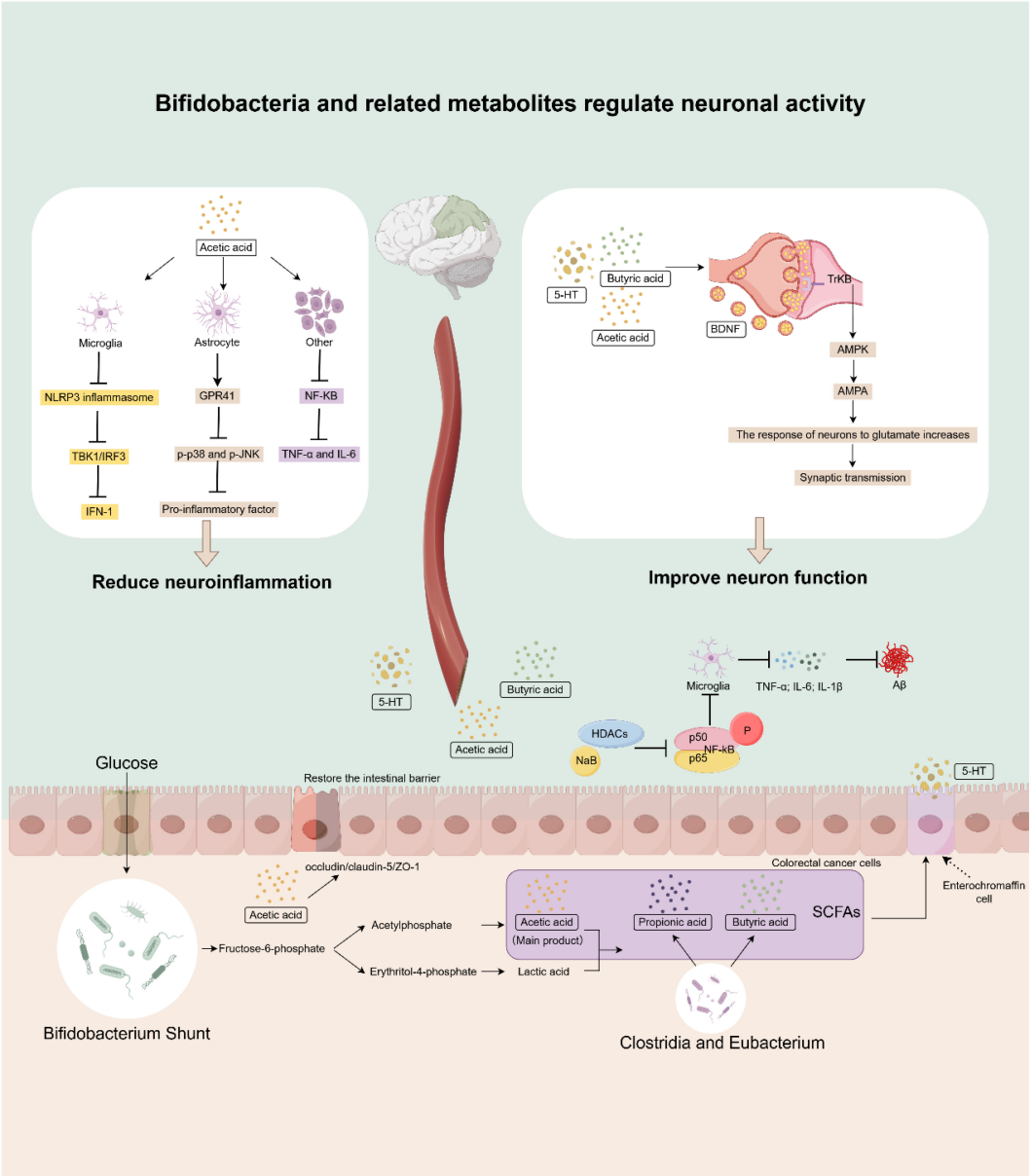

FIGURE 3
The mechanism by which Bifidobacteria and their related metabolites improve AD. The main product of SCFAs produced by Bifidobacteria is acetic acid. Acetic acid and lactic acid can serve as metabolic substrates for other microbial communities (Clostridia and Eubacterium), leading to the generation of propionic acid and butyric acid. Butyric acid, in turn, promotes the production of 5-HT in enterochromaffin cell. These metabolites improve AD by reducing the release of inflammatory factors, decreasing the production of Aβ, and enhancing neuronal function. (Image created using Figdraw).

axis has emerged as a significant candidate mechanism for probiotic intervention in neurodegenerative disorders (89). Although *Bifidobacterium* does not produce BDNF itself, multiple studies have demonstrated its capacity to significantly elevate BDNF levels in the host brain (90).

The mechanisms by which *Bifidobacterium* upregulates BDNF are multifaceted. At the molecular signaling level, BDNF activates its receptor, TrkB, to modulate core brain functions such as long-term potentiation (LTP), dendritic spine growth and maturation, and adult hippocampal neurogenesis (91, 92). At the epigenetic level, *Bifidobacterium* can promote BDNF expression by influencing histone modifications. For instance, *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI were shown to effectively enhance BDNF expression by increasing the trimethylation of histone H3 lysine 9 (H3K9me3), thereby ameliorating age-related cognitive deficits in mice (93).

However, a deeper upstream regulation underlying these mechanisms appears to be closely associated with the suppression of neuroinflammation driven by gut dysbiosis. Gut dysbiosis, particularly in aging or AD models, leads to an increased abundance of pro-inflammatory bacteria such as *Proteobacteria* and a concomitant rise in their LPS production (64). LPS can

compromise the BBB through multiple mechanisms, thereby promoting the development of various cerebral diseases, such as sepsis-associated encephalopathy (SAE) (44). The primary way LPS disrupts the BBB is by inducing inflammation and directly acting on endothelial cells: LPS stimulates NF-κB expression by binding to Toll-like receptor 4 (TLR4) (94). The activated NF-κB pathway subsequently enhances BBB permeability by reducing the expression of TJ proteins, such as Occludin (95, 96). This damage to the barrier allows circulating LPS and harmful chemical substances to penetrate the CNS more easily (44), consequently inducing CNS dysfunction. Activated NF-κB not only induces the release of pro-inflammatory cytokines like TNF-α and IL-1β but also suppresses BDNF expression while upregulating key enzymes in the Aβ production pathway: β- and γ-secretases (97, 98). This creates a vicious cycle of "inflammation-amyloidosis-BDNF suppression," ultimately leading to CI (99).

Against this background, numerous studies have provided direct evidence for the therapeutic effects of *Bifidobacterium*. For example, a combined intervention with *Bifidobacterium adolescentis* NK98 and *Lactobacillus reuteri* NK33 not only upregulated hippocampal BDNF expression but also synergistically inhibited the NF-κB signaling pathway, thereby mitigating neuroinflammation (100). Similarly, treatment with strains like *Bifidobacterium breve* CCFM1025 has been shown to enhance synaptic plasticity and elevate levels of BDNF and key synaptic proteins, including postsynaptic density protein 95 (PSD-95) (20). More recent studies have further elucidated the detailed mechanisms of this process. For instance, *Bifidobacterium longum* NK46, both alone and in combination with *Lactobacillus mucosae* NK41 (NKc), effectively suppressed the abundance of LPS-producing gut bacteria and reduced blood LPS levels, thereby blocking the aforementioned inflammatory cascade at its source (64). *In vivo* studies confirmed that oral administration of NK46 or NKc significantly inhibited NF-κB activation in the hippocampus of AD and aged mouse models (64, 101). This, in turn, relieved the suppression on BDNF, leading to a marked increase in hippocampal BDNF expression and the population of BDNF+ neurons, accompanied by an improvement in cognitive deficits (64, 99).

Notably, the benefits of *Bifidobacterium* also extend to associations with other pathological processes. For instance, in a model of CI induced by the periodontopathogen *Porphyromonas gingivalis*, a combination of *Bifidobacterium bifidum* NK391 and *Lactobacillus pentosus* NK357 similarly reversed the suppressed levels of hippocampal BDNF and N-methyl-D-aspartate receptor (NMDAR) by inhibiting the NF-κB pathway (66).

In conclusion, *Bifidobacterium* upregulates BDNF through a multi-layered mechanistic network. It may not only directly promote BDNF gene expression through epigenetic modifications (93), but more importantly, it alleviates the suppression of BDNF expression by reshaping the gut microbiota, inhibiting LPS production and absorption, and blocking NF-κB-mediated neuroinflammation. This process is tightly coupled with other functions, such as attenuating Aβ pathology and preserving synaptic function (64, 66, 91–93, 99, 102), providing a robust theoretical basis for improving AD.

3.4 Bifidobacteria improved AD by regulating neurotransmitters release

Neurotransmitters serve as fundamental mediators of interneuronal communication and are indispensable for the preservation of normal brain functionality (103, 104). These molecules not only facilitate the transmission of neural signals but also play a pivotal role in modulating cognitive processes, emotional responses, and behavioral outcomes (105). The objective of this section is to delineate the mechanisms by which Bifidobacteria modulate key neurotransmitters, including serotonin (5-HT), and gamma-aminobutyric acid (GABA), thereby exerting potential therapeutic effects on AD (Figure 2).

3.4.1 5-HT

5-HT, a neurotransmitter extensively researched in the CNS, is involved in both central and peripheral physiological processes, modulating a diverse array of functions (105). For instance, in AD mouse models, the accumulation of Aβ correlates with a decrease in 5-HT2A receptor expression (106), whereas targeting 5-HT1B and 5-HT2C receptors has demonstrated the potential to mitigate Aβ neurotoxicity and tau hyperphosphorylation (107, 108). Notably, over 90% of the body's 5-HT is synthesized by intestinal enterochromaffin (EC) cells, a process in which the gut microbiota and their metabolites, particularly SCFAs, are critical regulators (109). Studies have shown that these SCFAs, especially butyric acid, can directly stimulate EC cells, establishing a direct signaling axis within the "microbiota-gut-brain" communication network (110).

Based on this, *Bifidobacterium*, as a primary producer of SCFAs, is posited to have the potential to indirectly modulate central 5-HT levels (111–113). *Bifidobacterium animalis subsp. lactis* HN019 (*B. lactis* HN019TM) has been applied in infant foods and studies have demonstrated its benefits in maintaining normal physiological functions in the elderly, which may be related to the regulation of 5-HT signaling by SCFAs produced through microbial fermentation (19). Zhang S et al. supplemented APP/PS1 mice with prebiotics to stimulate the growth and development of gut probiotics, and found a significant increase in the relative abundance of Bifidobacteria, as well as alterations in the concentrations of neurotransmitters GABA and 5-HT in the brains of APP/PS1 mice, while reversing the cognitive dysfunction in APP/PS1 mice (114). Although this study employed prebiotics rather than direct probiotic supplementation, it provides crucial indirect evidence supporting a causal chain linking "increased *Bifidobacterium* abundance - elevated BDNF levels - amelioration of AD phenotypes."

3.4.2 GABA

GABA is the primary inhibitory neurotransmitter in the mammalian CNS (115). It mediates signaling between neurons, thereby modulating neuronal excitability by activating GABA receptors (116). In AD pathogenesis, GABAergic system dysregulation can lead to neuronal hyperexcitability, disrupted neural network activity, neuroinflammation, and synaptic

impairment (117). Theoretically, restoring the excitatory-inhibitory balance by enhancing GABAergic signaling represents a viable therapeutic strategy for AD (118, 119). The gut microbiota is considered a significant peripheral source of GABA, with certain *Bifidobacterium* strains possessing the genetic basis to convert glutamate into GABA (120).

Emerging research indicates that GABA in the human gastrointestinal tract may originate from the conversion of dietary monosodium glutamate (MSG) by gut microbiota (31, 121). Nevertheless, the capacity of gut-derived *Bifidobacterium* strains to synthesize GABA has not been extensively investigated. Presently, the primary genes implicated in GABA synthesis in *Bifidobacterium* are gadB and gadC (30). The gadB gene codes for glutamate decarboxylase, an enzyme dependent on pyridoxal phosphate that catalyzes the decarboxylation of glutamate to yield GABA, while the gadC gene codes for the glutamate/GABA antiporter, a protein that facilitates the exchange of intracellular GABA for external glutamate. Consequently, Duranti S et al. conducted an analysis on *Bifidobacterium* strains expressing the gadB and gadC genes, utilizing data from the NCBI gene database, and identified 81 strains from 1002 Bifidobacteria encoding gadB and gadC, including *B. adolescentis, B. angulatum, B. dentium, B. merycicum, B. moukalabense, B. ruminantium*, and *B. samirii* (30). Notably, the *Bifidobacterium adolescentis* strain exhibited the highest expression of Gad genes within its genome, and *in vitro* studies revealed its capacity to effectively convert over 65% of its precursors to GABA, such as *B. adolescentis* PRL2019 and *B. adolescentis* HD17T2H, indicating that this taxon of *Bifidobacterium* is a potent GABA producer within the genus (30). In order to assess the efficacy of various probiotic strains in fermenting milk to enhance GABA production, Héctor Tamés et al. discovered, via computational simulations and *in vitro* experiments, that a particular strain, IPA60004, not only exhibited robust survival rates but also resulted in elevated GABA concentrations in their milk samples (122). E. Barrett et al. determined that, upon assessing 91 strains of bacteria originating from the human intestine, the GABA synthesized by Bifidobacteria displayed significant variability, with *Lactobacillus brevis* and *Bifidobacterium dentium* being the most efficient GABA producers (31). Studies investigating the application of Bifidobacteria for enhancing AD symptoms through GABA modulation are not without limitations. While *in vivo* experiments have demonstrated that intestinal GABA synthesis can be augmented by the addition of Bifidobacteria, which in turn may lead to improved cognitive performance in murine models (123–126), the exact mechanism underlying these effects has yet to be completely clarified. Additional research is required to delineate the sequential processes and the cellular and molecular dynamics at play.

Significant hurdles exist in the identification and selection of probiotics for AD therapy through the utilization of current databases and clinical samples. Some studies on the improvement of AD by *Bifidobacterium* are presented in Table 2. Existing databases and clinical sample collections frequently exhibit constraints in terms of size and geographic diversity, substantially impacting the generalizability and dependability of the research outcomes (30). These constraints highlight the necessity for broader and more varied datasets to inform the selection of probiotics that could be effective in AD therapy.

5 Limitations

However, the "reconstruction" of the gut microbiota is not always complete or consistent. First, the extent of microbiota recovery is limited. In numerous studies, although favorable shifts in microbial composition occur, overall diversity and structure often do not fully restore to levels observed in healthy wild-type mice (130, 131, 133). The profound impact of AD pathology itself on the microbiota may make it difficult for simple supplementation with a few probiotics to fully reverse these changes (90). Second, strain- and host-specific effects are significant. Different *Bifidobacterium* strains (e.g., *B. longum* vs. *B. breve*) possess distinct metabolic characteristics and colonization abilities, leading to varying patterns of induced microbiota changes (133). Similarly, AD model mice with different genetic backgrounds exhibit distinct baseline microbiomes and responses to probiotics (64, 87, 102, 134), complicating direct comparison and extrapolation of research findings.

A key piece of evidence comes from the study by Hongwon Kim et al. (93). This study ingeniously compared the effects of probiotics (*B. bifidum* BGN4 and *B. longum* BORI) on young (3-month-old) and aged (16-month-old) mice. Results revealed that probiotic intervention significantly altered fecal microbiota composition in young mice but had minimal effect on elderly mice. However, in stark contrast to this "non-responsive" microbiota, probiotics similarly reversed DNA damage and apoptosis in elderly mice while improving age-related cognitive and memory deficits. This indicates that while *Bifidobacterium* supplementation consistently demonstrates positive effects on cognitive enhancement and neuroinflammation suppression, its capacity to remodel the gut microbiota is far from universal or uniform. Instead, it exhibits significant model dependency and age-related variability, constituting a prominent and central contradiction in current research (41, 47, 93).

Another core contradiction is the dissociation between cognitive improvement and core pathological changes. For instance, studies have observed enhanced performance in AD mice on water maze tests following supplementation with specific Bifidobacteria. However, some investigations do not demonstrate concurrent reductions in Aβ plaque burden or tau phosphorylation levels (50, 65, 135), particularly lacking corresponding data from human brains. Therefore, existing evidence remains insufficient to strongly demonstrate a direct link between *Bifidobacterium*-mediated cognitive improvement and core AD pathological products. A more plausible mechanism involves cognitive enhancement through pathways such as alleviating neuroinflammation, enhancing synaptic plasticity, or regulating neurotransmitter metabolism (41, 42, 47, 66, 128). This suggests that the "downstream effects" of microbiota restoration may

TABLE 2 Partial Findings of Bifidobacteria Improvement in AD (Animal studies).

No.	Bifidobacteria strains	Metabolites	Model	Findings/Mechanism	Intestinal microorganisms	Reference
1	*B. longum* NK46	BDNF	• LPS-treated 5xFAD-transgenic mice • Aged mice	• Levels of Aβ, BACE, and Psen were all reduced. • Y-maze task and other measures indicate improvements in cognitive and memory functions.	• The population of Proteobacteria, Verrucomicrobia, Akkermansiaceae, Sutterellaceae, and Desulfovibrionaceae was decreased. • The population of Odoribacteriaceae was increased.	(64)
2	Bifidobacteria		• WT mice • APP/PS1 mice	• A significant decrease in the level of soluble Aβ in the cortex of AD + Bi mice.		(127)
3	*B. breve* MCC1274		• WT mice	• Reduce levels of senescin-1 protein, soluble Aβ42 in the hippocampus, and phosphorylated tau protein. • Increase levels of synaptic proteins.		(87)
4	*B. bifidum* BGN4 and *B. longum* BORI	BDNF	Aged mice	• Open field tests and other measures suggest improvements in cognitive function.	• The abundance of Lachnoclostridium bacteria has decreased. • The abundance of while that of Clostridium ASF356 has increased.	(93)
5	*B. bifidum* P61	BDNF	Aged mice	• Y-maze task (YMT) suggests improvements in cognitive function.	• The population of Odoribacteraceae and Deferribacteriaceae was decreased. • The population of Akkermansiaceae and Bacteroidaceae was increased.	(65)
6	*B. bifidum* NK391	BDNF	CI mice	• YMT and novel object recognition test (NORT) suggest improvements in cognitive function.	• The population of Microbium genus, Erysipelothrix genus, and Acmannia genus was decreased.	(66)
7	*B.* CCFM1025	BDNF, acetate, and xanthurenic acid	5xFAD mice	• Accumulation of Aβ1–42 was significantly reduced, and synaptic plasticity was enhanced. • YMT suggests improvements in cognitive function;	• The population of *Bifidobacterium*, Mucispirillum, and Ruminococcus was increased.	(21)
8	*B. breve* HNXY26M4	Acetate and butyrate	APP/PS1 mice	• Accumulation of Aβ was significantly reduced. • YMT and NORT suggest improvements in cognitive function.	• The relative abundance of Lactobacillus and Acinetobacter was partially restored.	(128)
9	*B. bifidum* BGN4 and *B. longum* BORI	BDNF	AD mice	• Reduced hippocampal neuronal death in 5xFAD mice. • Restored BDNF and synaptic scaffolding proteins in the hippocampus of 5xFAD mice. • Reduced Aβ42; YMT suggests improvements in cognitive function.	• The population of Parvibacter, Incertae Sedis, and Oscillibacter was decreased. • The population of *Bifidobacterium*, Akkermansia, Faecalibacterium, Erysipelothrix, and Candidatus Stoquefichus was increased.	(99)
10	*B. breve* CCFM1025	Acetate	Aβ1-42-treated mice	• Reduce levels of Aβ1–42 in the hippocampus. • YMT and other measures suggest improvements in cognitive function.	• The relative abundance of Coprococcus was decreased. • The relative abundance of Akkermansia was increased.	(129)
11	*B. bifidum* TMC3115		APP/PS1 mice		• The relative abundance of Bacteroides was decreased. • The relative abundance of Acetobacter and Bacteroides was increased.	(130)
12	*B. breve* MCC1274		AppNL-G-F mice	• Reduces the production and deposition of β-amyloid in the hippocampus.	Not change.	(131)

(Continued)

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TABLE 2 Continued

No.	Bifidobacteria strains	Metabolites	Model	Findings/Mechanism	Intestinal microorganisms	Reference
				• Enhances ADAM10 protein levels in the hippocampal region of AppNL-G-F mice. • Improves post-transcriptional regulation of ADAM10. • Increases synaptic protein levels in the hippocampus. • Does not alter the phosphorylation status of tau protein. • NORT suggests improvements in cognitive function.		
13	*B. longum* NK46	BDNF	5XFAD-Tg and aged mice	• Reduce the accumulation of Aβ plaques. • YMT and other measures suggest improvements in cognitive function.	• The relative abundance of thick-walled bacteria and amoebobacteria was decreased. • The relative abundance of Bacteroides was increased.	(101)
14	*B. breve* A1	Acetate	Aβ25-35-treated mice	• YMT and other measures suggest improvements in cognitive function.	• The proportions of Faecalibacterium and Bacteroides were slightly lower. • The proportions of Actinobacteria and Bifidobacteria significantly increased.	(132)
15	*B. breve* CCFM1025 and *B. breve* JSWX22M4	BDNF and acetate	Aβ1-42-treated mice	• Reduce the accumulation of Aβ plaques. • YMT and other measures suggest improvements in cognitive function.		(129)
16	*B. bifidum* BROB	BDNF	Aβ1-42-treated mice	• passive avoidance test (shuttle box) suggests improvements in cognitive function.		(102)
17	*B. longum* NK173	BDNF	LPS-treated mice	• YMT and other measures suggest improvements in cognitive function.	• The relative abundance of phyla Firmicutes, Proteobacteria, and Proteobacteria was decreased. • The relative abundance of phylum Bacteroidetes was increased.	(133)
18	*B. longum* NK219		LPS-treated mice	• YMT and other measures suggest improvements in cognitive function.		(42)

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be more complex than anticipated, with cognitive improvements resulting from multifactorial interactions rather than being an inevitable consequence of a single pathological marker's improvement.

Furthermore, a significant challenge to the long-term efficacy of this approach is the transient nature of the microbial changes. Upon discontinuing probiotic supplementation, the gut microbiota of mice often reverts to its pre-intervention state within weeks (136–138). This indicates that oral administration of live bacteria alone may fail to achieve sustained microbial colonization and ecological reconstruction. The observed improvements are more likely a form of "functional regulation." During their transient presence in the gut, probiotics exert beneficial physiological effects through their metabolites (e.g., short-chain fatty acids) or interactions with the host immune system, rather than fundamentally altering the long-term structural composition of the microbiota (139–142). This also explains why some studies require long-term, continuous administration to sustain effects.

6 Conclusion and future prospects

This review has synthesized the current evidence linking gut Bifidobacteria to Alzheimer's disease (AD), revealing a landscape of promising therapeutic potential overshadowed by significant complexities and contradictions (143). While studies consistently report cognitive benefits associated with *Bifidobacterium* supplementation (51, 55, 129, 135), critical gaps remain, including the dissociation between cognitive improvement and core AD pathology, the strain- and host-specific nature of the effects, and the transient nature of microbial changes.

To transform these correlational insights into causative therapies, the field must evolve. Future research must prioritize establishing direct causality, moving beyond association. This will require innovative models, such as germ-free AD mice colonized with defined microbial communities, to dissect the precise role of *Bifidobacterium* and its key metabolites (e.g., specific SCFAs, tryptophan derivatives) in modulating neuroinflammation and synaptic function (17, 78, 144). Concurrently, critical, understudied parameters must be systematically addressed. Research must determine the optimal timing of intervention (pre-symptomatic vs. symptomatic stages), evaluate the synergistic potential of multi-strain formulations versus single strains, and elucidate the complex interactions with host diet and genetics. Finally, to bridge the translational gap, future clinical trials must be designed with enhanced rigor. This necessitates the incorporation of standardized cognitive endpoints, robust biomarker panels (e.g., neuroimaging, fluid biomarkers), and high-resolution metagenomic sequencing. By embracing these more sophisticated and mechanistic approaches, we can move from merely observing benefits to truly understanding and harnessing the microbiota-gut-brain axis for the development of effective, novel therapeutics against AD.

Author contributions

LP: Writing – original draft, Writing – review & editing. ZZ: Writing – review & editing, Conceptualization, Funding acquisition. YH: Writing – review & editing. HC: Writing – review & editing. YT: Funding acquisition, Writing – review & editing. HL: Conceptualization, Funding acquisition, Writing – review & editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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