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Review Article

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Exploring the Gut-Brain Connection: The Role of Microbiota in Alzheimer's Disease Pathogenesis

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ABSTRACT

Alzheimer's disease (AD), the primary cause of dementia accounting for 60% to 70% of cases globally, results in a gradual decline in cognitive abilities, affecting memory, executive function, and daily activities. Recent research highlights the essential involvement of the microbiota-gut-brain axis in AD pathogenesis, characterized by complex bidirectional signaling that modulates neuroinflammation, neurogenesis, neurotransmission, and immune functions. This manuscript extends the discussion beyond the gut alone by emphasizing the significance of the oral-gut microbiota axis as a dynamic and relatively under-investigated factor in AD progression. Microbial populations in both the oral cavity and gastrointestinal tract produce key neurotransmitters, such as gamma-aminobutyric acid, noradrenaline, and dopamine, as well as neuroactive metabolites like short-chain fatty acids, which together impact brain physiology. Disturbances in gut and oral microbial balance can compromise barrier integrity, promoting systemic inflammation and neuroinflammation, and facilitating amyloid-β plaque formation and tau-related changes typical of AD. This review introduces a novel probiotic, prebiotics, synbiotics, and postbiotics (PPSP) therapeutic model designed to modulate both oral and gut microbiota, aiming to restore homeostasis, regulate neuroimmune interactions, and counteract cognitive impairment. We comprehensively assess emerging clinical and translational findings supporting the effectiveness of microbiota-targeted therapies in the scope of this dual-axis framework, addressing both their potential to alter disease course and recognized limitations. By underscoring the importance of the integrated oral-gut microbiota axis alongside targeted PPSP interventions, this manuscript puts forth a paradigm-shifting conceptual strategy that may redefine approaches to AD management and improve cognitive outcomes.

Keywords: Alzheimer's Disease; Brain-Gut Axis; Microbiota; Probiotics; Prebiotics; Synbiotics

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INTRODUCTION

The human gut microbiota, which includes bacteria, fungi, viruses, and various other microorganisms, functions as a virtual organ, not just regulating digestion and immune responses but also playing a significant role in neurological processes. Over 90% of intestinal microbes are comprised of *Formicates*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*.[1]

We reference widely recognized taxonomic names (e.g., *Firmicutes*) while indicating their revised classifications (e.g., *Bacillota*).

The microbiota is now recognized as a newly identified organ that regulates intestinal function and diverse physio-pathological processes, such as modulation of the immune system, bone regeneration, and the prevention of cancer.[2] The gut microbiota is essential for sustaining host health by shaping immune responses, enabling the synthesis of key vitamins, and metabolizing dietary substrates that the host is unable to process independently.[3] For example, gut bacteria generate short-chain fatty acids (SCFAs; e.g., acetates, propionate, butyrate), which not only promote intestinal health but also exert systemic effects, including anti-inflammatory and neuroprotective actions.[4]

Moreover, the capacity of the microbiota to inhibit the colonization of pathogenic bacteria through competitive exclusion and the synthesis of antimicrobial molecules constitutes a fundamental component of its protective effect.[5,6]

The intricate interplay between the microbiota and the host highlights its role as a "virtual organ" and emphasizes its contribution to systemic health and disease mitigation (**Fig. 1**).[5] Recent studies provide evidence of its involvement in Alzheimer's disease (AD) pathogenesis mediated by the microbiota-gut-brain axis. This bidirectional communication pathway modulates neuroinflammation, amyloid-β (Aβ) deposition, and tau pathology, all characteristic features of AD.[7] While it is well established that the microbiota influences digestion and immunity, its potential roles in neurodegenerative disorders continue to be vigorously investigated. This review provides a critical assessment of the mechanistic associations between gut microbiota dysbiosis and AD, with particular attention to microbial metabolites, immune system alterations, and possible therapeutic strategies.[7,8]

GUT MICROBIOTA AND AD PATHOGENESIS

The microbiota–brain axis in neurological disease

The gut–brain axis constitutes a bidirectional neuro-immune-endocrine network that enables the intestinal microbiota to regulate central nervous system (CNS) homeostasis. Microbial metabolites, neurotransmitters, SCFAs, bacterial amyloids, and lipopolysaccharide (LPS) are capable of signaling via the vagus nerve or entering systemic circulation, thereby modulating neuro-inflammation, synaptic plasticity, and microglial activation.[9,10]

Age-related alterations in the gut microbiota, characterized by reductions in *Firmicutes* and *Bifidobacteria* and an increase in pro-inflammatory Bacteroidetes and pathobionts like *Escherichia coli*, are consistently documented in older adults and are further exacerbated in individuals with mild cognitive impairment (MCI) and AD (**Table 1**).[11-13] These microbial compositional changes elevate systemic levels of LPS and pro-inflammatory cytokines,

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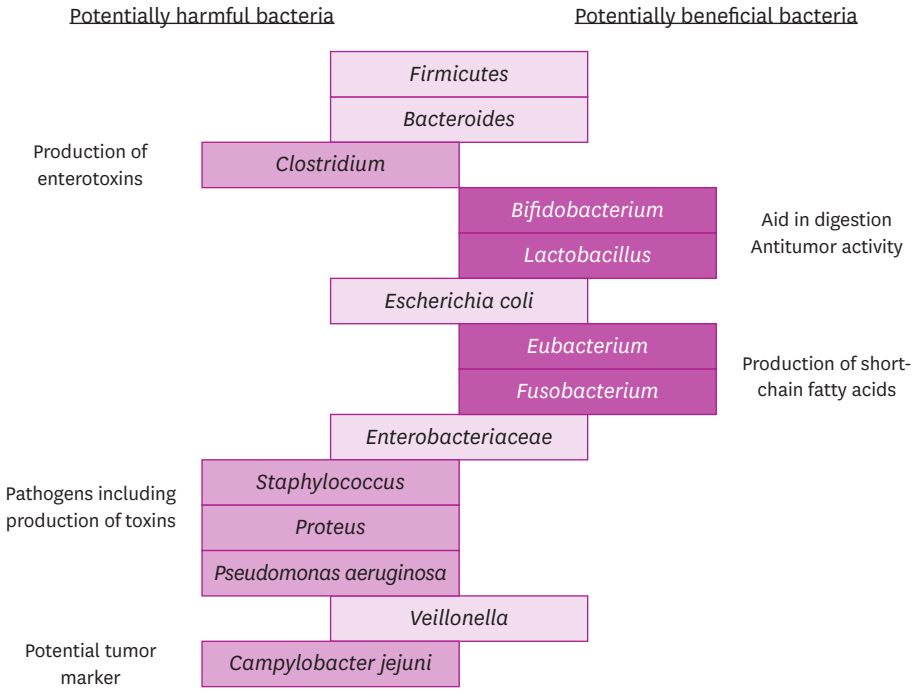

Fig. 1. The dual role of gut microbiota. Beneficial and pathogenic bacteria contribute to both gut health and disease risk. The gut microbiome contains commensal bacteria that confer protection and support gut integrity, while others are linked with disease development. Certain bacterial strains can generate toxins or exhibit antimicrobial resistance, which may increase the likelihood of adverse health outcomes. Although most *Escherichia coli* strains are non-pathogenic, a minority can cause infection.[5]

which (i) initiate or accelerate Aβ aggregation, (ii) hinder Aβ clearance, and (iii) promote tau hyper-phosphorylation and microglial dysfunction.[14] In contrast, germ-free or antibiotic-treated AD transgenic mice present with decreased cerebral Aβ plaque formation and reduced neuro-inflammation, whereas fecal microbiota transplantation from AD donors can confer cognitive impairments (CIs) upon recipient animals, demonstrating a causally transmissible microbial influence.[15-17]

Human studies remain predominantly correlational and are constrained by limited sample sizes, the confounding effects of medications and diet, and variability in sequencing methodologies. Despite these challenges, enterotype analyses indicate that an increased prevalence of enterotype III (*Bacteroides*-driven) is independently associated with a higher

Table 1. Gut-brain axis modulation in AD: mechanisms and research findings

Category	Examples	Mechanisms & effects	Findings in AD models/Clinical studies
Probiotics	*Bifidobacterium*, *Lactobacillus*	Influence gut microbiota structure, promote SCFA synthesis, decrease systemic and neuroinflammation. Support integrity of gut and blood-brain barriers, regulate neurotransmitter concentrations.	Demonstrate cognitive benefits and reduction of amyloid pathology in AD experimental models.
Prebiotics	Inulin, GOS, FOS	Preferentially promote growth of beneficial microbes, enhance SCFA synthesis, contribute to neuroprotective signaling.	Potential to improve metabolic and inflammatory states in individuals with cognitive impairment.
Synbiotics	Probiotics + Prebiotics	Synergistically improve gut microbiota diversity and promote community stability.	Limited clinical trials have demonstrated improved cognitive and metabolic outcomes in AD patients; however, well-powered, larger controlled studies are necessary to confirm these findings.
Postbiotics	SCFAs (e.g., butyrate), microbial peptides	Postbiotics exert anti-inflammatory and neuroprotective actions. Butyrate, for instance, mitigates neuroinflammation and facilitates synaptic plasticity.	Preclinical studies demonstrate a reduction in neuroinflammation and an enhancement of synaptic function due to postbiotic interventions.

AD: Alzheimer's disease, SCFA: short-chain fatty acid, GOS: galactooligosaccharides, FOS: fructooligosaccharides.

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risk of MCI and dementia, even after adjusting for established cerebro-spinal-fluid biomarkers. Meta-analyses additionally reveal that elevated levels of circulating LPS are linked to increased cortical amyloid deposition and a more rapid progression of cognitive decline.[16,17] Collectively, these findings suggest that gut dysbiosis may be a modifiable contributor to AD pathogenesis, yet the validation of microbiome-targeted interventions requires standardized translational research and large-scale longitudinal studies.[18]

Integrative perspective

Both gastrointestinal and oral microbiota exert crucial and convergent influences on AD pathogenesis by modulating neuroinflammation, intensifying Aβ and tau pathology, producing microbial metabolites capable of crossing blood–brain and other CNS barriers, and initiating systemic inflammatory and immune responses. These pathways designate the microbiome as a viable target for therapeutic intervention. For example, antibiotic modulation of gut microbiota reduces glial reactivity around Aβ plaques (**Fig. 2**),[19] further supporting the microbiota's role in AD-related neuroinflammation.[20,21]

Strategies to restore microbial homeostasis, including the use of probiotics, prebiotics, and enforcement of stringent oral hygiene, show therapeutic potential, but require robust validation in human clinical studies (**Table 2**).[7,14,19,22-24] The intricate nature and significant person-to-person variability of the microbiome emphasize the necessity for personalized approaches in dementia prevention and treatment.[25]

ORAL MICROBIOME AND AD

Emerging research provides compelling evidence for a strong association between oral health and the risk of dementia. A 2020 meta-analysis found that midlife tooth loss correlates with a 1.3- to 1.7-fold increased risk of cognitive decline and dementia, highlighting poor oral health as a potential early biomarker for neurodegenerative change.[26]

This association was further confirmed by a 15-year longitudinal cohort study published in 2023, which demonstrated that individuals with five or more missing teeth exhibited a 48% higher incidence of dementia compared to those with minimal tooth loss, emphasizing

Table 2. Research on the microbiota–dementia link

Study type	Key findings	Critical evaluation and limitations
Animal models	Probiotic interventions lead to significant decreases in amyloid plaque burden and neuroinflammation, thereby improving cognitive performance in rodent models of AD.	Although animal studies provide convincing evidence supporting the role of the microbiota in modulating AD pathology—such as reduced amyloid deposition in germ-free mice and the restoration of gut microbiota diversity and reduced AD pathology with fecal microbiota transplantation—the applicability to humans remains limited. The gut microbiota and immune system in rodents possess fundamental differences from those of humans, and these models largely reflect familial AD mutations, which restricts their relevance to sporadic AD.[7,14]
Human cohorts	Observational studies have identified dysbiosis, reflected in altered levels of pro- and anti-inflammatory bacterial taxa (e.g., increased *Escherichia/Shigella*, decreased *Eubacterium rectale*), which are associated with cognitive decline and dementia.	Human studies have established correlations between gut microbiota changes and dementia; however, the results show inconsistencies across different populations. These discrepancies are likely attributable to methodological differences, small sample sizes, confounding factors (e.g., diet, medication), and predominantly cross-sectional study designs. Such studies are unable to determine causality, and there are comparatively fewer data for MCI and vascular dementia than for AD.[22,23]
Clinical trials	Preliminary clinical trials employing probiotics or prebiotics suggest modest cognitive and metabolic benefits in individuals with mild cognitive impairment or early AD.	Most trials are limited by small cohort sizes, variability in probiotic strains and dosing, brief follow-up durations, and the use of different cognitive assessment tools, which undermines the generalizability of findings. In addition, a lack of mechanistic outcome measures in many trials hinders confirmation of microbiota-mediated effects. Consequently, clinical efficacy and definitive causal associations have not yet been demonstrated.[24]

AD: Alzheimer's disease.

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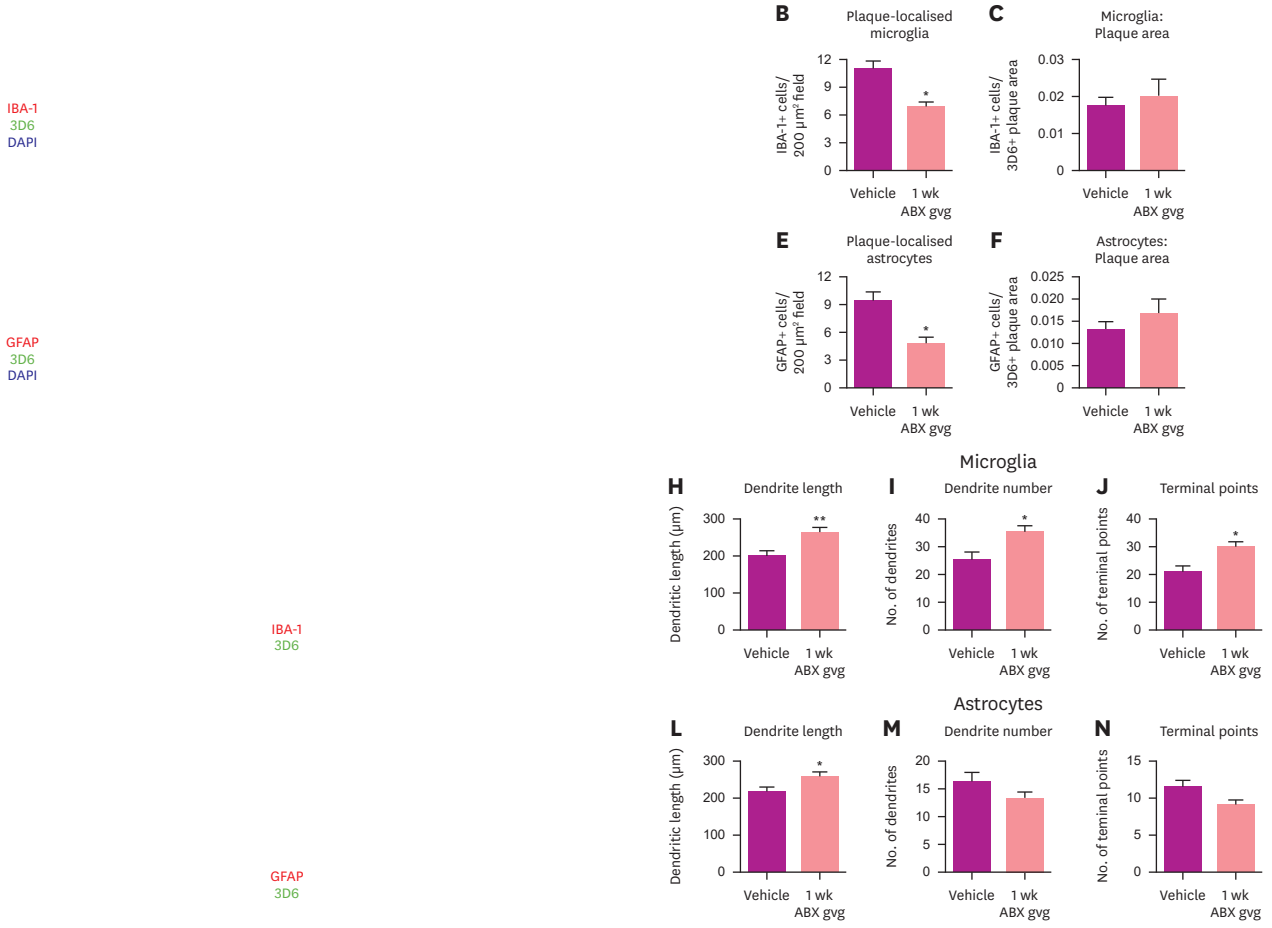

Fig. 2. Effects of 1-week ABX gvg treatment on glial cell reactivity in APPSWE/PSΔE9 mice. After 1 week of ABX gvg treatment, glial reactivity around plaques is diminished in APPSWE/PSΔE9 mice. (A) Representative images display IBA-1+ microglia (with DAPI staining) near Aβ plaques in 6.5-month-old APPSWE/PSΔE9 mice subjected to either vehicle or 1 week of ABX gvg, (B) Quantitative analysis demonstrates reduced numbers of IBA-1+ microglia associated with plaques post-ABX gvg (n=12, p<0.05), (C) Plaque-associated IBA-1+ microglia counts normalized by 3D6+ Aβ plaque size (n=12), (D) Representative images of GFAP+ astrocytes (DAPI stained) within plaque proximity under vehicle versus ABX gvg intervention, (E) Quantification reveals decreased GFAP+ astrocyte numbers around plaques following ABX gvg (n=12, p<0.05), (F) GFAP+ cell counts with respect to 3D6+ plaque area (n=12), (G) 3D reconstruction (IMARIS) of IBA-1+ microglial distribution by plaques, (H-J) Measures indicate significant decreases in dendritic length, total dendrite number, and terminal points in ABX gvg-treated mice (n=5, p<0.01/0.05), (K) Comparable reductions in dendrite morphology in GFAP+ astrocytes (n=5, p<0.05) visualized through 3D reconstructions. Data are expressed as mean ± standard error of measurement with 3D reconstructions. The data reproduced with permission from Minter et al.[19]
ABX: antibiotic, IBA-1: ionised calcium binding adaptor molecule 1, DAPI: 4',6-diamidino-2-phenylindole, Aβ: amyloid-β, GFAP: glial fibrillary acidic protein.
*p<0.05, **p<0.01.

tooth loss as a potentially modifiable risk factor.[27,28] Furthermore, inadequate oral hygiene practices amplify this risk; a 2021 study indicated that brushing teeth less than once per day was associated with a 22%–65% increased probability of tooth loss relative to brushing three or more times daily, with chronic oral inflammation suggested as a mediating mechanism.[29,30] Progress in microbiome research has clarified potential biological mechanisms linking oral health and dementia. The periodontal bacterium *Porphyromonas gingivalis* has consistently been detected in the brains of patients with AD, and its virulence factors, especially gingipain enzymes, are implicated in the generation of Aβ plaques and tau pathology characteristic of AD.[27] Experimental studies have demonstrated that oral infection with *P. gingivalis* results in brain colonization, elevated Aβ1–42 levels, neuroinflammation, and neuronal injury, all of which can be attenuated by gingipain inhibitors.[31] Metagenomic analyses have shown that AD brains display a 7-fold increase in oral bacterial diversity compared to controls, including species such as *Treponema denticola* and

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Fusobacterium nucleatum; meanwhile, Proteobacteria are predominant in the brain microbiome of non-AD subjects, implying that oral bacteria may infiltrate the brain even in the absence of disease.[7] Anaerobic oral pathogens such as *Prevotella intermedia* are disproportionately represented in AD patients and may contribute to neuroinflammation by activating TLR-4/NF-κB signaling pathways. Collectively, these observations support a conceptual framework in which compromised oral health, via tooth loss and persistent periodontal infection, drives systemic and neuroinflammatory processes that promote neurodegenerative alterations linked to dementia. This highlights the significance of proper oral hygiene and effective management of periodontal disease as possible approaches to lowering the risk of dementia.[32,33]

Recent studies emphasize the pivotal role of oral microbiota, particularly *P. gingivalis* and its gingipain proteases, in the pathogenesis of AD via well-defined mechanistic pathways. Gingipains facilitate amyloidogenesis and neuroinflammation by impairing host immune regulation and promoting the release of pro-inflammatory mediators.[34]

Importantly, these proteases interact with gut-derived microbial metabolites, such as LPSs and SCFAs, intensifying systemic inflammation and enhancing amyloid plaque formation.[35,36]

The interplay between oral *P. gingivalis* gingipains and gut microbial metabolites highlights a cooperative effect of oral and gut microbiota in advancing neurodegenerative processes. Consequently, comprehensive therapeutic approaches targeting these microbiome-associated pathways are vital for reducing amyloid deposition and neuroinflammatory responses in AD.[37]

INTESTINAL MICROBIOTA AND AD

Intestinal microbes generate a spectrum of metabolites essential for regulating physiological activities and maintaining human health.[38,39] The gut microbiota undergoes multiple compositional shifts in response to environmental and host-related factors.[40] In adults, the composition of these microorganisms remains relatively stable, yet this stability diminishes with advancing age, reaching its lowest point around 65 years, coinciding with the typical onset of AD.[41] A range of diseases, including AD, is closely linked to disturbances in the intestinal microbiome.[39]

Recent studies have extensively investigated the association between dysbiosis and the development of neurological diseases.[42-44] Compared to the control group, individuals with AD demonstrated reduced abundance of the phyla *Firmicutes* and *Actinobacteria*, along with increased levels of the phylum *Bacteroidetes*. Additionally, there is a lower abundance of species belonging to the families *Turicibacteraceae, Ruminococcaceae, Clostridium,* and *Clostridiaceae sensu* stricto in patients with AD.[45]

One study demonstrated that systemic administration of LPS in animal models resulted in amyloid accumulation and pathological features characteristic of AD. Furthermore, as amyloid plaques increased in the brains of Alzheimer's patients, there was a reported elevation in LPS levels and fragments of gram-negative bacteria relative to control groups.[46] Consequently, it has been suggested that the rising prevalence of *Escherichia coli*

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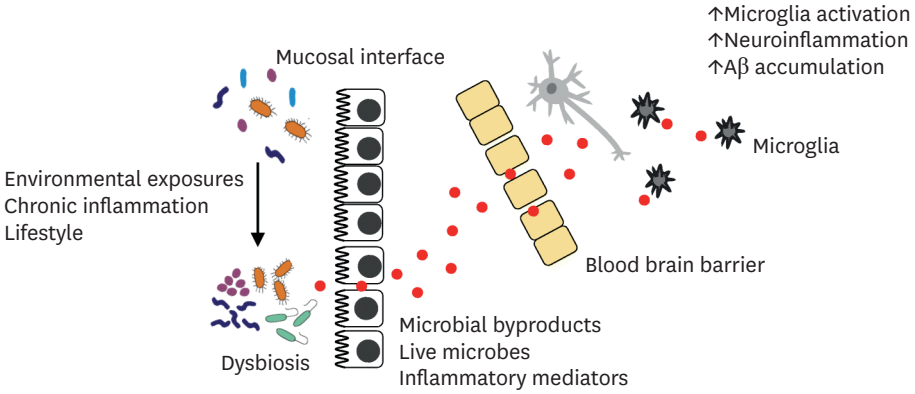

Fig. 3. Microbial dysbiosis impact on AD. A hypothetical mechanism through which remote microbial dysbiosis may influence the initiation and progression of AD.[47]
AD: Alzheimer's disease, Aβ: amyloid-β.

and other Gram-negative bacteria may elevate the amount of LPS translocating from the colon to the bloodstream and subsequently to the brain, thereby contributing to AD related pathology.[46] Collectively, these findings support the notion that dysbiosis may contribute to the development of neurological conditions, including AD (**Fig. 3**).[47] A proposed mechanism by which remote microbial dysbiosis could influence the onset and progression of AD. Reproduced with permission from.[47]

GUT MICROBIOTA-BASED BIOMARKER

Researchers employed a random forest classifier model to identify gut microbial markers associated with CI. Both healthy control and CI samples were utilized to construct the model. The study recognized 15 microbial markers, such as *Lactobacillus, Bifidobacterium*, and *Akkermansia*, that demonstrated significant diagnostic efficacy for CI patients. These findings indicate that such markers have potential utility in the early prediction and diagnosis of CI.[48] *Lactobacillus* and *Bifidobacterium* are 2 major gut bacterial genera that have been extensively investigated as potential indicators of a variety of health disorders. *Lactobacillus* species can be indicative of conditions like bacterial vaginosis (BV) and gastrointestinal diseases. A reduction in *Lactobacillus* species, specifically *Lactobacillus crispatus*, is frequently observed in BV.[49]

The sensitivity of detecting these microbial shifts depends on the methods used and can exceed 90% with advanced approaches. High specificity is also observed, particularly for certain species, since the absence of *L. crispatus* is indicative of an impaired vaginal microbiome. In gastrointestinal conditions, the detection or absence of particular *Lactobacillus* strains can serve as an indicator for diseases such as irritable bowel syndrome and inflammatory bowel disease (IBD).[50]

Bifidobacterium abundance is typically reduced in individuals with obesity, type 2 diabetes, and IBD. Detection methodologies demonstrate sensitivity rates between 80% and 95%. The specificity of *Bifidobacterium* also remains high, with certain species strongly correlated with a healthy gut. Comparable microbial markers have been applied for the prediction and diagnosis of colorectal cancer and hepatocellular carcinoma. Given the challenges in reversing CI in elderly populations, utilizing gut microbiota as a biomarker may aid both its diagnosis and prevention.[51,52]

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The combined use of *Lactobacillus* and *Bifidobacterium* allows for a more comprehensive assessment of both gut and vaginal microbial environments. The effectiveness of these bacteria as biomarkers is influenced by methodological factors, such as the use of molecular techniques or culture-based detection.[53]

Another investigation demonstrated a positive association between amyloid pathology, various bacterial products (including LPS and short chain fatty acids), inflammatory mediators, and biomarkers of endothelial dysfunction in AD. Additionally, the study observed a negative correlation between amyloid uptake and butyrate, as well as the anti-inflammatory cytokine IL10. Together, these results highlight a relationship between gut microbiota-derived factors, systemic inflammatory responses, and cerebral amyloidosis mediated by endothelial dysfunction, implying that SCFAs and LPS may contribute to AD pathology.[54]

Bacteroidetes, a prominent gut bacterial phylum, are capable of secreting pro-inflammatory neurotoxins that exacerbate systemic inflammation. The impact of these toxins becomes increasingly pronounced as GI and blood- brain barrier permeability heightens with advancing age and disease. *Bacteroidetes'* lipopolysaccharides (BF-LPSs) can activate the NF-kB (p50/p65) complex, an important mediator of inflammatory neurodegenerative processes.[54]

Furthermore, dietary polyphenols with antioxidative and anti-inflammatory capacities have been shown to ameliorate gut dysbiosis by enhancing populations of beneficial microbes. Targeted modulation of the gut using polyphenols may offer preventive and therapeutic benefits for AD and other neurodegenerative disorders. These compounds can neutralize free radicals, suppress pro-inflammatory cytokine production, enhance anti-inflammatory cytokine expression, and contribute to the maintenance of gut microbial balance. Nevertheless, their limited bioavailability points to a need for further investigation to optimize their potential in neurodegenerative disease prevention and management.[55] Substantial evidence defines an interaction between the gut microbiota and the brain in Parkinson's disease via immune signaling, amino acid metabolic pathways, and the nervous system, described as the "gut microbiota-brain axis," which has wide-ranging effects on neurochemical processes.[56] Interest is increasing in the association between dietary polyphenols and the prevention of AD. Present in plant-based foods, polyphenols demonstrate neuroprotection through antioxidant and anti-inflammatory mechanisms, inhibition of Aβ deposition, reduction in tau phosphorylation, and promotion of neurogenesis and synaptic plasticity, with epidemiological and clinical research supporting these neuroprotective properties.[57,58]

PROBIOTICS, PREBIOTICS, SYNBIOTICS, AND POSTBIOTICS (PPSP)

Expanding on the prior analysis of gut microbiota-derived biomarkers, with a focus on the influence of SCFAs and LPSs on barrier integrity and neuroinflammation, this section examines microbiota-directed therapeutic approaches designed to reestablish microbial balance and alleviate AD pathology. Due to the mechanistic associations between microbial metabolites and neurodegenerative processes, approaches that regulate the gut microbiome present promising options for therapeutic innovation.[59,60]

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Table 3. Comparing evidence from animal models vs. human studies

Aspect	Animal models	Human studies
Evidence of causality	Robust causal inference is provided by interventional approaches (germ-free models, FMT, probiotics).	Evidence is mainly correlational; no conclusive causal relationship can be confirmed due to the observational nature of these studies.
Microbiota alterations	Reproducible dysbiosis signatures have been connected with amyloid reduction and modulation of neuroinflammation.	Patterns of dysbiosis differ among cohorts and ethnicities, and a universal profile has not been established.
Cognitive outcomes	Marked cognitive benefits are observed following microbiota-targeted interventions.	Cognitive benefits observed in clinical trials are inconsistent or limited; additional studies are required.
Methodological limitations	Variations in microbiota profiles and immune reactions across species complicate translational efforts.	Small sample sizes, presence of confounding variables, and brief follow-up periods, as well as variation in probiotic regimens and assessment tools.
Disease focus	Research predominantly targets familial AD models, with sparse data on sporadic or vascular dementia forms.	The majority of studies focus on AD and MCI groups; there is a notable lack of research involving other dementia types, restricting broader insights.

FMT: fecal microbiota transplantation, AD: Alzheimer's disease, MCI: mild cognitive impairment.

Probiotics, including specific strains of *Lactobacillus* and *Bifidobacterium*, consist of live microorganisms that contribute to restoring gut eubiosis. Supporting this, antibiotic-induced microbiota disruption has been shown to reduce plaque-associated microglial and astrocyte activation in AD models (**Fig. 2**),[19] underscoring the role of microbial balance in modulating neuroinflammation.

Studies in AD models indicate that these probiotics can increase butyrate concentrations, inhibit microglial NF-κB activity, decrease Aβ deposition, and enhance both intestinal and blood-brain barrier function (**Table 3**).[60] Prebiotics such as non-digestible fibers, including inulin, fructooligosaccharides, galactooligosaccharides, and β-glucans, selectively support the proliferation of advantageous bacteria, resulting in higher SCFA output, diminished systemic LPS migration, and reduced neuroinflammation in the hippocampus. Synbiotics, which combine probiotic strains with compatible prebiotic substrates, have produced enhanced outcomes, including greater microbial diversity, increased SCFA synthesis, and more substantial cognitive benefits in early-stage AD populations when compared to the use of either component individually (**Fig. 2**).[61]

Postbiotics consist of microbial metabolites including butyrate, propionate, muramyl dipeptide, and additional bioactive peptides, and confer direct neuroprotective activities. These agents suppress NLRP3 inflammasome activation, restrict tau hyperphosphorylation, safeguard neuronal histone acetylation, and inhibit synaptic deterioration. Collectively, the PPSP model offers an integrated therapeutic paradigm targeting the gut-brain axis, with the aim of mitigating neuroinflammation and CI in AD.[59,61]

CONCLUSION

This manuscript presents an emerging conceptual framework that integrates the oral-gut microbiota axis with PPSP therapeutics, PPSP, as a novel approach to maintaining microbial homeostasis and supporting metabolic regulation. While it is established that a healthy gut microbiome, despite individual variability, influences intestinal functionality and systemic processes such as immune modulation, bone repair, and tumor suppression, our research distinctly highlights the essential interaction between oral and gut microbial communities in mediating these outcomes. Notably, the framework introduces the concept of psychobiotics, a unique subset of postbiotics, applied within the context of the oral-gut axis to target gut-brain communication pathways involved in neurodegenerative conditions such as AD. Although ongoing RCTs on psychobiotics in AD demonstrate encouraging preliminary

results, methodological challenges remain, including limited sample sizes, variable interventions, brief intervention periods, and the absence of standardized cognitive outcome measures, thus underscoring the need for robust, large-scale trials.

Recent studies indicate that dysbiosis within both oral and gut microbiota exacerbates AD pathology by promoting Aβ deposition and neuroinflammation, highlighting the potential value of modulating these microbial environments as a dual-axis therapeutic strategy. We recommend that future investigations place emphasis on longitudinal, large-scale cohort studies to clarify the causal associations between specific oral and gut microbial signatures and AD susceptibility, as well as to identify optimal psychobiotic strains that support cognitive health. Additionally, advancements such as engineered probiotics and precision microbiome therapies hold promise for enhancing the specificity and effectiveness of PPSP-based interventions. In practice, this framework supports implementing public health initiatives that encourage consumption of prebiotic-rich (e.g., garlic, onions, bananas) and probiotic-rich (e.g., yogurt, kefir, fermented vegetables) foods, in combination with individualized nutrition strategies informed by microbiome profiling. Overall, the integrated oral-gut-PPSP paradigm represents an innovative direction in neurodegenerative disease prevention, leveraging microbiome-mediated therapy to potentially disrupt the progression of AD through modulation of the gut-brain axis.

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