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Next Generation Probiotics and Postbiotics: Modulating the Gut Brain Axis in Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's disease is a progressive neurodegenerative condition involving cognitive impairment, amyloid β deposition, inflammation, and oxidative stress. The gut-brain axis plays a crucial role in neurological health, as gut microbiota influence brain function through various mechanisms, including immune, metabolic, and neuronal pathways. Probiotics have been known to modulate gut microbiota and enhance cognitive effects in Alzheimer's disease for a long time. However, next-generation probiotics and postbiotics present more specific and promising methods to curtail neuroinflammation and amyloid pathology.

Purpose: This review evaluates the potential of next-generation probiotics and postbiotics in Alzheimer's disease, focusing on their neuroprotective mechanisms, safety, preclinical efficacy, and translational prospects.

Method: We conducted a comprehensive literature search using databases such as PubMed, Google Scholar, and Scopus, focusing on studies published up to 2025. Relevant preclinical and clinical studies were screened, and data on mechanism, efficacy, and translational potential were summarised.

Result: Evidence indicates that next-generation probiotics restore gut microbial equilibrium, decrease pro-inflammatory cytokines, promote mitophagy, and fortify the intestinal and blood-brain barriers. These actions enhance cognition, decrease amyloid and tau pathology, and safeguard neurons. Postbiotics have comparable neuroprotective actions, with additional benefits of stability and ease of standardisation. Challenges to clinical translation include variability in formulation, poor understanding of gut-brain interactions, degradation during passage through the gastrointestinal tract, and interindividual variability in the composition of the microbiome.

Conclusion: Modulation of the gut-brain axis through next-generation probiotics and postbiotics is a promising multi-targeted approach for Alzheimer's disease, conferring neuroprotection and potentially disease-modifying effects. Future research will include the creation of targeted NGP strains, isolation of neuroactive postbiotic compounds, concurrent use of microbiome-derived therapies with standard treatment of AD, and tailoring interventions according to personalised gut profiles. These strategies can potentially boost cognitive performance, retard disease progression, and enhance quality of life for AD patients.

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1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, accounting for over 60–70% of dementia all over the world. It causes progressive loss of mental, behavioural, functional, and learning abilities (Kumar *et al.*, 2015). In 2021, an estimated 57 million individuals globally had dementia, with more than 60% residing in low- and middle-income nations. Nearly 10 million new cases are diagnosed every year. Dementia is brought about by various diseases and injuries to the brain. The majority of cases are of AD, which accounts for 60–70% of all instances (2021 Alzheimer's Disease Facts and Figures, 2021). Today in 2025, an estimated 7.2 million Americans, 65 and older, suffer from AD. If no medical advancements are made to prevent or treat AD, this number could rise to 13.8 million by 2060 (2025 Alzheimer's Disease Facts and Figures, 2025). Despite major research progress, current AD drugs only offer temporary cognitive relief and cannot halt or reverse neurodegeneration (Imbimbo *et al.*, 2005).

AD progression is driven by two major pathogenic processes. First, the abnormal cleavage of the amyloid precursor protein leads to the accumulation of amyloid-β peptides, particularly Aβ-42, which form extracellular plaques. This process causes oxidative stress, neuroinflammation, and synaptic impairment (Stancu *et al.*, 2014; Zhu *et al.*, 2015). Second, tau protein becomes hyperphosphorylated, dissociating from microtubules and forming intracellular neurofibrillary tangles that block neuronal transport and accelerate cell death. Both mechanisms are synergistic, with amyloid deposition often leading and enhancing tau pathology, resulting in widespread neurodegeneration (Dos Santos Picanco *et al.*, 2018).

Importantly, these molecular pathologies converge on synapses, the functional unit of cognition, making synaptic dysfunction central to clinical decline. In addition to these processes, synaptic degradation has been identified as the most accurate predictor of cognitive dysfunction in AD. Memory impairment is largely associated with synapse loss, rather than amyloid plaques or neurofibrillary tangles. Soluble Aβ disrupts glutamatergic neurotransmission, causing synaptic dysfunction and tau phosphorylation, contributing to early cognitive decline. Furthermore, excess glutamate or poor clearance by astrocytes activates NMDA receptors, causing excitotoxicity, neuronal injury, and memory loss (Hardingham *et al.*, 2002; Ittner *et al.*, 2010). Together, amyloid, tau, and excitotoxic processes set the stage for progressive synaptic loss and network disconnection that underlie clinical dementia.

The inflammatory hypothesis of Alzheimer's disease proposes that persistent neuroinflammation, predominantly mediated by activated microglia, causes neuronal damage via cytokines, reactive oxygen species, and reactive nitrogen species. Amyloid β (Aβ) increases inflammation by causing microglia to generate neurotoxic mediators such as TNF−α, nitric oxide, and free radicals (Yu *et al.*, 2024). The interaction of inflammatory and oxidative processes eventually leads to progressive brain damage and cognitive impairment. Emerging evidence links these mechanisms to mitochondrial dysfunction, poor autophagy, and gut-brain axis dysregulation, opening new treatment possibilities (D'Alessandro *et al.*, 2025; Greer, 2000).

Numerous therapeutic approaches have been tested in clinical trials over several decades; however, current therapies for Alzheimer's disease (AD) are symptomatic rather than curative. These medications temporarily ease cognitive problems without slowing or reversing the underlying neurodegenerative process (Passeri *et al.*, 2022). Since the efficacy of existing FDA-approved medications, which mostly target single pathways such as acetylcholinesterase (AChE) inhibition or N-methyl-D-aspartate (NMDA) receptor modulation, new multifunctional therapies are needed.

As a result, research has focused on preventative techniques and therapies that aim to reduce Alzheimer's disease risk by addressing upstream pathogenic mechanisms and modifiable lifestyle variables (Hossain & Hussain, 2025). This broader, multi-targeted strategy motivates exploration of the peripheral system, such as the gut microbiome, which influences brain health. The gut microbiome comprises bacteria, viruses, and other microorganisms inhabiting the intestinal tract. These microorganisms aid digestion, create useful molecules such as short-chain fatty acids, protect the body from toxins, and boost the immune system. Finally, bacteria from phyla Bacteroidetes and Firmicutes account for 90% of the adult human intestinal microbiota, with the rest from Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia (Rinninella *et al.*, 2019).

An imbalance in gut microbes, known as dysbiosis (Figure 1), can lead to diseases like diabetes, obesity, cancer, heart disease, arthritis, and inflammatory bowel diseases (Kesika *et al.*, 2021). An increasing number of studies have found that variations in gut microbiota composition relate to changes in brain function and behaviour, a process known as the microbiota-gut-brain axis (Socała *et al.*, 2021). This bidirectional communication involves the vagus nerve, gut hormone-secreting cells, the enteric nervous system, and the HPA axis. Metabolites produced by gut microorganisms include neurotransmitters, tryptophan compounds, and short-chain fatty acids (SCFAs), all of which have an impact on brain function, inflammation, and the blood-brain barrier. SCFAs, including butyrate, can reduce inflammation in brain cells and promote healthy brain function. Problems with gut-brain communication have been linked to neurodegenerative disorders such as Alzheimer's disease, pointing to the gut-brain connection as a possible target for novel therapeutic techniques (Zhong *et al.*, 2021).

Preclinical and early clinical studies suggest that manipulation of gut microbes or their metabolites can influence central inflammation tone, synaptic function, and cognitive outcomes in AD models. Microbiota-driven interventions, including probiotics, postbiotics, and next-generation probiotics (NGPs), have therefore attracted growing interest as potential strategies to restore microbial balance and support cognitive function. Next-generation probiotics can influence brain function through vagal pathways and microbial production of neurotransmitters (e.g., GABA, acetylcholine) and serotonin precursors (Ansari *et al.*, 2023; Faraji *et al.*, 2025; Kumar *et al.*, 2024). Several strains, including *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, and *Saccharomyces boulardii*, have been proven in Alzheimer's models to reduce inflammation, reinforce gut and blood-brain barriers, and produce metabolites that promote brain health (Un-Nisa *et al.*, 2022).

Furthermore, postbiotics or microbial metabolites can enhance gut and brain health by providing advantages like probiotics but without the use of live bacteria. They can modify the immune system, reduce inflammation, and increase gut barrier function, providing many of the same health benefits as probiotics without the need for live bacteria. Postbiotics could be particularly beneficial in the case of Alzheimer's disease because they decrease neuroinflammation, enhance gut-brain interaction, and enhance metabolites like short-chain fatty acids, which defend brain cells and cognitive function. Their safety and stability make them an appropriate supplement or alternative to probiotics for use in microbiota-based AD therapy (Rafique *et al.*, 2023). Conventional probiotics and postbiotics are restricted by inconsistent colonisation, unstable storage, and variable dosing. Next-generation probiotics (NGPs) address these challenges by using precisely characterised strains with a defined mechanism of action to modulate the gut ecosystem, reduce oxidative stress, and control inflammation (Abouelela & Helmy, 2024). Postbiotics show immunomodulatory, anti-inflammatory, antibacterial, and antioxidant effects that preserve gut barrier integrity and microbial balance. Their stability, focused effects, and scalability make them interesting candidates for therapeutic development, functional foods, and precision medicine, as well as possible treatment for neurodegenerative illnesses like AD (Pattapulavar *et al.*, 2025).

This review not only summarises current evidence for the gut-brain axis in Alzheimer's disease but also provides a novel and integrative perspective by highlighting next-generation probiotics and postbiotics, an area still poorly explored in AD. Unlike earlier reviews that largely focus on traditional probiotics or general microbiome associations, this paper emphasises the mechanistic and translational potential of microbiota-derived therapeutics as multi-targeted adjuncts to conventional drugs. By addressing current knowledge gaps and proposing directions for preclinical and clinical validation, this review aims to advance a paradigm shift away from an exclusively neurocentric approach to an integrative, gut-centric therapeutic framework for AD.

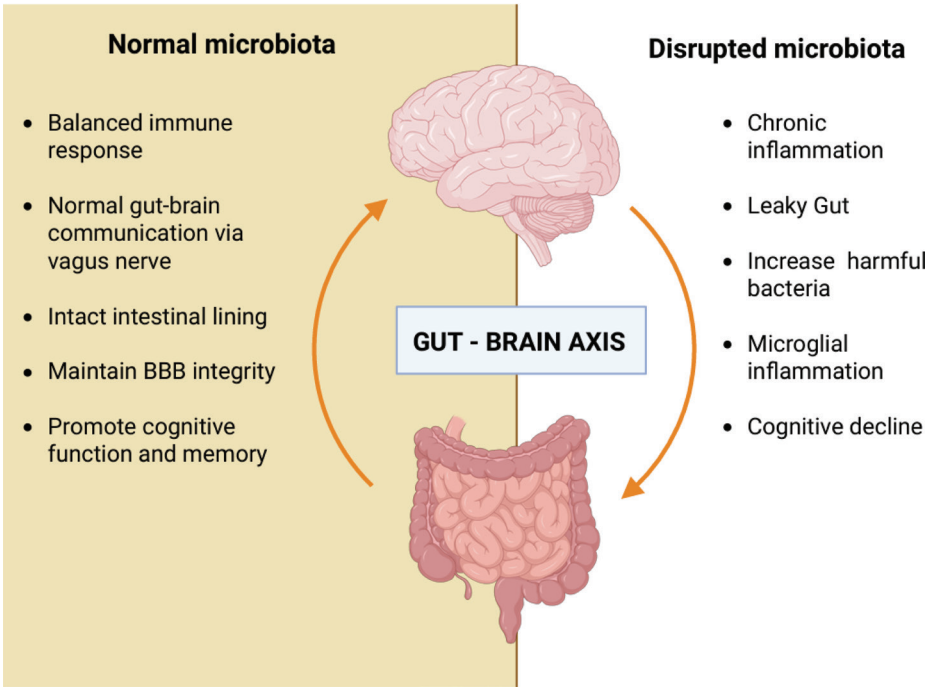

Figure 1: Comparison of Normal Versus Disrupted Gut Microbiota: Healthy Microbiota Maintains Gut-Brain Homeostasis, While Dysbiosis Increases Pro-Inflammatory Signals, Contributing to Blood-Brain Barrier Dysfunction and Neuroinflammation.

2. Gut-Brain Axis and Alzheimer's Disease (AD)

The gut, the largest absorption organ, and its microbiota, the human body's largest microbial reservoir, together form the Microbiota-Gut (MG) System. Their interactions influence physiological and pathological responses throughout the body. Among the organs affected, the central nervous system (CNS) is in continuous contact with the microbiota-gut through the bidirectional microbiota-gut-brain axis (MGBA), where the intestinal microflora has a key regulatory role (Cryan *et al.*, 2019; Giovannini *et al.*, 2021).

Abnormal composition of gut microbiota, or dysbiosis, has been implicated in a range of neuropsychiatric diseases and AD (Doifode *et al.*, 2021). MGBA disturbances contribute to AD pathogenesis through interconnected neuronal, endocrine, immunological, and metabolic signalling pathways. Overall, these pathways demonstrate that gut microbiota composition can have profound downstream effects on AD pathology, linking peripheral metabolic and immune signals to central neurodegenerative processes. Among the various mechanisms mediating communication within the microbiota–gut–brain axis, the neural pathway represents the primary and most direct route linking gut microbial activity to central nervous system function. The gut and brain communicate via two basic neuroanatomical channels. The first is direct signalling via the vagus nerve (VN) and autonomic nervous system (ANS), while the second is bidirectional communication via the enteric nervous system (ENS), ANS, and VN (Yan *et al.*, 2024).

The vagus, the longest parasympathetic nerve extending from the medulla to the gut, contains about 20% efferent and 80% afferent fibres. It regulates gastrointestinal motility, secretion, and anti-inflammatory reflexes (Dolphin *et al.*, 2022; Yan *et al.*, 2024). Thus, vagal signalling disruption from dysbiosis may mediate the link between peripheral microbial changes and CNS dysfunction. Dysbiosis-induced vagal signalling disruption may therefore act as a critical mediator linking peripheral microbial changes to central nervous system dysfunction.

Dysbiosis may also trigger systemic and neuroinflammation, alter neurotransmitter release (serotonin, GABA), and contribute to cognitive dysfunction in AD. In contrast, the vagus nerve may modulate gut microbial composition, preserving balance between eubiosis and dysbiosis (Park & Wu, 2022).

Beyond direct neural signalling, the metabolic pathway provides an indirect but equally significant pathway. Human metabolism is the result of both microbial and host enzymatic activities. Gut bacteria ferment undigested dietary material, producing metabolites such as SCFAs, bile acids, choline, and tryptophan derivatives that are essential for metabolic and neurological balance.

Microbial fermentation produces SCFAs, like acetate, propionate, and butyrate, that cross the blood-brain barrier by modulating neurotransmitter synthesis, neuroinflammation, and neurogenesis via G-protein-coupled receptors (GPR41, GPR43) and histone deacetylase (HDAC) inhibition (O'Riordan *et al.*, 2022; Gao *et al.*, 2009). The gut microbial metabolism of choline produces trimethylamine-N-oxide (TMAO), which causes aggregation of amyloid β, hyperphosphorylation of tau, oxidative stress, and cognitive impairments (Hu *et al.*, 2023).

Alterations in bile acid metabolism also affect mitochondrial function, neuronal energy balance, and insulin signalling, linking dysbiosis to metabolic dysregulation in the AD brain. Collectively, these microbial metabolites act as critical mediators between gut health and neuronal integrity, providing mechanistic insight into how dysbiosis can accelerate AD pathology.

The gut-brain axis also exerts significant neuroendocrine and immunomodulatory control, influencing neuroinflammatory responses in AD. The gut hosts the densest population of immune cells—B cells, T cells, macrophages, and dendritic cells—whose functions are tightly regulated by microbial composition. Gut microorganisms control the maturation of gut-associated lymphoid tissue (GALT) and influence both innate and adaptive immune responses (Hooper *et al.*, 2012; Olszak *et al.*, 2012). Dysbiosis disrupts the balance, resulting in higher levels of proinflammatory cytokines (IL-1β, TNF-α, IL-6) and chemokines that penetrate the blood-brain barrier and activate glial cells. This cascade leads to chronic neuroinflammation, which is a characteristic of Alzheimer's disease. Microglial and astrocyte activity is further regulated by microbial metabolites, which influence BBB permeability, neuronal survival, and synaptic plasticity (Erny *et al.*, 2015; Fung *et al.*, 2017). These endocrine and immune pathways underscore the centrality of gut-derived signals in modulating both inflammation and neuronal resilience in AD.

3. Evidence of Gut Dysbiosis in AD

Recent clinical and preclinical research consistently shows gut microbial changes in AD. Several independent cohorts have found reduced beneficial taxa (e.g., *Bifidobacterium*, *Lactobacillus*, *Firmicutes*) and increased proinflammatory taxa such as *Escherichia/Shigella* and *Proteobacteria*, which correlate with elevated peripheral inflammation markers and amyloid burden (Zou *et al.*, 2024). Dysbiosis triggers the release of LPS and other endotoxins from these gram-negative bacteria. These enter the bloodstream, impair BBB integrity, activate microglia, and cause neuronal damage (Banks & Erickson, 2010). LPS binds to TLR4 (toll-like receptor), which is expressed on endothelial cells, microglial cells, and astrocytes (Tsioti *et al.*, 2023). This BBB disruption allows immune cells, cytokines, and circulating toxins to enter the CNS (Figure 2). Microbial amyloid proteins and bacterial metabolites can seed or accelerate brain amyloid aggregation, linking gut dysbiosis to amyloidogenesis (Harach *et al.*, 2017; Sampson *et al.*, 2020). These microbial, metabolic, and immune alterations together drive synaptic dysfunction, neuronal loss, and cognitive decline in Alzheimer's disease (Liu *et al.*, 2020). Taken together, these findings support the gut microbiota as a potential therapeutic target, where modulation of microbial composition or function could be beneficial after AD progression.

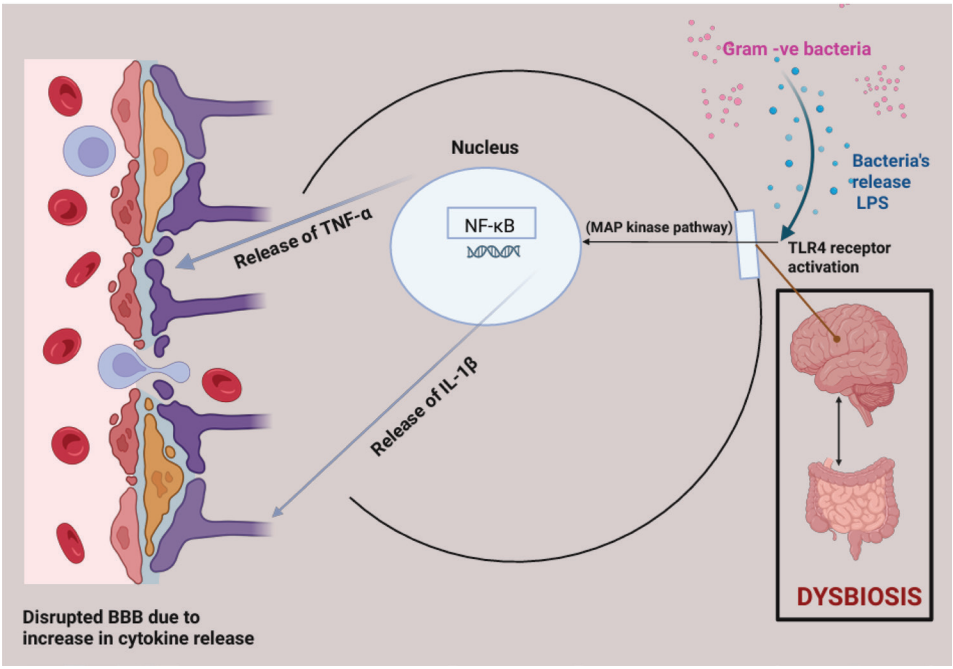

Figure 2: The Gut-Brain Axis Process in Alzheimer's Disease Involves Elevated Levels of Gram-Negative Bacteria, Which in Turn Increase Lipopolysaccharide (LPS) Levels and Activate TLR4 Receptors. This Activates the MAP Kinase Signalling Pathway, Resulting in Increased Proinflammatory Cytokine Production That Compromises the BBB Integrity, Hence Contributing to Neuroinflammation in AD.

4. From Probiotics to Next-Generation Probiotics

In 2001, the World Health Organisation defined probiotics as live microorganisms that, when consumed in sufficient quantities, benefit the host's health. Lactobacillus, Bifidobacterium, Enterococcus, Lactococcus, and Streptococcus species are the most widely used probiotics (Sarita *et al.*, 2025). Several other bacterial strains are now being used therapeutically for AD and other cognitive disorders (Table 1). These beneficial microorganisms primarily inhabit the human gastrointestinal tract, where they play a key role in maintaining gut health and overall physiological balance. Probiotics predominantly live within the human intestine, where they ensure a healthy balance of gut microbiota (Chandrasekaran *et al.*, 2024).

Most probiotic bacteria occur naturally in the gut, while some are added to foods to enhance nutrition and digestion. They aid digestion and also regulate the immune system and inflammation. They help maintain microbial balance, strengthen immunity, and reduce intestinal inflammation (Aleman & Yadav, 2023).

According to studies, probiotics promote health in several important ways. They produce antibacterial compounds that stop dangerous bacteria from growing, adhere to the gut lining, and aid in strengthening the intestinal barrier. These antibacterial compounds can be of various types, such as bacteriocins that mainly originate through the RBC of bacteria; some examples are nisin (Shin *et al.*, 2016), reutericin (Toba *et al.*, 1991), lactacin (Barefoot & Klaenhammer, 1984); hydrogen peroxide, which is produced when genes coding for the enzymes NADH peroxidase and catalase are absent (Hertzberger *et al.*, 2014; Kazemipoor *et al.*, 2012); short-chain fatty acids (Huang *et al.*, 2011); reuterin, which is produced in the presence of glycerol (Cleusix *et al.*, 2007); and many organic acids such as lactic acid and acetic acid (Tejero-Sariñena *et al.*, 2012), etc.

Beyond these effects, probiotics interact with host cells and pathogens via surface molecules and adhesion factors (Lebeer *et al.*, 2010), quorum-sensing interference (Piewngam *et al.*, 2018), modulation of signalling pathways such as MAPK and NFκB (Thomas & Versalovic, 2010), and epigenetic modulations (Bhat *et al.*, 2019). Additionally, probiotics influence the expression of genes in pathogenic bacteria, decrease their ability to adhere to the gut wall, compete with pathogens for adhesion sites, and control the body's immune responses (M. J. Kang *et al.*, 2023; Maftei *et al.*, 2024; Mohamed, 2024; Singh & Agarwal, 2022).

Their ability to modify the gut environment, particularly by altering pH, further enhances their protective function. Probiotics can outcompete pathogens by altering the pH of

their environment. Similar to pathogens, probiotics bind to mucosal adhesion sites, decreasing the chance that probiotics will be washed out as well as the chance that pathogens will adhere (Williams, 2010). Given these multifaceted actions, the therapeutic use of probiotics depends on careful selection of appropriate strains and formulations. Probiotic efficacy depends on strain genetics, formulation, intended use, and shelf life. This is due to the wide range of nutritional and medicinal benefits that probiotics offer (Gul & Durante-Mangoni, 2024). Which probiotic strain to use depends on its production, effects, and benefits to the host's health.

4.1. Limitations and Safety Concerns of Conventional Probiotics

Traditional probiotics present several limitations that have prompted the development of Next-Generation Probiotics (NGPs). Although they offer broad health benefits, conventional probiotics often lack clinical consistency and show limited applicability. Clinical trials frequently employ different strains, dosages, and methodologies, making comparisons and generalisation difficult. Additionally, strain-specific effectiveness poses a major challenge, as some strains work only in certain disease conditions but fail in others (Shanahan, 2003). Even within the same species, probiotic efficacy can vary substantially, and no single strain can deliver all possible benefits. This strain-dependent variability has significant implications for food applications and safety. Numerous probiotic species, such as *Lactococcus lactis*, *Lactobacillus* species, *Streptococcus*, *Enterococcus*, *Bifidobacterium* species, *Pediococcus*, and *Propionibacterium* species, are commonly incorporated into foods. Selecting the appropriate strain is essential to prevent nutrient loss, formation of harmful amines, and growth of opportunistic pathogens (Bhadoria & Mahapatra, 2011).

Some probiotic strains may also harbour antibiotic-resistance genes (Mohamed, 2024). Although the U.S. Food and Drug Administration (FDA) consider probiotics safe, *Bifidobacterium*, *Lactobacillus*, *Streptococcus*, and *Clostridium* species have not been associated with safety issues in Alzheimer's disease (AD). However, probiotics should be avoided in AD patients receiving immunosuppressive treatments such as chemotherapy (Sanders *et al.*, 2010). Several cases of bacteremia, fungemia, and sepsis have been reported in patients treated with *Saccharomyces boulardii*. Wombwell *et al.* (2021) performed a retrospective analysis of all *S. boulardii*-induced fungemia cases and identified an incidence rate of 0.11%—a low but not negligible risk (Wombwell *et al.*, 2021). Similar risks have been highlighted in other studies (Lherm *et al.*, 2002). The likely mechanism involves translocation of the organism from the gut into the bloodstream through a compromised intestinal barrier (Poncelet *et al.*, 2021). Contamination via catheters or environmental exposure may also contribute (Hennequin *et al.*, 2000). In rare cases, probiotic bacteria may carry antibiotic-resistance genes and transfer them to other bacteria, including pathogenic strains that cause infection. These risks persist regardless of the strain variations or the species studied in humans or animals (Siripaopradit *et al.*, 2024).

Clinical inconsistencies further highlight these limitations. For instance, Agahi *et al.* evaluated the effects of probiotics on cognitive function using the Test Your Memory (TYM) assessment and found no significant improvement. Potential reasons include population differences, variations in probiotic potency, and the short duration of the intervention. The 12-week supplementation period may have been insufficient to elicit measurable improvements in mild cognitive impairment (MCI) or Alzheimer's disease (AD) (Agahi *et al.*, 2018).

4.2. Emergence and Therapeutic Potential of Next-Generation Probiotics

NGPs emerged in response to the drawbacks associated with traditional probiotics. O'Toole introduced the term "Next-Generation Probiotics" in 2017 to describe live microorganisms identified through gut microbiota analyses that can confer health benefits when consumed in appropriate amounts (Jan *et al.*, 2024). Examples of NGPs include *Bifidobacterium* species, *Prevotella copri*, *Akkermansia muciniphila*, *Bacteroides fragilis*, *Christensenella minuta*, *Faecalibacterium prausnitzii*, and *Parabacteroides goldsteinii*. The therapeutic applications of these bacteria are currently being explored across multiple disease conditions (Chang *et al.*, 2019).

NGPs have demonstrated benefits in cardiovascular disorders, gastrointestinal diseases, cancer, lactose intolerance, and hypertension. Notably, some NGPs possess antioxidant and anti-inflammatory properties, offering promising potential in neurological protection. They have also been shown to reduce oxidative stress (Sáez *et al.*, 2012). Several genes within these organisms encode reactive oxygen species (ROS) or oxygen-detoxifying enzymes, including flavodiiron proteins, rubrerythrins (Rbr), reverse rubrerythrins, superoxide reductases, and alkyl peroxidases. Strains with more robust detoxification systems show increased survival during prolonged exposure to atmospheric oxygen (Botin *et al.*, n.d.). Another mechanism involves enhancement of antioxidative enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase, as demonstrated by Mao *et al.* in their study on the NGP candidate *Blautia producta* (Mao *et al.*, 2023).

Although their role in neurodegenerative disorders remains under investigation, emerging evidence is

promising. In 2025, Xu *et al.* examined the effects of *Akkermansia muciniphila* in Parkinson's disease and found that oral administration reduced dopaminergic neuron loss and improved motor functions by restoring gut microbial balance and increasing butyrate production. The elevated butyrate suppressed microglial activation, thereby decreasing neuroinflammation and protecting neurons (Xu *et al.*, 2025). This work highlights that *A. muciniphila* exerts neuroprotective effects through the gut-brain axis via butyrate-mediated modulation of microglia-driven inflammation. Comparable findings have been reported for other NGP candidates in various neurological disorders.

Another promising NGP is *Blautia wexlerae*. Cox *et al.* observed significantly reduced levels of *B. wexlerae* in patients with progressive multiple sclerosis (MS), with lower abundance correlating with increased inflammation. This suggests that *B. wexlerae* plays a protective, anti-inflammatory role in maintaining gut-immune homeostasis, and restoring its levels may offer therapeutic benefits in MS (Cox *et al.*, 2021).

NGPs act through multiple mechanisms, one of which includes inhibition of the NLRP3 inflammasome—an inflammatory pathway implicated in the pathogenesis of Alzheimer's disease (Tan *et al.*, 2013). For example, Qian *et al.* demonstrated that the *Akkermansia muciniphila*-derived protein Amuc_2109 strengthens intestinal barrier function, preserves gut microbial balance, and reduces colonic inflammation. This occurs through suppression of the NLRP3 inflammasome pathway, thereby limiting pro-inflammatory cytokine release and tissue injury. These findings indicate that Amuc_2109 may prevent inflammation-driven diseases by modulating NLRP3 activity (Qian *et al.*, 2022).

Table 1: Summary of Research Studies on Various Probiotic Strains Studied in Alzheimer's Disease

Strain of Probiotics	**Therapeutic Effects in Alzheimer's Disease**	**Reference**
Lactobacillus rhamnosus	Ameliorates cognitive impairment in Aβ-induced mice, protects the antioxidant system, improves mitochondrial function, enhances synaptic function, regulates neuroinflammation and neurotoxicity, and improves gut microbiota dysbiosis	Hye Ji Choi, 2025
Lactobacillus rhamnosus	*L. rhamnosus* positively impacts cognitive deficits and neuroinflammation in this AD model.	Heydari, R., 2025
Lactobacillus rhamnosus	LGG helps prevent sepsis-associated cognitive deficits and protects hippocampal neurons.	Wang, L., 2024
Lactobacillus rhamnosus	Protects neurons from oxidative stress and reduces ROS. Inhibits AChE activity. Modulates neuroinflammation and apoptosis via MyD88/NF-kB and JNK/Bax pathways. Proven safe by genomic and antibiotic testing.	Lee, J. Y., 2025
Lactobacillus plantarum	*Lactobacillus plantarum* improved cognitive function, antioxidant levels, AChE activity, and cortical histology in $AlCl_3$-induced Alzheimer's rats.	Abdellatief, H., 2024
Lactobacillus plantarum	*Lactobacillus plantarum* HEAL9 alleviated cognitive decline, improved colonic motility, and reduced brain and gut inflammation in early-stage Alzheimer's mice.	Di Salvo, C., 2024
Lactobacillus plantarum	In this study, *Lactobacillus plantarum* (as part of the lactobacilli mixture) helped prevent Aβ formation, improved learning and memory, and mitigated *P. gingivalis*-induced neuroinflammation in rats.	Kazemi, N., 2024
Lactobacillus plantarum	In this study, *Lactobacillus plantarum* (DMS 20174) exhibited anti-Alzheimer effects by reducing acetylcholinesterase (AChE), oxidative stress (MDA) levels, enhancing gut *Lactobacilli* counts, and improving antimicrobial, antioxidant, and anti-cholinesterase activities.	Sakr, E. A. E., 2023
Lactobacillus acidophilus	In this research, *Lactobacillus acidophilus* showed a therapeutic role in Alzheimer's disease by inhibiting acetylcholinesterase and tyrosinase, suggesting potential for treatment and prevention of neurodegenerative disorders.	I, Mohammad, 2024
Bifidobacterium longum	Improves cognitive function by enhancing memory, attention, and visuospatial abilities, and modulates gut microbiota to support brain health.	Shaoqi Shi, 2022
Bifidobacterium longum	*Bifidobacterium longum* (NK46) mitigates cognitive decline in Alzheimer's disease by reducing gut dysbiosis, neuroinflammation, amyloid-β accumulation, and apoptosis while enhancing intestinal barrier and BDNF expression.	Hae-Ji Lee *et al.*, 2019
Bifidobacterium breve	Alleviates memory impairment and cognitive dysfunction by reducing tau hyperphosphorylation, chronic stress, and enhancing synaptic density and neuronal activity in Alzheimer's disease.	Abdelhamid, M., 2024
Bifidobacterium breve	Enhances cognition, inhibits neuroinflammation, improves synaptic function, and restores gut microbiota-metabolite balance, especially when combined with environmental enrichment (EE).	Gaungsu Zhu, 2024

5. Understanding Postbiotics in Alzheimer's Disease

The term *postbiotic* refers to bioactive substances derived from dead or inactivated microorganisms. These may consist of whole inactivated microbial cells or specific cellular components such as cell wall fragments. Many postbiotic formulations also include beneficial microbial products—such as proteins, peptides, or metabolites—although these additional elements are not strictly required for classification as a postbiotic (Vinderola *et al.*, 2022).

Tsilingiri and Rescigno (2013) further define postbiotics as compounds produced or released by microorganisms during metabolism that exert direct or indirect beneficial effects on host health. This perspective supports the growing view that postbiotics are promising alternatives to probiotics, offering comparable benefits through non-living microbial components. Although postbiotics do not contain viable bacteria, they deliver similar therapeutic advantages without risks associated with live microbes.

Postbiotics encompass several categories, including exopolysaccharides, cell-free extracts, enzymes, short-chain fatty acids (SCFAs), cell-free supernatants, bacterial lysates, and numerous other microbe-derived metabolites (Żółkiewicz *et al.*, 2020). Owing to this diversity, postbiotics can influence multiple physiological systems, broadening their therapeutic potential.

They target the metabolic system and are thus valuable in managing obesity and diabetes by enhancing insulin sensitivity, regulating glucose and lipid metabolism, and modulating gut hormones (Lange *et al.*, 2023). Postbiotics also benefit the cardiovascular system by reducing blood pressure. SCFAs produced through microbial fermentation of dietary fibre modulate cardiovascular health by activating G-protein coupled receptors (GPR41/43), enhancing endothelial nitric oxide production, improving vascular function, and exerting anti-inflammatory effects through histone deacetylase inhibition (Nogal *et al.*, 2021).

Postbiotics additionally modulate immune responses. Heat-killed multi-strain preparations influence CD14+ monocytes by stimulating cytokine production, with combined bacterial–yeast formulations demonstrating synergistic immunomodulatory activity (Roberts *et al.*, 2024).

Functionally, postbiotics provide a range of health benefits. They help reduce cholesterol by producing SCFAs such as acetate and propionate, which downregulate HMG-CoA reductase—thereby decreasing endogenous cholesterol synthesis (Parnell & Reimer, 2010). They attenuate inflammation by lowering pro-inflammatory markers including TNF-α, IL-1β, and IL-6, while modulating TLR4 expression (Abbas *et al.*, 2025). Their antioxidant properties are mediated through reductions in MDA levels and increases in antioxidant enzymes such as SOD, CAT, and GSH, or through enhanced free-radical scavenging (Abbas *et al.*, 2025; Asadi *et al.*, 2024). Postbiotics also help prevent obesity, regulate immune function, and inhibit abnormal cell proliferation by inducing apoptosis (Kim *et al.*, 2022). (Figure 3)

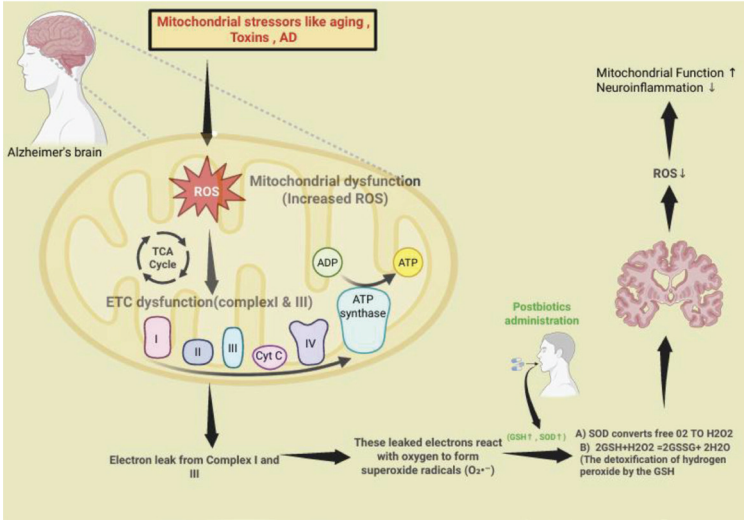

Figure 3: When Postbiotics Act on a Dysfunctional Mitochondrion with Increased ROS, They Increase the GSH and SOD Levels. GSH Is a Major Intracellular Antioxidant. During Oxidative Phosphorylation, Electrons Leak from the Complexes I and III of the ETC. These Leaked Electrons React With O_2 To Form Superoxide Radicals. Superoxide is Subsequently Converted into Hydrogen Peroxide by Mitochondrial Superoxide Dismutase (MnSOD). Detoxification of H_2O_2 By the GSH System. GSH Exists in Reduced Form (GSH) and Oxidised Form (GSSG). The GSH/GSSG Ratio Is a Marker of Cellular Redox Status. Hence, These Effects Together Decrease Oxidative Damage and Improve Mitochondrial Function, Thus Improving AD Symptoms.

Postbiotics offer several practical advantages as well. They are easy to store, transport, and preserve, and they have a substantially longer shelf life than probiotics—up to five years (Sreeja & Prajapati, 2013). They are also safer, as they provide health benefits without the risks associated with live microorganisms. This enhanced stability and safety make postbiotics particularly suitable for immunocompromised populations, including elderly or chronically ill individuals (Imperial & Ibana, 2016). Additionally, while probiotics may harbour undesirable genes such as virulence or antibiotic resistance determinants, postbiotics are free from these risks.

Preclinical studies have shown positive associations between probiotic-derived secretomes and ageing-related as well as neurodegenerative processes in the central nervous system (Hamdi *et al.*, 2025). Beyond their anti-inflammatory, antioxidant, and immunomodulatory functions, postbiotics also contribute to maintaining the integrity of the blood–brain barrier (BBB), a critical factor in the management of neurological disorders (Parker *et al.*, 2020). They help restore tight junction morphology in endothelial cells, thereby strengthening BBB function (Algieri *et al.*, 2023). This is particularly important in Alzheimer's disease (AD), where BBB disruption is a hallmark pathological feature.

Furthermore, evidence suggests that the depletion of SCFAs—often resulting from chronic gut dysbiosis or antibiotic exposure—increases BBB permeability, leading to mood disturbances and cognitive impairments in animal models (Knox *et al.*, 2022).

5.1. Neuroprotective Mechanisms and Therapeutic Implications of Postbiotics in Alzheimer's Disease

Researchers examined the effects of administering short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate, on Alzheimer's disease in APP/PS1 mice, a widely used AD model, in a study by Zajac *et al.* The SCFAs were externally administered to observe their effects on gene expression, brain activity, inflammation, and amyloid-β accumulation. SCFA treatment altered gut microbiota composition, reduced inflammatory gene expression, and regulated microglial activity. The findings suggest that SCFAs can influence brain inflammation through the gut–brain axis, highlighting their therapeutic potential in Alzheimer's disease despite mixed effects on amyloid plaque levels (Zajac *et al.*, 2022).

In vitro (cell culture) studies have shown that postbiotics and beneficial gut bacteria can modulate key pathways implicated in AD. These laboratory findings further support the link between microbial metabolites and neuronal protection. Ahmed *et al.* cultured different commensal gut bacteria and screened their ability to synthesise neuroactive metabolites, including SCFAs and tryptophan derivatives, along with their antioxidant and anti-inflammatory effects (Ahmed *et al.*, 2019). Their results demonstrated strong neuroprotective activity. When neuronal and microglial cells were exposed to bacterial supernatants, strains producing butyrate and indole derivatives reduced oxidative stress, inflammation, and cellular injury. These observations emphasise the therapeutic promise of gut-derived metabolites in addressing neuroinflammation and oxidative stress, both central to AD pathogenesis.

Another study by Choi *et al.* explored how Lactobacillus plantarum, a well-recognised postbiotic producer, might mitigate oxidative stress, a major contributor to AD. Using L. plantarum 200655, they created a fermented soy yoghurt and supplemented it with fructooligosaccharides to form a synbiotic mixture. The study assessed its ability to protect neuronal cells from hydrogen peroxide-induced oxidative injury. The L. plantarum–FOS soy yoghurt enhanced antioxidant activity, reduced reactive oxygen species (ROS) levels, and improved neuronal survival compared to controls (Choi *et al.*, 2022). These findings suggest that this synbiotic soy yoghurt may function as a potent antioxidant and neuroprotective functional food capable of preventing oxidative stress–mediated neuronal injury associated with AD development.

In another investigation, Zhou *et al.* examined the impact of dietary fibre and microbiota-derived metabolites on Alzheimer's disease in 5XFAD mice, a robust AD model. The high-fibre diet increased SCFA production, and these metabolites activated specific signalling pathways responsible for neuroprotection. SCFAs acted through their receptors GPR41 and GPR43 to enhance memory, reduce amyloid plaque burden, and protect neurons from injury. However, when these receptors were absent, the beneficial effects disappeared, leading to greater cognitive decline and more severe AD pathology (Zhou *et al.*, 2023). This study highlights the critical role of fibre-derived metabolites in maintaining brain health through the gut–brain axis and slowing Alzheimer's-like disease progression.

Postbiotics may also enhance brain plasticity and cognitive function by increasing levels of brain-derived neurotrophic factor (BDNF), which supports neuronal growth, communication, and survival (Sarkar *et al.*, 2025).

In addition to their metabolic advantages, postbiotics modulate key neurotransmitters associated with cognition and emotional regulation. Serotonin, which influences mood, memory, and cognition, plays a significant role in Alzheimer's disease. Research indicates serotonin levels are reduced by about 40% in AD-affected brains (Yun *et al.*, 2015). Postbiotics may help maintain healthy serotonin levels. Reduced serotonin contributes to depression

and cognitive impairment in AD. GABA and other neurotransmitters are equally important for synaptic stability and mental health; maintaining their balance may help protect neuronal function and slow AD progression (Sarkar *et al.*, 2025).

Ageing increases vulnerability to inflammation, activating macrophages, monocytes, and neutrophils. This elevates pro-inflammatory cytokines such as IFN-γ, TNF-α, and IL-6, contributing to inflamm-ageing—commonly observed in neurodegenerative disorders including AD. This chronic inflammatory state accelerates neurodegeneration (Rahman & Dandekar, 2023). In AD, these cytokines can activate the NLRP3 inflammasome, influence the HPA axis, and trigger cortisol release. Persistent cortisol elevation heightens systemic stress and reduces immune sensitivity to anti-inflammatory signals. Several postbiotics counteract this through strong anti-inflammatory properties (Kaufmann *et al.*, 2017). Heat-killed bacteria (HKB) and cell-free supernatants (CFS) suppress NF-κB, a major regulator of inflammation, thereby decreasing IL-6, IL-1β, and TNF-α levels and contributing to reduced neuroinflammation (Jastrząb *et al.*, 2021).

Wu *et al.* demonstrated that Lactobacillus plantarum postbiotics protected mice from Salmonella-induced brain dysfunction via the gut–brain axis. The postbiotics reduced brain inflammation, prevented tissue damage, and improved cognition and behaviour by decreasing anxiety- and depression-like symptoms. They also regulated crucial neuroactive molecules including serotonin, GABA, BDNF, dopamine, acetylcholine, and neuropeptide-γ. These mechanisms are directly relevant to AD, where neuroinflammation, neurotransmitter imbalance, and gut–brain axis disruption contribute to disease progression, suggesting that Lactobacillus plantarum-derived postbiotics may offer neuroprotective benefits (Wu *et al.*, 2022). Overall, evidence indicates that postbiotics—bioactive metabolites derived from probiotics—can protect the brain by modulating the gut–brain axis, reducing neuroinflammation, and restoring neurotransmitter balance. These mechanisms align with core pathological processes in AD, making postbiotics promising therapeutic and preventive strategies.

6. Current Evidence in AD: Preclinical & Clinical Studies

Animal models of AD tend to have lower levels of body SCFAs due to alterations in the gut microbiota. To address this imbalance, studies suggest that next-generation probiotics may help relieve AD symptoms (Table 2). These findings collectively highlight the therapeutic relevance of modulating the gut microbiota in AD management. Moreover, studies of Parkinson's disease or multiple sclerosis also offer clues for AD treatment, as they share similar pathways and symptoms. This comparative approach broadens our understanding, as shared mechanisms such as neuroinflammation, oxidative stress, and mitochondrial dysfunction are common across neurodegenerative disorders. Yue *et al.*, for example, studied a next-generation probiotic, *Lactococcus lactis* MG1363-pMG36e-GLP-1, in a Parkinson model. This GLP-1-secreting strain enhanced motor performance, diminished oxidative damage and iron accumulation, and safeguarded dopaminergic neurons by suppressing ferroptosis, indicating its candidacy as a probiotic-based neuroprotective treatment (Yue *et al.*, 2022). This oxidative stress regulation and neuronal protection mechanism could apply to AD pathology, showing translational potential.

Both next-generation probiotics and postbiotics under preclinical and clinical trials for Alzheimer's disease show promise in modulating gut–brain interactions and promoting neuroprotection. Together, these studies establish a foundation for understanding how microbiota-targeted interventions could influence cognitive outcomes.

Ulsemer *et al.* (2012) conducted a study to evaluate the safety of *Bacteroides xylanisolvens* DSM 23964 for probiotic application. Before clinical translation, however, establishing the safety profile of a potential NGP candidate is essential. The strain lacked virulence factors, was sensitive to key antibiotics, and carried a chromosomal β-lactamase gene without plasmids, reducing antibiotic resistance risk. These findings indicate that it is tentatively safe for additional probiotic assessment (Ulsemer *et al.*, 2012). Similarly, Sokol *et al.* also found that *Faecalibacterium prausnitzii* is an anti-inflammatory gut bacterium that is decreased in people with Crohn's disease. Parallel evidence from gut inflammatory disorders provides insights into NGPs with strong anti-inflammatory properties. This bacterium makes metabolites, like SCFAs, that stop NF-κB signalling and lower pro-inflammatory cytokines. This helps keep the immune system and gut in balance (Sokol *et al.*, 2008). Due to its anti-inflammatory and immunomodulatory properties, *F. prausnitzii* is considered a promising candidate for AD, which may mitigate gut-driven inflammation and neuroinflammation. In addition to *F. prausnitzii*, other butyrate-producing bacteria are also being explored for their neuroprotective potential.

Butyricicoccus pullicaecorum is also a butyrate-producing bacterium, and thus it is a potential postbiotic source (Maiuolo *et al.*, 2024). In a randomised, double-blind, placebo-controlled crossover study, its safety was tested in 30 healthy volunteers. Participants were given 10^8 CFU of *B. pullicaecorum* or placebo orally once daily for 4 weeks with a 3-week washout period. No major adverse

effects or changes in blood chemistry, bowel function, or gut microbiota were observed. Overall, *B. pullicaecorum* was safe and well tolerated, indicating that it may be used as a next-generation probiotic to improve gut health and increase colonic butyrate production, which may help with neuroinflammatory and neurodegenerative diseases like AD. Beyond clinical safety, recent in vitro investigations are uncovering the mechanistic underpinnings of how NGPs and their postbiotics exert neuroprotective actions (Boesmans *et al.*, 2018).

Current in vitro research is looking into the therapeutic potential of next-generation probiotics and their postbiotics in AD. Wang *et al.* in 2025, for instance, looked into *Akkermansia muciniphila* and one of its metabolites, propionic acid, on hippocampal neuronal cells. Propionic acid inhibited the expression of the mitochondrial fission protein Drp1 via the GPR41 receptor and promoted mitophagy through the PINK1/Parkin pathway with the activation of GPR43 receptors. These cellular results were in line with data in AD mouse models, suggesting that what is observed in vitro has implications for Alzheimer's pathology. It is suggested in this study that microbiota-derived metabolites can regulate neuronal mitochondrial activity and autophagy, providing new leads into unique therapeutic interventions for AD (Z. Wang *et al.*, 2025). Overall, these accumulating preclinical findings lay the groundwork for clinical translation of microbiota-based strategies, including NGPs and postbiotics, in AD management. The Table 2 summarises key preclinical studies exploring the neuroprotective and disease-modifying effects of next-generation probiotics in AD-related and symptomatic models. It highlights the Probiotic strains used, Animal type, Study model, Mechanism of action and Effect on AD pathology of the research.

Table 2: Summary of Preclinical Studies Investigating the Therapeutic Potential of Next-Generation Probiotics in Alzheimer's Disease

NGP strain	Animal / Cell used	Study Model	Mechanism of Action	Effect on Alzheimer's Pathology	Author name / year
Akkermansia muciniphila (Akk)	APP/PS1 mice	In vivo	Anti-inflammatory, gut barrier restoration, anti-amyloid β, metabolic regulation, and cognitive improvement.	Improved metabolic function, intestinal barrier integrity, and amyloid β accumulation, and enhanced cognitive performance in APP/PS1 Alzheimer's mice, suggesting its potential as a next-generation probiotic for AD prevention and treatment. (Ou *et al.*, 2020)	Xiaojuan Hu, 2023
Akkermansia muciniphila	AD like rat model	In vivo	Restoration of Gut microbiota balance, short-chain fatty acid (SCFA) production, anti-inflammatory effects, and reduction of amyloid deposition.	A. muciniphila improved cognitive function in AD-like rats by modulating gut microbiota and reducing Aβ deposition. (He *et al.*, 2022)	Xiaoya He, 2022
Akkermansia muciniphila	AD rats	In vivo	Restores gut microbial balance. Increase SCFA-and neurotransmitter–producing bacteria. Reduce proinflammatory bacteria. Lowering brain Aβ deposition. Improves peripheral metabolism.	A. muciniphila treatment improved memory reduced anxiety-like behaviour and lowered pro-inflammatory cytokines in AD rats. (Maftoon *et al.*, 2024)	Hamideh Maftoon *et al.*, 2024
Akkermansia muciniphila	APP/PS1 transgenic mice	In vivo	Modulated gut microbiota composition, increased SCFA production, normalised microglial abundance, reduced neuroinflammation, and improved glucose metabolism.	Long-term administration of Akkermansia muciniphila and GOS improved metabolic health, reduced neuroinflammation, and alleviated cognitive and behavioural deficits in APP/PS1 mice. (Kunevičius *et al.*, 2025)	Arnas Kunevičius, 2025
Akkermansia muciniphila	FXFAD mice model	In vivo, in vitro	Regulating GPR41/43-mediated mitochondrial homeostasis, reducing DRP1-dependent mitochondrial fission, and PINK1/PARKIN-mediated mitophagy.	Administration of A. muciniphila and its metabolite propionic acid improved cognition and restored mitochondrial homeostasis in Alzheimer's disease models by regulating DRP1 through GPR41 and enhancing PINK1/PARKIN-mediated mitophagy via GPR43. (Z. Wang *et al.*, 2025)	Zifan Wang *et al.*, 2025

Akkermansia muciniphila	C58BL/6 mice	In vivo	Upregulated BDNF → improved neuroplasticity, enhanced spatial working memory.	Memory improved and modest metabolic benefits (Ahn *et al.*, 2025)	Ji-Seon Ahn *et al.*, 2025
Akkermansia muciniphila	EAE mice	In vivo	Gut microbiota modulation, improved intestinal barrier, reduced Th17 and NLRP3 neuroinflammation	A. muciniphila supplementation reduced disease severity, improved cognitive function, and decreased neuroinflammation in EAE mice, suggesting it may also have potential therapeutic benefits in Alzheimer's disease by modulating neuroinflammation and gut-brain interactions. (X. Li *et al.*, 2025)	Xiaobing Li *et al.*, 2025
Akkermansia muciniphila	Hepatic injury mouse model	In vivo	Improved cognitive function by restoring BDNF and serotonin expression in the gut and brain, reduced tissue damage, and modulated gut-liver-brain axis signalling; also, effects in liver tissue.	A. muciniphila supplementation improved cognitive dysfunction, BDNF and serotonin levels, and reduced tissue damage in liver injury models, suggesting it may have potential therapeutic relevance for Alzheimer's disease via gut-brain axis modulation. (E. J. Kang *et al.*, 2024)	Eun Ji Kang *et al.*, 2024
Akkermansia muciniphila	C57BL/6	In vivo	Reduced pro-inflammatory pathways, particularly IL-6, in the blood and hippocampus, leading to improved cognitive function.	A. muciniphila supplementation improved cognitive function in aged mice by reducing IL-6-mediated inflammation, suggesting it may have potential therapeutic relevance for Alzheimer's disease through anti-inflammatory gut-brain axis modulation. (X. Zhu *et al.*, 2023)	Xiaoqi Zhu *et al.*, 2023
Akkermansia muciniphila	C57BL/6 mice	In vivo and in vitro	Restored SCFAs, suppressed microglial activation, and preserved synapse and cognition.	A. muciniphila supplementation alleviated SD-induced cognitive dysfunction and synaptic loss via SCFAs-mediated microglial homeostasis, suggesting it may have potential therapeutic relevance for Alzheimer's disease by preventing neuroinflammation and synapse loss. (N. Li *et al.*, 2023)	Li *et al.*, 2023
Faecalibacterium praus	NA	In silico/ Bioinformatic (metagenomic analysis)	NA	The study found significant gut microbial dysbiosis in Alzheimer's disease patients, with increased abundance of Faecalibacterium, Bacteroides, and Phocaeicola, suggesting alterations in gut microbiota composition may be linked to AD pathogenesis. Among these, Faecalibacterium prausnitzii has shown potential in the treatment of Alzheimer's disease due to its anti-inflammatory and neuroprotective properties. (Jahvnavi *et al.*, 2025)	Jahnavi *et al.*, 2025
Faecalibacterium prausnitzii	PD mouse model	In vivo	F. prausnitzii acts via gut microbiome restoration, immune modulation, and anti-inflammatory pathways to exert neuroprotective effects.	Oral Faecalibacterium prausnitzii improved symptoms and reduced pathology in Parkinson's mouse models, suggesting it may also have neuroprotective potential in Alzheimer's disease. (Moiseyenko *et al.*, 2025)	Moise Yenko, 2025
Bacteroides uniformis	Sprague Dawley SPF rats	In vivo	Bacteroides uniformis works by modulating the gut microbiome, enhancing SCFA production, suppressing inflammation, and regulating neuroendocrine pathways to exert neuroprotective and behaviour-improving effects.	A mixture including Bacteroides uniformis reduced anxiety and depression-like behaviours in rats, suggesting its potential as a therapeutic candidate for Alzheimer's disease. (Meng *et al.*, 2025)	Meng, 2025

Clostridium butyricum	ICV-STZ mice	In vivo	Modulates the gut-brain axis, strengthens the intestinal barrier, and reduces neuroinflammation via TLR4/MYD88 signalling.	Clostridium butyricum improved cognitive dysfunction, reduced tau hyperphosphorylation, restored hippocampal structure, and modulated gut microbiota and neuroinflammation in ICV-STZ-induced AD mice. (Su *et al.*, 2023)	Su, 2023
Clostridium butyricum	C57BL/6 mice	In vivo	Secretes GLP-1 to activate GLP-1R, promotes PINK1/ parkin-mediated mitophagy, reduces oxidative stress, restores gut microbiota, and enhances intestinal barrier via GPR41/43 signalling.	B. butyricum-GLP-1 improved motor dysfunction, reduced α-synuclein aggregation, enhanced dopaminergic neuron survival, promoted mitophagy, restored gut microbiota, and strengthened the intestinal barrier in MPTP-induced Parkinson's disease mice, suggesting it may also have potential in Alzheimer's treatment. (Y. Wang *et al.*, 2023)	Wang, 2023
Clostridium butyricum	APP/PS1 mice	In vivo	Modulates gut microbiota, increases acetate-producing bacteria and SCFAs, strengthens intestinal barrier (Claudin 1, ZO-1, Occludin), reduces neuroinflammation and apoptosis via JNK/CDK5/GS K-3 β and JAK/SAT pathways.	CBM588 improved cognitive function, reduced Aβ deposition and Tau hyperphosphorylation, enhanced intestinal barrier integrity, and increased acetate levels in APP/PS1 mice, showing potential as a therapeutic strategy for Alzheimer's disease. (Shiqing *et al.*, 2025)	Ye, 2025
Clostridium butyricum	Adult male rats	In vivo	Modulates gut microbiota, increases SCFAs, strengthens tight junction proteins (claudin-5, occludin) in gut and brain, and reduces inflammatory cytokines (IL-1β, TNF-α).	Clostridium butyricum improved cognitive function, reduced systemic and neuroinflammation, and enhanced gut-brain barrier integrity in HFD-induced rats, suggesting it may also have potential in Alzheimer's treatment. (Elberry *et al.*, 2025)	Elberry, 2025
Clostridium butyricum	NA	In vivo	Restores gut microbiota, reduces intestinal barrier inflammation, and protects hippocampal neurons via the gut-brain axis.	Clostridium butyricum improved cognitive function, hippocampal synaptic homeostasis in obesity-induced mice, indicating potential for Alzheimer's treatment. (Zheng *et al.*, 2024)	Mingxuan Zheng, 2024
Clostridium butyricum	C57BL/6N mice	In vivo	Clostridium butyricum improves AD by modulating the TLR$/MYD88/NF-kB pathways, enhancing gut barrier (occludin/ZO-1), restoring microbiota balance, and reducing hippocampal tau hyperphosphorylation.	Clostridium butyricum improved cognitive function, reduced neuroinflammation, restored intestinal barrier integrity, and modulated gut microbiota in ICV-STZ-induced Alzheimer's disease mice, suggesting potential therapeutic value for AD. (Su *et al.*, 2023)	Yunfang Su, 2023

7. Challenges and Limitations

The development of postbiotics and new-generation probiotics still faces many challenges. One of the most significant challenges is that there are no standard procedures to produce them, which results in variations in quality, potency, and formulation. Due to this, findings from studies differ and are occasionally difficult to replicate. As a result, comparative evaluation of therapeutic outcomes becomes complicated, slowing regulatory approval and large-scale clinical translation (Aran *et al.*, 2025). Also, the gut-brain axis is a multifaceted system that incorporates the immune system, neurotransmitters, and blood-brain barrier. Scientists are still working on fully comprehending how postbiotics and NGPs impact these pathways in AD (Patricio-Martínez *et al.*, 2025).

Most evidence to date has been on animal or lab studies, with only a few having advanced to clinical trials (Abouelela & Helmy, 2024). Strong clinical data are required by regulatory agencies before their approval as treatments, thus the delay in their progress (Tiwari *et al.*, 2024). Another challenge is making these chemicals remain active after

they are introduced into the body; stomach acid, digestive enzymes, and gut movement may degrade them before they act on their target location, reducing their efficacy (Chang *et al.*, 2019).

While they are mostly safe, not much is known about their long-term impact, particularly in older people. This highlights the importance of longitudinal studies to assess chronic exposure effects, especially in vulnerable populations such as the elderly (Głowacka *et al.*, 2024). Additionally, safety research is necessary to ensure they don't result in any adverse reactions. Finally, not everyone reacts the same way to these therapies. Variations in genes, diet, and intestinal microbiome can affect how well they work, so personalised strategies may be necessary for optimal success (Mishra *et al.*, 2023).

8. Future Perspectives

Over the next few years, treatments for AD will increasingly leverage the gut-brain axis to decrease brain inflammation, amyloid accumulation, and memory loss. To achieve this, researchers are focusing on strategies that target gut-microbiota balance as a means of influencing CNS health (Patricio-Martínez *et al.*, 2025). Through the restoration of a normal gut microbiota, next-gen probiotics and postbiotics could slow the disease instead of merely alleviating its symptoms.

Postbiotics possess a few advantages over conventional probiotics: they are safer, more stable, and simpler to standardise. This makes them especially indicated for aged AD patients, whose immune systems tend to be weaker. Scientists are currently isolating individual neuroactive postbiotic molecules, including SCFAs, tryptophan metabolites, and bacterial extracellular vesicles, that have direct effects on brain health by modulating microglial activation, oxidative stress, and neuronal survival (Głowacka *et al.*, 2024). Future research also involves the development of sophisticated NGP strains that can deliver anti-inflammatory molecules, neurotrophic factors, or antioxidant metabolites into the gut, thus influencing brain function via the gut-brain axis. Building on these findings, future directions focus on engineering NGP strains capable of targeted molecular delivery to enhance gut-brain communication (Siripaopradit *et al.*, 2024).

Yet more clinical trials are required to reveal fully how each probiotic strain functions in AD, how it's best to use them, and whether any side effects occur. The future management of AD will probably involve a combination of microbiome therapy and personalised medicine. Based on a patient's individual gut microbiome profile, physicians might select specific postbiotics or NGP strains most appropriate for individual needs (Kashyap *et al.*, 2017; Patricio-Martínez *et al.*, 2025). Scientists also expect to combine microbiome-based therapies with existing AD therapies like Donepezil, Memantine, or diet therapies. This could be effective in increasing drug efficacy, decreasing necessary doses, and lowering side effects. Even though preclinical findings are encouraging, extensive clinical confirmation is missing. These interventions may potentially be included in nutritional recommendations or functional food programmes to help delay cognitive decline in ageing populations and, in doing so, reduce the global burden of dementia.

9. Conclusion

The study of next-generation probiotics (NGPs) and postbiotics has revealed a promising new frontier in Alzheimer's disease (AD) treatment by targeting the gut-brain axis. Evidence from preclinical studies shows that specific probiotic strains, such as Akkermansia muciniphila, Clostridium butyricum, and Faecalibacterium prausnitzii, have multiple neuroprotective effects by restoring gut microbial balance, increasing short-chain fatty acid production, modulating neurotransmitters, strengthening intestinal and blood-brain barriers, and reducing neuroinflammation and oxidative stress. Postbiotics, which are non-living microbial derivatives, offer similar benefits while also improving safety, stability, and standardisation, making them ideal for elderly or immunocompromised populations. Despite the compelling preclinical evidence, several challenges prevent clinical translation. Variability in postbiotic and NGP formulations, limited understanding of complex gut-brain interactions, potential degradation in the gastrointestinal tract, and individual differences in microbiome composition highlight the need for a standardised protocol and longitudinal studies. Addressing these issues will be critical to designing effective and personalised microbiome-based therapies. Future directions involve isolating specific neuroactive postbiotic molecules, engineering targeted NGP strains capable of delivering anti-inflammatory, neurotrophic, and antioxidant metabolites, and combining microbiome-based strategies with conventional AD therapies to enhance efficacy while reducing side effects. Personalised approaches based on individual gut microbiome profiles may optimise therapeutic outcomes and pave the way for precision in Alzheimer's disease. Above all, well-controlled clinical trials are urgently required to confirm the therapeutic efficacy and safety of NGPs and postbiotics in human populations.

In conclusion, modulation of the gut-brain axis via NGPs and postbiotics represents a novel, multi-targeted strategy that goes beyond symptomatic relief to potentially slow or modify disease progression. By leveraging these

microbial interventions' neuroprotective, anti-inflammatory, and metabolic benefits, this approach provides a promising path for innovative, safe, and personalised AD therapies, ultimately contributing to improved cognitive health and quality of life for affected individuals.

Abbreviations

AD: Alzheimer's Disease; **Aβ:** Amyloid-β; **Aβ-42:** Amyloid-β 42 peptide; **FDA:** Food and Drug Administration; **AChE:** Acetylcholinesterase; **NMDA:** N-Methyl-D-Aspartate; **NGPs:** Next-Generation Probiotics; **SCFAs:** Short-Chain Fatty Acids; **GABA:** Gamma-Aminobutyric Acid; **CNS:** Central Nervous System; **MG:** Microbiota-Gut; **MGBA:** Microbiota-Gut-Brain Axis; **VN:** Vagus Nerve; **ANS:** Autonomic Nervous System; **ENS:** Enteric Nervous System; **GPR41 / GPR43:** G-Protein-Coupled Receptor 41 / 43; **HDAC:** Histone Deacetylase; **TMAO:** Trimethylamine-N-Oxide; **GALT:** Gut-Associated Lymphoid Tissue; **IL-1β:** Interleukin 1 beta; **TNF-α:** Tumour Necrosis Factor alpha; **IL-6:** Interleukin 6; **BBB:** Blood-Brain Barrier; **LPS:** Lipopolysaccharide; **TLR4:** Toll-Like Receptor 4; **MAPK:** Mitogen-Activated Protein Kinase; **NFκB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **RBC:** Ribosomal Binding Component; **MCI:** Mild Cognitive Impairment; **ROS:** Reactive Oxygen Species; **CAT:** Catalase; **SOD:** Superoxide Dismutase; **HMG-CoA:** 3-Hydroxy-3-Methylglutaryl-Coenzyme A; **FOS:** Fructooligosaccharides; **BDNF:** Brain-Derived Neurotrophic Factor; **HKB:** Heat-Killed Bacteria; **CSF:** Cell-Free Supernatant; **CFU:** Colony-Forming Units; **Drp1:** Dynamin-related Protein 1; **PINK1:** PTEN-Induced Kinase 1.

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Authorship Contribution

Mariyam Hussain: Conceptualisation, Data curation, Formal Analysis, Resource, Software, Writing-original draft, Writing- review and editing, Validation and Visualisation, *Mohammad Ikram:* Conceptualisation, Data curation, Formal Analysis, Resource, Software, Writing-original draft, Writing- review and editing, Validation and Visualisation.

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The authors declare no conflict of interest.

References

2021 Alzheimer's disease facts and figures. (2021). *Alzheimer's & Dementia*, *17*(3), 327–406. https://doi.org/10.1002/alz.12328

2025 Alzheimer's disease facts and figures. (2025). *Alzheimer's & Dementia*, *21*(4), e70235. https://doi.org/10.1002/alz.70235

Abbas, Z., Ahmad, B., Tong, Y., Zhang, J., Wu, S., Wang, J., Li, Z., Liu, T., Liu, Y., Wei, X., Si, D., & Zhang, R. (2025). Mulberry-derived postbiotics alleviate LPS-induced intestinal inflammation and modulate gut microbiota dysbiosis. *Food & Function*, *16*(11), 4437–4450. https://doi.org/10.1039/D4FO05503A

Abdelhamid, M., Jung, C.-G., Zhou, C., Inoue, R., Chen, Y., Sento, Y., Hida, H., & Michikawa, M. (2024). Potential Therapeutic Effects of Bifidobacterium breve MCC1274 on Alzheimer's Disease Pathologies in AppNL-G-F Mice. *Nutrients*, *16*(4), 538. https://doi.org/10.3390/nu16040538

Abdellatief, H. (2024). In vivo evaluation of anti- Alzheimer impact of Asparagus sprengeri and Lactobacillus plantarum. *Bulletin of Egyptian Society for Physiological Sciences*, *44*(3), 121–131.

Abouelela, M. E., & Helmy, Y. A. (2024). Next-Generation Probiotics as Novel Therapeutics for Improving Human Health: Current Trends and Future Perspectives. *Microorganisms*, *12*(3), 430. https://doi.org/10.3390/microorganisms12030430

Agahi, A., Hamidi, G. A., Daneshvar, R., Hamdieh, M., Soheili, M., Alinaghipour, A., Esmaeili Taba, S. M., & Salami, M. (2018). Does Severity of Alzheimer's Disease Contribute to Its Responsiveness to Modifying Gut Microbiota? A Double Blind Clinical Trial. *Frontiers in Neurology*, *9*, 662. https://doi.org/10.3389/fneur.2018.00662

Ahmed, S., Busetti, A., Fotiadou, P., Vincy Jose, N., Reid, S., Georgieva, M., Brown, S., Dunbar, H., Beurket-Ascencio, G., Delday, M. I., Ettorre, A., & Mulder, I.

E. (2019). In vitro Characterization of Gut Microbiota-Derived Bacterial Strains With Neuroprotective Properties. *Frontiers in Cellular Neuroscience*, *13*, 402. https://doi.org/10.3389/fncel.2019.00402

Ahn, J.S., Kim, S., Han, E.J., Hong, S.T., & Chung, H.J. (2025). Increasing spatial working memory in mice with Akkermansia muciniphila. *Communications Biology*, *8*(1), 546. https://doi.org/10.1038/s42003-025-07975-3

Aleman, R. S., & Yadav, A. (2023). Systematic Review of Probiotics and Their Potential for Developing Functional Nondairy Foods. *Applied Microbiology*, *4*(1), 47–69. https://doi.org/10.3390/applmicrobiol4010004

Algieri, F., Tanaskovic, N., Rincon, C. C., Notario, E., Braga, D., Pesole, G., Rusconi, R., Penna, G., & Rescigno, M. (2023). Lactobacillus paracasei CNCM I-5220-derived postbiotic protects from the leaky-gut. *Frontiers in Microbiology*, *14*, 1157164. https://doi.org/10.3389/fmicb.2023.1157164

Ansari, F., Neshat, M., Pourjafar, H., Jafari, S. M., Samakkhah, S. A., & Mirzakhani, E. (2023). The role of probiotics and prebiotics in modulating of the gut-brain axis. *Frontiers in Nutrition*, *10*. https://doi.org/10.3389/fnut.2023.1173660

Anti-Neurodegenerative Activity Of The Probiotic Strain Lactobacillus Acidophilus. (n.d.). ResearchGate. Retrieved October 25, 2025. https://doi.org/10.56936/18290825-3.v18.2024-93

Aran, K. R., Porel, P., Hunjan, G., Singh, S., Gupta, G. D., & Rohit. (2025). Postbiotics as a therapeutic tool in Alzheimer's disease: Insights into molecular pathways and neuroprotective effects. *Ageing Research Reviews*, *106*, 102685. https://doi.org/10.1016/j.arr.2025.102685

Asadi, Z., Abbasi, A., Ghaemi, A., Montazeri, E. A., & Akrami, S. (2024). Investigating the properties and antibacterial, antioxidant, and cytotoxicity activity of postbiotics derived from Lacticaseibacillus casei on various gastrointestinal pathogens in vitro and in food models. *GMS Hygiene and Infection Control*, *19*, Doc60. https://doi.org/10.3205/dgkh000515

Banks, W. A., & Erickson, M. A. (2010). The blood–brain barrier and immune function and dysfunction. *Neurobiology of Disease*, *37*(1), 26–32. https://doi.org/10.1016/j.nbd.2009.07.031

Barefoot, S. F., & Klaenhammer, T. R. (1984). Purification and characterization of the Lactobacillus acidophilus bacteriocin lactacin B. *Antimicrobial Agents and Chemotherapy*, *26*(3), 328–334. https://doi.org/10.1128/aac.26.3.328

Bhadoria, P. B. S., & Mahapatra, S. C. (2011). Prospects, Technological Aspects and Limitations of Probiotics – A Worldwide Review. *European Journal of Nutrition & Food Safety*, 23–42.

Bhat, M. I., Kumari, A., Kapila, S., & Kapila, R. (2019). Probiotic lactobacilli mediated changes in global epigenetic signatures of human intestinal epithelial cells during Escherichia coli challenge. *Annals of Microbiology*, *69*(6), 603–612. https://doi.org/10.1007/s13213-019-01451-0

Boesmans, L., Valles-Colomer, M., Wang, J., Eeckhaut, V., Falony, G., Ducatelle, R., Van Immerseel, F., Raes, J., & Verbeke, K. (2018). Butyrate Producers as Potential Next-Generation Probiotics: Safety Assessment of the Administration of *Butyricicoccus pullicaecorum* to Healthy Volunteers. *mSystems*, *3*(6), 10.1128/msystems.00094-18. https://doi.org/10.1128/msystems.00094-18

Botin, T., Ramirez-Chamorro, L., Vidic, J., Langella, P., Martin-Verstraete, I., Chatel, J.-M., & Auger, S. (n.d.). The Tolerance of Gut Commensal Faecalibacterium to Oxidative Stress Is Strain Dependent and Relies on Detoxifying Enzymes. *Applied and Environmental Microbiology*, *89*(7), e00606-23. https://doi.org/10.1128/aem.00606-23

Chandrasekaran, P., Weiskirchen, S., & Weiskirchen, R. (2024). Effects of Probiotics on Gut Microbiota: An Overview. *International Journal of Molecular Sciences*, *25*(11), 6022. https://doi.org/10.3390/ijms25116022

Chang, C.J., Lin, T.L., Tsai, Y.L., Wu, T.R., Lai, W.F., Lu, C.C., & Lai, H.C. (2019). Next generation probiotics in disease amelioration. *Journal of Food and Drug Analysis*, *27*(3), 615–622. https://doi.org/10.1016/j.jfda.2018.12.011

Choi, G.-H., Bock, H.J., Lee, N.K., & Paik, H.D. (2022). Soy yogurt using Lactobacillus plantarum 200655 and fructooligosaccharides: Neuroprotective effects against oxidative stress. *Journal of Food Science and Technology*, *59*(12), 4870–4879. https://doi.org/10.1007/s13197-022-05575-1

Choi, H. J., Lee, H. L., Kim, I. Y., Ju, Y. H., Heo, Y. M., Na, H. R., Lee, J. Y., Choi, S.-I., & Heo, H. J. (2025). Oral Administration of Lactobacillus gasseri and Lacticaseibacillus rhamnosus Ameliorates Amyloid Beta (Aβ)-Induced Cognitive Impairment by Improving Synaptic Function Through Regulation of TLR4/Akt Pathway. *Antioxidants*, *14*(2), 139. https://doi.org/10.3390/antiox14020139

Cleusix, V., Lacroix, C., Vollenweider, S., Duboux, M., & Le Blay, G. (2007). Inhibitory activity spectrum of reuterin produced by Lactobacillus reuteri against

intestinal bacteria. *BMC Microbiology*, *7*(1), 101. https://doi.org/10.1186/1471-2180-7-101

Cox, L. M., Maghzi, A. H., Liu, S., Tankou, S. K., Dhang, F. H., Willocq, V., Song, A., Wasén, C., Tauhid, S., Chu, R., Anderson, M. C., De Jager, P. L., Polgar-Turcsanyi, M., Healy, B. C., Glanz, B. I., Bakshi, R., Chitnis, T., & Weiner, H. L. (2021). Gut Microbiome in Progressive Multiple Sclerosis. *Annals of Neurology*, *89*(6), 1195–1211. https://doi.org/10.1002/ana.26084

Cryan, J. F., O'Riordan, K. J., Cowan, C. S. M., Sandhu, K. V., Bastiaanssen, T. F. S., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., Golubeva, A. V., Guzzetta, K. E., Jaggar, M., Long-Smith, C. M., Lyte, J. M., Martin, J. A., Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E., … Dinan, T. G. (2019). The Microbiota-Gut-Brain Axis. *Physiological Reviews*, *99*(4), 1877–2013. https://doi.org/10.1152/physrev.00018.2018

D'Alessandro, M. C. B., Kanaan, S., Geller, M., Praticò, D., & Daher, J. P. L. (2025). Mitochondrial dysfunction in Alzheimer's disease. *Ageing Research Reviews*, *107*, 102713. https://doi.org/10.1016/j.arr.2025.102713

Di Salvo, C., D'Antongiovanni, V., Benvenuti, L., d'Amati, A., Ippolito, C., Segnani, C., Pierucci, C., Bellini, G., Annese, T., Virgintino, D., Colucci, R., Antonioli, L., Fornai, M., Errede, M., Bernardini, N., & Pellegrini, C. (2024). *Lactiplantibacillus plantarum* HEAL9 attenuates cognitive impairment and progression of Alzheimer's disease and related bowel symptoms in SAMP8 mice by modulating microbiota-gut-inflammasome-brain axis. *Food & Function*, *15*(20), 10323–10338. https://doi.org/10.1039/D4FO02075H

Doifode, T., Giridharan, V. V., Generoso, J. S., Bhatti, G., Collodel, A., Schulz, P. E., Forlenza, O. V., & Barichello, T. (2021). The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. *Pharmacological Research*, *164*, 105314. https://doi.org/10.1016/j.phrs.2020.105314

Dolphin, H., Dukelow, T., Finucane, C., Commins, S., McElwaine, P., & Kennelly, S. P. (2022). "The Wandering Nerve Linking Heart and Mind" – The Complementary Role of Transcutaneous Vagus Nerve Stimulation in Modulating Neuro-Cardiovascular and Cognitive Performance. *Frontiers in Neuroscience*, *16*. https://doi.org/10.3389/fnins.2022.897303

Dos Santos Picanco, L. C., Ozela, P. F., De Fatima De Brito Brito, M., Pinheiro, A. A., Padilha, E. C., Braga, F. S., De Paula Da Silva, C. H. T., Dos Santos, C. B. R., Rosa, J. M. C., & Da Silva Hage-Melim, L. I. (2018). Alzheimer's Disease: A Review from the Pathophysiology to Diagnosis, New Perspectives for Pharmacological Treatment. *Current Medicinal Chemistry*, *25*(26), 3141–3159. https://doi.org/10.2174/0929867323666161213101126

Elberry, D. A., Gamal, M., Gawish, Z., Hegazy, E. A., Hosny, S. A., Rashed, L. A., Mehesen, M. N., & ShamsEldeen, A. M. (2025). Amelioration of gut dysbiosis-induced cognitive deterioration by repeated administration of human clostridium butyricum: Targeting intestinal and blood–brain barrier. *Future Journal of Pharmaceutical Sciences*, *11*(1), 87. https://doi.org/10.1186/s43094-025-00836-0

Erny, D., Hrabě De Angelis, A. L., Jaitin, D., Wieghofer, P., Staszewski, O., David, E., Keren-Shaul, H., Mahlakoiv, T., Jakobshagen, K., Buch, T., Schwierzeck, V., Utermöhlen, O., Chun, E., Garrett, W. S., McCoy, K. D., Diefenbach, A., Staeheli, P., Stecher, B., Amit, I., & Prinz, M. (2015). Host microbiota constantly controls maturation and function of microglia in the CNS. *Nature Neuroscience*, *18*(7), 965–977. https://doi.org/10.1038/nn.4030

Faraji, N., Payami, B., Ebadpour, N., & Gorji, A. (2025). Vagus nerve stimulation and gut microbiota interactions: A novel therapeutic avenue for neuropsychiatric disorders. *Neuroscience & Biobehavioral Reviews*, *169*, 105990. https://doi.org/10.1016/j.neubiorev.2024.105990

Fung, T. C., Olson, C. A., & Hsiao, E. Y. (2017). Interactions between the microbiota, immune and nervous systems in health and disease. *Nature Neuroscience*, *20*(2), 145–155. https://doi.org/10.1038/nn.4476

Gao, Z., Yin, J., Zhang, J., Ward, R. E., Martin, R. J., Lefevre, M., Cefalu, W. T., & Ye, J. (2009). Butyrate Improves Insulin Sensitivity and Increases Energy Expenditure in Mice. *Diabetes*, *58*(7), 1509–1517. https://doi.org/10.2337/db08-1637

Giovannini, M. G., Lana, D., Traini, C., & Vannucchi, M. G. (2021). The Microbiota–Gut–Brain Axis and Alzheimer Disease. From Dysbiosis to Neurodegeneration: Focus on the Central Nervous System Glial Cells. *Journal of Clinical Medicine*, *10*(11), 2358. https://doi.org/10.3390/jcm10112358

Głowacka, P., Oszajca, K., Pudlarz, A., Szemraj, J., & Witusik-Perkowska, M. (2024). Postbiotics as Molecules Targeting Cellular Events of Aging Brain-The Role in Pathogenesis, Prophylaxis and Treatment of Neurodegenerative Diseases. *Nutrients*, *16*(14), 2244. https://doi.org/10.3390/nu16142244

Greer, M. M. Jr. (2000). Inflammation and the pathophysiology of Alzheimer's disease. *Dialogues in Clinical Neuroscience*, *2*(3), 233–239. https://doi.org/10.31887/DCNS.2000.2.3/mgreer

Gul, S., & Durante-Mangoni, E. (2024). Unraveling the Puzzle: Health Benefits of Probiotics—A Comprehensive Review. *Journal of Clinical Medicine*, *13*(5), 1436. https://doi.org/10.3390/jcm13051436

Hamdi, A., Lloyd, C., Eri, R., & Van, T. T. H. (2025). Postbiotics: A Promising Approach to Combat Age-Related Diseases. *Life*, *15*(8), 1190. https://doi.org/10.3390/life15081190

Harach, T., Marungruang, N., Duthilleul, N., Cheatham, V., Mc Coy, K. D., Frisoni, G., Neher, J. J., Fåk, F., Jucker, M., Lasser, T., & Bolmont, T. (2017). Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. *Scientific Reports*, *7*(1), 41802. https://doi.org/10.1038/srep41802

Hardingham, G. E., Fukunaga, Y., & Bading, H. (2002). Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. *Nature Neuroscience*, *5*(5), 405–414. https://doi.org/10.1038/nn835

He, X., Yan, C., Zhao, S., Zhao, Y., Huang, R., & Li, Y. (2022). The preventive effects of probiotic Akkermansia muciniphila on D-galactose/AlCl3 mediated Alzheimer's disease-like rats. *Experimental Gerontology*, *170*, 111959. https://doi.org/10.1016/j.exger.2022.111959

Hennequin, C., Kauffmann-Lacroix, C., Jobert, A., Viard, J. P., Ricour, C., Jacquemin, J. L., & Berche, P. (2000). Possible role of catheters in Saccharomyces boulardii fungemia. *European Journal of Clinical Microbiology & Infectious Diseases: Official Publication of the European Society of Clinical Microbiology*, *19*(1), 16–20. https://doi.org/10.1007/s100960050003

Hertzberger, R., Arents, J., Dekker, H. L., Pridmore, R. D., Gysler, C., Kleerebezem, M., & de Mattos, M. J. T. (2014). H2O2 Production in Species of the Lactobacillus acidophilus Group: A Central Role for a Novel NADH-Dependent Flavin Reductase. *Applied and Environmental Microbiology*, *80*(7), 2229–2239. https://doi.org/10.1128/AEM.04272-13

Heydari, R., Khosravifar, M., Abiri, S., Dashtbin, S., Alvandi, A., Nedaei, S. E., Salimi, Z., Zarei, F., & Abiri, R. (2025). A domestic strain of *Lactobacillus rhamnosus* attenuates cognitive deficit and pro-inflammatory cytokine expression in an animal model of Alzheimer's disease. *Behavioural Brain Research*, *476*, 115277. https://doi.org/10.1016/j.bbr.2024.115277

Hooper, L. V., Littman, D. R., & Macpherson, A. J. (2012). Interactions Between the Microbiota and the Immune System. *Science*, *336*(6086), 1268–1273. https://doi.org/10.1126/science.1223490

Hossain, M. S., & Hussain, M. H. (2025). Multi-Target Drug Design in Alzheimer's Disease Treatment: Emerging Technologies, Advantages, Challenges, and Limitations. *Pharmacology Research & Perspectives*, *13*(4), e70131. https://doi.org/10.1002/prp2.70131

Hu, X., Zhang, Y., Gu, C., Wu, R., Yao, Y., Gao, F., Luo, L., & Zhang, Y. (2023). TMAO promotes dementia progression by mediating the PI3K/Akt/mTOR pathway. *Tissue and Cell*, *81*, 102034. https://doi.org/10.1016/j.tice.2023.102034

Huang, C. B., Altimova, Y., Myers, T. M., & Ebersole, J. L. (2011). Short- and medium-chain fatty acids exhibit antimicrobial activity for oral microorganisms. *Archives of Oral Biology*, *56*(7), 650–654. https://doi.org/10.1016/j.archoralbio.2011.01.011

Imbimbo, B. P., Lombard, J., & Pomara, N. (2005). Pathophysiology of Alzheimer's Disease. *Neuroimaging Clinics of North America*, *15*(4), 727–753. https://doi.org/10.1016/j.nic.2005.09.009

Imperial, I. C. V. J., & Ibana, J. A. (2016). Addressing the Antibiotic Resistance Problem with Probiotics: Reducing the Risk of Its Double-Edged Sword Effect. *Frontiers in Microbiology*, *07*. https://doi.org/10.3389/fmicb.2016.01983

Ittner, L. M., Ke, Y. D., Delerue, F., Bi, M., Gladbach, A., Van Eersel, J., Wölfing, H., Chieng, B. C., Christie, M. J., Napier, I. A., Eckert, A., Staufenbiel, M., Hardeman, E., & Götz, J. (2010). Dendritic Function of Tau Mediates Amyloid-β Toxicity in Alzheimer's Disease Mouse Models. *Cell*, *142*(3), 387–397. https://doi.org/10.1016/j.cell.2010.06.036

Jahvnavi, Garg, P., & Srivastava, P. (2025). Metagenomics study reveals altered composition of Avispirillum, Phocaeicola, Bacteroides, and Faecalibacterium in the gut of patients suffering with Alzheimer's disease. *Ecological Genetics and Genomics*, *34*, 100322. https://doi.org/10.1016/j.egg.2025.100322

Jan, T., Negi, R., Sharma, B., Kumar, S., Singh, S., Rai, A. K., Shreaz, S., Rustagi, S., Chaudhary, N., Kaur, T., Kour, D., Sheikh, M. A., Kumar, K., Yadav, A. N., & Ahmed, N. (2024). Next generation probiotics for human health: An emerging perspective. *Heliyon*, *10*(16), e35980. https://doi.org/10.1016/j.heliyon.2024.e35980

Jastrząb, R., Graczyk, D., & Siedlecki, P. (2021). Molecular and Cellular Mechanisms Influenced by Postbiotics. *International Journal of Molecular Sciences*, *22*(24), 13475. https://doi.org/10.3390/ijms222413475

Kang, E. J., Cha, M.-G., Kwon, G.-H., Han, S. H., Yoon, S. J., Lee, S. K., Ahn, M. E., Won, S.-M., Ahn, E. H., & Suk, K. T. (2024). Akkermansia muciniphila improve cognitive dysfunction by regulating BDNF and serotonin pathway in gut-liver-brain axis. *Microbiome*, *12*(1), 181. https://doi.org/10.1186/s40168-024-01924-8

Kang, M. J., Jeong, H., Kim, S., Shin, J., Song, Y., Lee, B.H., Park, H.G., Lee, T.H., Jiang, H.H., Han, Y.S., Lee, B.G., Lee, H.J., Park, M.J., & Park, Y.S. (2023). Structural analysis and prebiotic activity of exopolysaccharide produced by probiotic strain Bifidobacterium bifidum EPS DA-LAIM. *Food Science and Biotechnology*, *32*(4), 517–529. https://doi.org/10.1007/s10068-022-01213-w

Kashyap, P. C., Chia, N., Nelson, H., Segal, E., & Elinav, E. (2017). Microbiome at the Frontier of Personalized Medicine. *Mayo Clinic Proceedings*, *92*(12), 1855–1864. https://doi.org/10.1016/j.mayocp.2017.10.004

Kaufmann, F. N., Costa, A. P., Ghisleni, G., Diaz, A. P., Rodrigues, A. L. S., Peluffo, H., & Kaster, M. P. (2017). NLRP3 inflammasome-driven pathways in depression: Clinical and preclinical findings. *Brain, Behavior, and Immunity*, *64*, 367–383. https://doi.org/10.1016/j.bbi.2017.03.002

Kazemi, N., Khorasgani, M. R., Noorbakhshnia, M., Razavi, S. M., Narimani, T., & Naghsh, N. (2024). Protective effects of a lactobacilli mixture against Alzheimer's disease-like pathology triggered by Porphyromonas gingivalis. *Scientific Reports*, *14*(1), 27283. https://doi.org/10.1038/s41598-024-77853-1

Kazemipoor, M., Radzi, C. W. J. W. M., Begum, K., & Yaze, I. (2012). *Screening of antibacterial activity of lactic acid bacteria isolated from fermented vegetables against food borne pathogens* (Version 1). arXiv. https://doi.org/10.48550/ARXIV.1206.6366

Kesika, P., Suganthy, N., Sivamaruthi, B. S., & Chaiyasut, C. (2021). Role of gut-brain axis, gut microbial composition, and probiotic intervention in Alzheimer's disease. *Life Sciences*, *264*, 118627. https://doi.org/10.1016/j.lfs.2020.118627

Kim, Y., Kim, H. J., & Ji, K. (2022). The Proliferation Inhibitory Effect of Postbiotics Prepared from Probiotics with Antioxidant Activity against HT-29 Cells. *Applied Sciences*, *12*(24), 12519. https://doi.org/10.3390/app122412519

Knox, E. G., Aburto, M. R., Clarke, G., Cryan, J. F., & O'Driscoll, C. M. (2022). The blood-brain barrier in aging and neurodegeneration. *Molecular Psychiatry*, *27*(6), 2659–2673. https://doi.org/10.1038/s41380-022-01511-z

Kumar, A., Singh, A., & Ekavali. (2015). A review on Alzheimer's disease pathophysiology and its management: An update. *Pharmacological Reports*, *67*(2), 195–203. https://doi.org/10.1016/j.pharep.2014.09.004

Kumar, A., Sivamaruthi, B. S., Dey, S., Kumar, Y., Malviya, R., Prajapati, B. G., & Chaiyasut, C. (2024). Probiotics as modulators of gut-brain axis for cognitive development. *Frontiers in Pharmacology*, *15*, 1348297. https://doi.org/10.3389/fphar.2024.1348297

Kunevičius, A., Vijaya, A. K., Atzeni, A., Mingaila, J., Šimoliūnė, I., Jamontas, R., Keževičiūtė, E., Gueimonde, M., Meškys, R., Baltriukienė, D., Arboleya, S., & Burokas, A. (2025). Intermittent supplementation with Akkermansia muciniphila and galactooligosaccharides modulates Alzheimer's disease progression, gut microbiota, and colon short-chain fatty acid profiles in mice. *Frontiers in Aging Neuroscience*, *17*, 1617980. https://doi.org/10.3389/fnagi.2025.1617980

Lange, O., Proczko-Stepaniak, M., & Mika, A. (2023). Short-Chain Fatty Acids—A Product of the Microbiome and Its Participation in Two-Way Communication on the Microbiome-Host Mammal Line. *Current Obesity Reports*, *12*(2), 108–126. https://doi.org/10.1007/s13679-023-00503-6

Lebeer, S., Vanderleyden, J., & De Keersmaecker, S. C. J. (2010). Host interactions of probiotic bacterial surface molecules: Comparison with commensals and pathogens. *Nature Reviews. Microbiology*, *8*(3), 171–184. https://doi.org/10.1038/nrmicro2297

Lee, H.-J., Lee, K.-E., Kim, J.-K., & Kim, D.-H. (2019). Suppression of gut dysbiosis by Bifidobacterium longum alleviates cognitive decline in 5XFAD transgenic and aged mice. *Scientific Reports*, *9*(1), 11814. https://doi.org/10.1038/s41598-019-48342-7

Lee, J. Y., Kim, J. H., Park, J.-Y., Kim, B.-K., Heo, H. J., & Choi, S.-I. (2025). Neuroprotective Effect of Lactobacillus gasseri MG4247 and Lacticaseibacillus rhamnosus MG4644 Against Oxidative Damage via NF-κB Signaling Pathway. *Fermentation*, *11*(7), 385. https://doi.org/10.3390/fermentation11070385

Lherm, T., Monet, C., Nougière, B., Soulier, M., Larbi, D., Le Gall, C., Caen, D., & Malbrunot, C. (2002). Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. *Intensive Care Medicine*, *28*(6), 797–801. https://doi.org/10.1007/s00134-002-1267-9

Li, N., Tan, S., Wang, Y., Deng, J., Wang, N., Zhu, S., Tian, W., Xu, J., & Wang, Q. (2023). *Akkermansia muciniphila* supplementation prevents cognitive impairment in sleep-deprived mice by modulating microglial engulfment of synapses. *Gut Microbes*, *15*(2), 2252764. https://doi.org/10.1080/19490976.2023.2252764

Li, X., Lin, D., Hu, X., Shi, X., Huang, W., Ouyang, Y., Chen, X., Xiong, Y., Wu, X., Hong, D., & Chen, H. (2025). *Akkermansia muciniphila* Modulates Central Nervous System Autoimmune Response and Cognitive Impairment by Inhibiting Hippocampal NLRP3 -

Mediated Neuroinflammation. *CNS Neuroscience & Therapeutics*, *31*(3), e70320. https://doi.org/10.1111/cns.70320

Liu, S., Gao, J., Zhu, M., Liu, K., & Zhang, H.-L. (2020). Gut Microbiota and Dysbiosis in Alzheimer's Disease: Implications for Pathogenesis and Treatment. *Molecular Neurobiology*, *57*(12), 5026–5043. https://doi.org/10.1007/s12035-020-02073-3

Maftei, N.-M., Raileanu, C. R., Balta, A. A., Ambrose, L., Boev, M., Marin, D. B., & Lisa, E. L. (2024). The Potential Impact of Probiotics on Human Health: An Update on Their Health-Promoting Properties. *Microorganisms*, *12*(2), 234. https://doi.org/10.3390/microorganisms12020234

Maftoon, H., Davar Siadat, S., Tarashi, S., Soroush, E., Basir Asefi, M., Rahimi Foroushani, A., & Mehdi Soltan Dallal, M. (2024). Ameliorative effects of Akkermansia muciniphila on anxiety-like behavior and cognitive deficits in a rat model of Alzheimer's disease. *Brain Research*, *1845*, 149280. https://doi.org/10.1016/j.brainres.2024.149280

Maiuolo, J., Bulotta, R. M., Ruga, S., Nucera, S., Macrì, R., Scarano, F., Oppedisano, F., Carresi, C., Gliozzi, M., Musolino, V., Mollace, R., Muscoli, C., & Mollace, V. (2024). The Postbiotic Properties of Butyrate in the Modulation of the Gut Microbiota: The Potential of Its Combination with Polyphenols and Dietary Fibers. *International Journal of Molecular Sciences*, *25*(13), 6971. https://doi.org/10.3390/ijms25136971

Mao, B., Guo, W., Liu, X., Cui, S., Zhang, Q., Zhao, J., Tang, X., & Zhang, H. (2023). Potential Probiotic Properties of Blautia producta Against Lipopolysaccharide-Induced Acute Liver Injury. *Probiotics and Antimicrobial Proteins*, *15*(3), 785–796. https://doi.org/10.1007/s12602-023-10044-y

Meng, C., Feng, S., Hao, Z., & Liu, H. (2025). A combination of potential psychobiotics alleviates anxiety and depression behaviors induced by chronic unpredictable mild stress. *NPJ Biofilms and Microbiomes*, *11*(1), 147. https://doi.org/10.1038/s41522-025-00779-7

Mishra, V., Yadav, D., Solanki, K. S., Koul, B., & Song, M. (2023). A Review on the Protective Effects of Probiotics against Alzheimer's Disease. *Biology*, *13*(1), 8. https://doi.org/10.3390/biology13010008

Mohamed, M. Y. (2024). Probiotics Benefits, Potential Limitations and Risks. *Egyptian Academic Journal of Biological Sciences. C, Physiology and Molecular Biology*, *16*(1), 253–276. https://doi.org/10.21608/eajbsc.2024.344590

Moiseyenko, A., Antonello, G., Schonhoff, A. M., Boktor, J. C., Long, K., Dirks, B., Oguienko, A. D., Winnett, A. V., Simpson, P., Daeizadeh, D., Ismagilov, R. F., Krajmalnik-Brown, R., Segata, N., Waldron, L. D., & Mazmanian, S. K. (2025). Faecalibacterium prausnitzii , *depleted in the Parkinson's disease microbiome, improves motor deficits in α-synuclein overexpressing mice*. Physiology. https://doi.org/10.1101/2025.09.18.677192

Nogal, A., Valdes, A. M., & Menni, C. (2021). The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health. *Gut Microbes*, *13*(1), 1897212. https://doi.org/10.1080/19490976.2021.1897212

Olszak, T., An, D., Zeissig, S., Vera, M. P., Richter, J., Franke, A., Glickman, J. N., Siebert, R., Baron, R. M., Kasper, D. L., & Blumberg, R. S. (2012). Microbial Exposure During Early Life Has Persistent Effects on Natural Killer T Cell Function. *Science*, *336*(6080), 489–493. https://doi.org/10.1126/science.1219328

O'Riordan, K. J., Collins, M. K., Moloney, G. M., Knox, E. G., Aburto, M. R., Fülling, C., Morley, S. J., Clarke, G., Schellekens, H., & Cryan, J. F. (2022). Short chain fatty acids: Microbial metabolites for gut-brain axis signalling. *Molecular and Cellular Endocrinology*, *546*, 111572. https://doi.org/10.1016/j.mce.2022.111572

Ou, Z., Deng, L., Lu, Z., Wu, F., Liu, W., Huang, D., & Peng, Y. (2020). Protective effects of Akkermansia muciniphila on cognitive deficits and amyloid pathology in a mouse model of Alzheimer's disease. *Nutrition & Diabetes*, *10*(1), 12. https://doi.org/10.1038/s41387-020-0115-8

Park, S., & Wu, X. (2022). Modulation of the Gut Microbiota in Memory Impairment and Alzheimer's Disease via the Inhibition of the Parasympathetic Nervous System. *International Journal of Molecular Sciences*, *23*(21), 13574. https://doi.org/10.3390/ijms232113574

Parker, A., Fonseca, S., & Carding, S. R. (2020). Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. *Gut Microbes*, *11*(2), 135–157. https://doi.org/10.1080/19490976.2019.1638722

Parnell, J. A., & Reimer, R. A. (2010). Effect of prebiotic fibre supplementation on hepatic gene expression and serum lipids: A dose–response study in JCR:LA-cp rats. *British Journal of Nutrition*, *103*(11), 1577–1584. https://doi.org/10.1017/S0007114509993539

Passeri, E., Elkhoury, K., Morsink, M., Broersen, K., Linder, M., Tamayol, A., Malaplate, C., Yen, F. T., & Arab-Tehrany, E. (2022). Alzheimer's Disease: Treatment Strategies and Their Limitations. *International Journal of Molecular Sciences*, *23*(22), 13954. https://doi.org/10.3390/ijms232213954

Patricio-Martínez, A., Patricio, F., Macuil-Chapuli, E., Martínez-Juárez, E. Á., Flores-Díaz, S., Cedillo-Ramírez, M. L., & Limón, I. D. (2025). The role of probiotics, prebiotics, and postbiotics: Cellular and molecular pathways activated on glial cells in Alzheimer's disease. *Frontiers in Neuroscience*, *19*, 1598011. https://doi.org/10.3389/fnins.2025.1598011

Piewngam, P., Zheng, Y., Nguyen, T. H., Dickey, S. W., Joo, H.-S., Villaruz, A. E., Glose, K. A., Fisher, E. L., Hunt, R. L., Li, B., Chiou, J., Pharkjaksu, S., Khongthong, S., Cheung, G. Y. C., Kiratisin, P., & Otto, M. (2018). Pathogen elimination by probiotic Bacillus via signaling interference. *Nature*, *562*(7728), 532–537. https://doi.org/10.1038/s41586-018-0616-y

Poncelet, A., Ruelle, L., Konopnicki, D., Miendje Deyi, V. Y., & Dauby, N. (2021). Saccharomyces cerevisiae fungemia: Risk factors, outcome and links with S. boulardii-containing probiotic administration. *Infectious Diseases Now*, *51*(3), 293–295. https://doi.org/10.1016/j.idnow.2020.12.003

Qian, K., Chen, S., Wang, J., Sheng, K., Wang, Y., & Zhang, M. (2022). A β-N-acetylhexosaminidase Amuc_2109 from Akkermansia muciniphila protects against dextran sulfate sodium-induced colitis in mice by enhancing intestinal barrier and modulating gut microbiota. *Food & Function*, *13*(4), 2216–2227. https://doi.org/10.1039/d1fo04094d

Rafique, N., Jan, S. Y., Dar, A. H., Dash, K. K., Sarkar, A., Shams, R., Pandey, V. K., Khan, S. A., Amin, Q. A., & Hussain, S. Z. (2023). Promising bioactivities of postbiotics: A comprehensive review. *Journal of Agriculture and Food Research*, *14*, 100708. https://doi.org/10.1016/j.jafr.2023.100708

Rahman, Z., & Dandekar, M. P. (2023). Implication of Paraprobiotics in Age-Associated Gut Dysbiosis and Neurodegenerative Diseases. *NeuroMolecular Medicine*, *25*(1), 14–26. https://doi.org/10.1007/s12017-022-08722-1

Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G. A. D., Gasbarrini, A., & Mele, M. C. (2019). What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms*, *7*(1), 14. https://doi.org/10.3390/microorganisms7010014

Roberts, K. D., Ahmed, S., San Valentin, E., Di Martino, L., McCormick, T. S., & Ghannoum, M. A. (2024). Immunomodulatory Properties of Multi-Strain Postbiotics on Human CD14+ Monocytes. *Life*, *14*(12), 1673. https://doi.org/10.3390/life14121673

Sáez, D., Fernández, P., Rivera, A., Andrews, E., & Oñate, A. (2012). Oral immunization of mice with recombinant Lactococcus lactis expressing Cu,Zn superoxide dismutase of Brucella abortus triggers protective immunity. *Vaccine*, *30*(7), 1283–1290. https://doi.org/10.1016/j.vaccine.2011.12.088

Sakr, E., Farid, O., & Mohamed, M. (2022). The potential of Fermented Asparagus sprengeri extract by Lactobacillus plantarum DMS 20174 on Antioxidant Properties and Memory Retention in vitro and in vivo. *Egyptian Journal of Chemistry*, *0*(0), 0–0. https://doi.org/10.21608/ejchem.2022.141992.6211

Sampson, T. R., Challis, C., Jain, N., Moiseyenko, A., Ladinsky, M. S., Shastri, G. G., Thron, T., Needham, B. D., Horvath, I., Debelius, J. W., Janssen, S., Knight, R., Wittung-Stafshede, P., Gradinaru, V., Chapman, M., & Mazmanian, S. K. (2020). A gut bacterial amyloid promotes α-synuclein aggregation and motor impairment in mice. *eLife*, *9*, e53111. https://doi.org/10.7554/eLife.53111

Sanders, M. E., Akkermans, L. M. A., Haller, D., Hammerman, C., Heimbach, J., Hörmannsperger, G., Huys, G., Levy, D. D., Lutgendorff, F., Mack, D., Phothirath, P., Solano-Aguilar, G., & Vaughan, E. (2010). Safety assessment of probiotics for human use. *Gut Microbes*, *1*(3), 164–185. https://doi.org/10.4161/gmic.1.3.12127

Sarita, B., Samadhan, D., Hassan, M. Z., & Kovaleva, E. G. (2025). A comprehensive review of probiotics and human health-current prospective and applications. *Frontiers in Microbiology*, *15*, 1487641. https://doi.org/10.3389/fmicb.2024.1487641

Sarkar, S., Maparu, K., & Aran, K. R. (2025). Postbiotics as a Therapeutic Tool in Depression: Exploring into Molecular Pathways and Neuroprotective Effects. *Probiotics and Antimicrobial Proteins*. https://doi.org/10.1007/s12602-025-10703-2

Shanahan, F. (2003). Probiotics: A Perspective on Problems and Pitfalls. *Scandinavian Journal of Gastroenterology*, *38*(237), 34–36. https://doi.org/10.1080/00855910310001476

Shi, S., Zhang, Q., Sang, Y., Ge, S., Wang, Q., Wang, R., & He, J. (2022). Probiotic Bifidobacterium longum BB68S Improves Cognitive Functions in Healthy Older Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients*, *15*(1), 51. https://doi.org/10.3390/nu15010051

Shin, J. M., Gwak, J. W., Kamarajan, P., Fenno, J. C., Rickard, A. H., & Kapila, Y. L. (2016). Biomedical applications of nisin. *Journal of Applied Microbiology*, *120*(6), 1449–1465. https://doi.org/10.1111/jam.13033

Shiqing, Y., Xinjie, L., Xiaotong, Z., Jiayan, C., Jiahai, L., Xiaodong, C., Yongliang, L., & Xiang, L. (2025). *Clostridium butyricum* enhances cognitive function

in APP/PS1 mice by modulating neuropathology and regulating acetic acid levels in the gut microbiota. *Microbiology Spectrum*, *13*(8), e00178-25. https://doi.org/10.1128/spectrum.00178-25

Singh, D., & Agarwal, V. (2022). Herbal antibacterial remedy against upper respiratory infection causing bacteria and in vivo safety analysis. *Vegetos*, *35*(1), 264–268. https://doi.org/10.1007/s42535-021-00281-3

Siripaopradit, Y., Chatsirisakul, O., Ariyapaisalkul, T., & Sereemaspun, A. (2024). Exploring the gut-brain axis in alzheimer's disease treatment via probiotics: Evidence from animal studies-a systematic review and meta-analysis. *BMC Neurology*, *24*(1), 481. https://doi.org/10.1186/s12883-024-03978-5

Socała, K., Doboszewska, U., Szopa, A., Serefko, A., Włodarczyk, M., Zielińska, A., Poleszak, E., Fichna, J., & Wlaź, P. (2021). The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. *Pharmacological Research*, *172*, 105840. https://doi.org/10.1016/j.phrs.2021.105840

Sokol, H., Pigneur, B., Watterlot, L., Lakhdari, O., Bermúdez-Humarán, L. G., Gratadoux, J.-J., Blugeon, S., Bridonneau, C., Furet, J.-P., Corthier, G., Grangette, C., Vasquez, N., Pochart, P., Trugnan, G., Thomas, G., Blottière, H. M., Doré, J., Marteau, P., Seksik, P., & Langella, P. (2008). Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(43), 16731–16736. https://doi.org/10.1073/pnas.0804812105

Sreeja, V., & Prajapati, J. B. (2013). Probiotic Formulations: Application and Status as Pharmaceuticals—A Review. *Probiotics and Antimicrobial Proteins*, *5*(2), 81–91. https://doi.org/10.1007/s12602-013-9126-2

Stancu, I.-C., Vasconcelos, B., Terwel, D., & Dewachter, I. (2014). Models of β-amyloid induced Tau-pathology: The long and "folded" road to understand the mechanism. *Molecular Neurodegeneration*, *9*(1), 51. https://doi.org/10.1186/1750-1326-9-51

Su, Y., Wang, D., Liu, N., Yang, J., Sun, R., & Zhang, Z. (2023). Clostridium butyricum improves cognitive dysfunction in ICV-STZ-induced Alzheimer's disease mice via suppressing TLR4 signaling pathway through the gut-brain axis. *PLOS ONE*, *18*(6), e0286086. https://doi.org/10.1371/journal.pone.0286086

Tan, M.-S., Yu, J.-T., Jiang, T., Zhu, X.-C., & Tan, L. (2013). The NLRP3 Inflammasome in Alzheimer's Disease. *Molecular Neurobiology*, *48*(3), 875–882. https://doi.org/10.1007/s12035-013-8475-x

Tejero-Sariñena, S., Barlow, J., Costabile, A., Gibson, G. R., & Rowland, I. (2012). In vitro evaluation of the antimicrobial activity of a range of probiotics against pathogens: Evidence for the effects of organic acids. *Anaerobe*, *18*(5), 530–538. https://doi.org/10.1016/j.anaerobe.2012.08.004

Thomas, C. M., & Versalovic, J. (2010). Probiotics-host communication. *Gut Microbes*, *1*(3), 148–163. https://doi.org/10.4161/gmic.1.3.11712

Tiwari, A., Ika Krisnawati, D., Susilowati, E., Mutalik, C., & Kuo, T.-R. (2024). Next-Generation Probiotics and Chronic Diseases: A Review of Current Research and Future Directions. *Journal of Agricultural and Food Chemistry*, *72*(50), 27679–27700. https://doi.org/10.1021/acs.jafc.4c08702

Toba, T., Samant, S. K., Yoshioka, E., & Itoh, T. (1991). Reutericin 6, a new bacteriocin produced by Lactobacillus reuteri LA 6. *Letters in Applied Microbiology*, *13*(6), 281–286. https://doi.org/10.1111/j.1472-765X.1991.tb00629.x

Tsilingiri, K., & Rescigno, M. (2013). Postbiotics: What else? *Beneficial Microbes*, *4*(1), 101–107. https://doi.org/10.3920/BM2012.0046

Tsioti, I., Steiner, B. L., Escher, P., Zinkernagel, M. S., Benz, P. M., & Kokona, D. (2023). Endothelial Toll-like receptor 4 is required for microglia activation in the murine retina after systemic lipopolysaccharide exposure. *Journal of Neuroinflammation*, *20*(1), 25. https://doi.org/10.1186/s12974-023-02712-1

Ulsemer, P., Toutounian, K., Schmidt, J., Karsten, U., & Goletz, S. (2012). Preliminary safety evaluation of a new Bacteroides xylanisolvens isolate. *Applied and Environmental Microbiology*, *78*(2), 528–535. https://doi.org/10.1128/AEM.06641-11

Un-Nisa, A., Khan, A., Zakria, M., Siraj, S., Ullah, S., Tipu, M. K., Ikram, M., & Kim, M. O. (2022). Updates on the Role of Probiotics against Different Health Issues: Focus on Lactobacillus. *International Journal of Molecular Sciences*, *24*(1), 142. https://doi.org/10.3390/ijms24010142

Vinderola, G., Sanders, M. E., & Salminen, S. (2022). The Concept of Postbiotics. *Foods*, *11*(8), 1077. https://doi.org/10.3390/foods11081077

Wang, L., Zhao, R., Li, X., Shao, P., Xie, J., Su, X., Xu, S., Huang, Y., & Hu, S. (2024). Lactobacillus rhamnosus GG improves cognitive impairments in mice with sepsis. *PeerJ*, *12*, e17427. https://doi.org/10.7717/peerj.17427

Wang, Y., Chen, W., Han, Y., Xu, X., Yang, A., Wei, J., Hong, D., Fang, X., & Chen, T. (2023). Neuroprotective effect of engineered Clostridium butyricum-pMTL007-GLP-1 on Parkinson's disease

mice models via promoting mitophagy. *Bioengineering & Translational Medicine*, *8*(3), e10505. https://doi.org/10.1002/btm2.10505

Wang, Z., Wang, C., Yuan, B., Liu, L., Zhang, H., Zhu, M., Chai, H., Peng, J., Huang, Y., Zhou, S., Liu, J., Wu, L., & Wang, W. (2025). Akkermansia muciniphila and its metabolite propionic acid maintains neuronal mitochondrial division and autophagy homeostasis during Alzheimer's disease pathologic process via GPR41 and GPR43. *Microbiome*, *13*(1), 16. https://doi.org/10.1186/s40168-024-02001-w

Williams, N. T. (2010). Probiotics. *American Journal of Health-System Pharmacy*, *67*(6), 449–458. https://doi.org/10.2146/ajhp090168

Wombwell, E., Bransteitter, B., & Gillen, L. R. (2021). Incidence of Saccharomyces cerevisiae fungemia in hospitalised patients administered Saccharomyces boulardii probiotic. *Mycoses*, *64*(12), 1521–1526. https://doi.org/10.1111/myc.13375

Wu, Y., Wang, Y., Hu, A., Shu, X., Huang, W., Liu, J., Wang, B., Zhang, R., Yue, M., & Yang, C. (2022). Lactobacillus plantarum-derived postbiotics prevent Salmonella-induced neurological dysfunctions by modulating gut-brain axis in mice. *Frontiers in Nutrition*, *9*, 946096. https://doi.org/10.3389/fnut.2022.946096

Xu, K., Wang, G., Gong, J., Yang, X., Cheng, Y., Li, D., Sheng, S., & Zhang, F. (2025). Akkermansia muciniphila protects against dopamine neurotoxicity by modulating butyrate to inhibit microglia-mediated neuroinflammation. *International Immunopharmacology*, *152*, 114374. https://doi.org/10.1016/j.intimp.2025.114374

Yan, L., Li, H., Qian, Y., Zhang, J., Cong, S., Zhang, X., Wu, L., Wang, Y., Wang, M., & Yu, T. (2024). Transcutaneous vagus nerve stimulation: A new strategy for Alzheimer's disease intervention through the brain-gut-microbiota axis? *Frontiers in Aging Neuroscience*, *16*. https://doi.org/10.3389/fnagi.2024.1334887

Yu, Y., Yu, S., Battaglia, G., & Tian, X. (2024). Amyloid-β in Alzheimer's disease: Structure, toxicity, distribution, treatment, and prospects. *Ibrain*, ibra.12155. https://doi.org/10.1002/ibra.12155

Yue, M., Wei, J., Chen, W., Hong, D., Chen, T., & Fang, X. (2022). Neurotrophic Role of the Next-Generation Probiotic Strain L. lactis MG1363-pMG36e-GLP-1 on Parkinson's Disease via Inhibiting Ferroptosis. *Nutrients*, *14*(22), 4886. https://doi.org/10.3390/nu14224886

Yun, H.-M., Park, K.-R., Kim, E.-C., Kim, S., & Hong, J. T. (2015). Serotonin 6 receptor controls Alzheimer's disease and depression. *Oncotarget*, *6*(29), 26716–26728. https://doi.org/10.18632/oncotarget.5777

Zajac, D. J., Shaw, B. C., Braun, D. J., Green, S. J., Morganti, J. M., & Estus, S. (2022). Exogenous Short Chain Fatty Acid Effects in APP/PS1 Mice. *Frontiers in Neuroscience*, *16*, 873549. https://doi.org/10.3389/fnins.2022.873549

Zheng, M., Ye, H., Yang, X., Shen, L., Dang, X., Liu, X., Gong, Y., Wu, Q., Wang, L., Ge, X., Fang, X., Hou, B., Zhang, P., Tang, R., Zheng, K., Huang, X.-F., & Yu, Y. (2024). Probiotic *Clostridium butyricum* ameliorates cognitive impairment in obesity via the microbiota-gut-brain axis. *Brain, Behavior, and Immunity*, *115*, 565–587. https://doi.org/10.1016/j.bbi.2023.11.016

Zhong, S.-R., Kuang, Q., Zhang, F., Chen, B., & Zhong, Z.-G. (2021). Functional roles of the microbiota-gut-brain axis in Alzheimer's disease: Implications of gut microbiota-targeted therapy. *Translational Neuroscience*, *12*(1), 581–600. https://doi.org/10.1515/tnsci-2020-0206

Zhou, Y., Xie, L., Schröder, J., Schuster, I. S., Nakai, M., Sun, G., Sun, Y. B. Y., Mariño, E., Degli-Esposti, M. A., Marques, F. Z., Grubman, A., Polo, J. M., & Mackay, C. R. (2023). Dietary Fiber and Microbiota Metabolite Receptors Enhance Cognition and Alleviate Disease in the 5xFAD Mouse Model of Alzheimer's Disease. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *43*(37), 6460–6475. https://doi.org/10.1523/JNEUROSCI.0724-23.2023

Zhu, G., Guo, M., Zhao, J., Zhang, H., Wang, G., & Chen, W. (2024). Environmental enrichment in combination with *Bifidobacterium* breve HNXY26M4 intervention amplifies neuroprotective benefits in a mouse model of Alzheimer's disease by modulating glutamine metabolism of the gut microbiome. *Food Science and Human Wellness*, *13*(2), 982–992. https://doi.org/10.26599/FSHW.2022.9250084

Zhu, L., Zhong, M., Elder, G. A., Sano, M., Holtzman, D. M., Gandy, S., Cardozo, C., Haroutunian, V., Robakis, N. K., & Cai, D. (2015). Phospholipid dysregulation contributes to ApoE4-associated cognitive deficits in Alzheimer's disease pathogenesis. *Proceedings of the National Academy of Sciences*, *112*(38), 11965–11970. https://doi.org/10.1073/pnas.1510011112

Zhu, X., Shen, J., Feng, S., Huang, C., Wang, H., Huo, F., & Liu, H. (2023). Akkermansia muciniphila, which is enriched in the gut microbiota by metformin, improves cognitive function in aged mice by reducing the proinflammatory cytokine interleukin-6. *Microbiome*, *11*(1), 120. https://doi.org/10.1186/s40168-023-01567-1

Żółkiewicz, J., Marzec, A., Ruszczyński, M., & Feleszko, W. (2020). Postbiotics—A Step Beyond Pre- and Probiotics. *Nutrients*, *12*(8), 2189. https://doi.org/10.3390/nu12082189

Zou, X., Zou, G., Zou, X., Wang, K., & Chen, Z. (2024). Gut microbiota and its metabolites in Alzheimer's disease: From pathogenesis to treatment. *PeerJ*, *12*, e17061. https://doi.org/10.7717/peerj.17061