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Gut Dysbiosis in Alzheimer's Disease Pathogenesis and Therapeutic Implications

Iqra Nadeem

ABSTRACT

Alzheimer's disease (AD) is a type of neurodegenerative disease that is characterized by cognitive decline, memory loss, and the deposition of amyloid plaques and tau tangles in the brain. Although the pathogenesis of AD has traditionally been connected to genetic, environmental, and neurobiological factors, the role of the gut microbiota in AD progression remains unclear. Dysregulation of gut microbiota—dysbiosis—may lead to imbalances in microbial diversity and metabolite production, which directly affect the development and progression of AD. This study reviews the relationship between gut dysbiosis and AD, focusing on therapeutic interventions targeting gut microbiota, including prebiotics, probiotics, and fecal microbiota transplantation. We discuss the novel mechanisms by which microbial metabolites, immune activation, and gut-derived signals can exacerbate AD symptoms. Additionally, we highlight the theoretical potential of microbiome editing using CRISPR-Cas9 as a future novel approach to address dysbiosis in AD. By advancing the understanding of the role of dysbiosis in AD, this review proposes a research direction to address existing gaps and facilitate the development of microbiome-based therapeutic strategies.

Keywords: Gut-brain axis, Amyloid plaque, Tau hyperphosphorylation, Microbiome editing, Fecal microbiota transplantation

Introduction

Alzheimer's disease (AD) is a multifactorial, progressive neurodegenerative condition that affects over fifty million people around the world and represents the most prevalent form of dementia. Between 2000 and 2019, the number of deaths caused by AD increased by approximately one and a half times.^{1,2} The clinical manifestation of AD is characterized by a gradual decline in memory accompanied by several cognitive abnormalities, memory loss, disorientation, and an impairment in daily functioning. Patients are typically identified either at the late or irreversible stage of AD, with an average survival period of 4–8 years following diagnosis.³ Exploring novel underlying mechanisms is crucial for identifying biomarkers to improve AD diagnostic and therapeutic strategies. In particular, microbial metabolites, immune modulation, and microbial load could serve as novel biomarkers for early detection and personalized treatment approaches.

The “amyloid cascade” hypothesis suggests that AD pathology is driven by the accumulation of amyloid- β (A β) plaques and neurofibrillary tangles forming in the brain.⁴ Hyperphosphorylation of tau proteins is a typical hallmark of AD, contributing to neuronal death by disrupting cellular function and triggering

neuroinflammation in multiple regions of the brain, such as the neocortex, amygdala, hippocampus, and the basal forebrain (nucleus basalis of Meynert).⁵ Over the last several years, numerous anti-amyloid therapies targeting the aggregation of A β or tau proteins have failed to yield a significant improvement in cognitive outcomes for AD patients.^{6,7} Consequently, researchers are investigating alternative neuroinflammatory pathways, including microglial activation, the release of cytokines, disruption of the blood-brain barrier (BBB), and gut-brain axis (GBA), to find an effective cure for AD.⁸

In recent years, GBA, a complex bidirectional communication network between the gastrointestinal (GI) tract and central nervous system (CNS), has been increasingly implicated in AD pathogenesis. GBA is demonstrated to mediate brain function through the production of microbial metabolites such as short-chain fatty acids (SCFAs) (e.g., butyrate, propionate, and acetate), tryptophan metabolites, and lipopolysaccharides (LPS) which influence regulation of neuroinflammatory mechanisms, and activation of the vagus nerve by impacting mood, cognition, and neuroprotection.^{9–11} The GI tract harbors a variety of microorganisms, including bacteria, fungi, viruses, and archaea, which collectively form the gut microbiota. Dysbiosis, an alteration in the composition of gut microbiota, has been shown to disrupt key functions of GBA by enhancing the deposition of A β plaque, leading to an earlier and faster onset of AD.^{12,13} The association between dysbiosis and AD is supported by the growing discovery of gut microbiome genes; however, the specific metabolites produced by these microbes' driving neurodegeneration are yet to be discovered. For example, genes encoding bacterial amyloids (e.g., curli from *Escherichia coli* and TasA from *Bacillus subtilis*) have been linked to amyloid cross-seeding, potentially influencing AD pathology. Other genes involved in SCFA production, such as butyryl-CoA: acetate CoA-transferase in *Faecalibacterium prausnitzii*, modulate neuroinflammatory pathways, further highlighting the gut microbiota's role in neurodegeneration.¹⁴ There is a limited understanding of the interplay between gut microbiota changes and alterations in the permeability of the BBB at the early onset of AD.^{15,16} In addition, while it is established that dysbiosis modulates neuroinflammation, the specific immune pathways implicated in the progression of AD have not been elucidated.

This review aims to delve into the underexplored role of dysbiosis and its potential influence on AD by examining how microbial imbalances contribute to neuroinflammation, BBB dysfunction, and the deposition of A β and tau. It also discusses the microbiota-based novel

interventions to restore the microbiome and mitigate AD progression while proposing future research directions to address existing gaps in our understanding of the microbiome's role in neurodegenerative diseases.

Dysbiosis and Its Impact on Neuroinflammation in AD Microbial Imbalance and Immune Activation

The gut microbiota plays a critical role in modulating immune responses through microbial metabolites and neuroinflammatory pathways.¹⁷ Dysbiosis is linked to altered gut homeostasis and facilitates the invasion of bacteria and their metabolite products, LPS, into circulation. LPS, an endotoxin derived from gram-negative bacteria, is a potent activator of neuroinflammation. Lipopolysaccharides binding protein (LBP), an acute phase protein, is also identified as an inflammatory biomarker of bacterial translocation from the gut in AD.¹⁸ Persistent exposure to LPS and dysregulated LBP activity result in BBB disruption, and their infiltration into the CNS by inflammatory mediators increases neurodegeneration. In mice models, a demonstration of systemic LPS administration showed the activation of the microglial cells by binding to the TLR4 receptor. This interaction triggered the downstream signaling of nuclear factor kappa B (NF- κ B) and the release of pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6 by promoting A β deposition and tau phosphorylation.¹⁹ Both human and murine studies showed a positive correlation between elevated LPS levels and neuronal damage, memory deficits, and cognitive decline.²⁰ Numerous studies have shown a higher abundance of

Bacteroides fragilis, *Escherichia coli*, and *Firmicutes*-associated species (e.g., *Clostridium perfringens*) in AD patients, contributing to elevated serum LPS levels and cognitive decline (Figure 1).^{21,22}

In contrast, beneficial microbes such as *Lactobacillus* and *Bifidobacterium* produce metabolites, particularly SCFAs butyrate, acetate, and propionate that exhibit anti-inflammatory functions. Studies have shown that supplementation with *Lactobacillus* and *Bifidobacterium* inhibited microglial activation and release of pro-inflammatory cytokines through SCFA production.²³ Similar studies also found butyrate attenuated neuroinflammatory markers by decreasing NF- κ B signaling and preventing neurodegeneration in AD.²⁴ Disruption of dysbiosis not only enhances systemic inflammation but also accelerates amyloid plaque deposition and tau phosphorylation. Immune cells over and under-activation by microbial imbalance is proposed as a critical pathway in the AD progression.

Role of Microbiota in Modulating BBB

The BBB acts as a selective barrier for the brain by regulating the elimination of harmful substances, including microbial components such as LPS, from the bloodstream and preventing their entry into the brain parenchyma. Dysfunction of BBB characterizes hallmarks of AD pathophysiology by facilitating the release of neurotoxic molecules, including A β , tau oligomers, reactive oxygen species (ROS), and pro-inflammatory cytokines (e.g., TNF- α , IL-1 β , and IL-6), into the CNS.^{25,26} Emerging evidence specifically highlights the

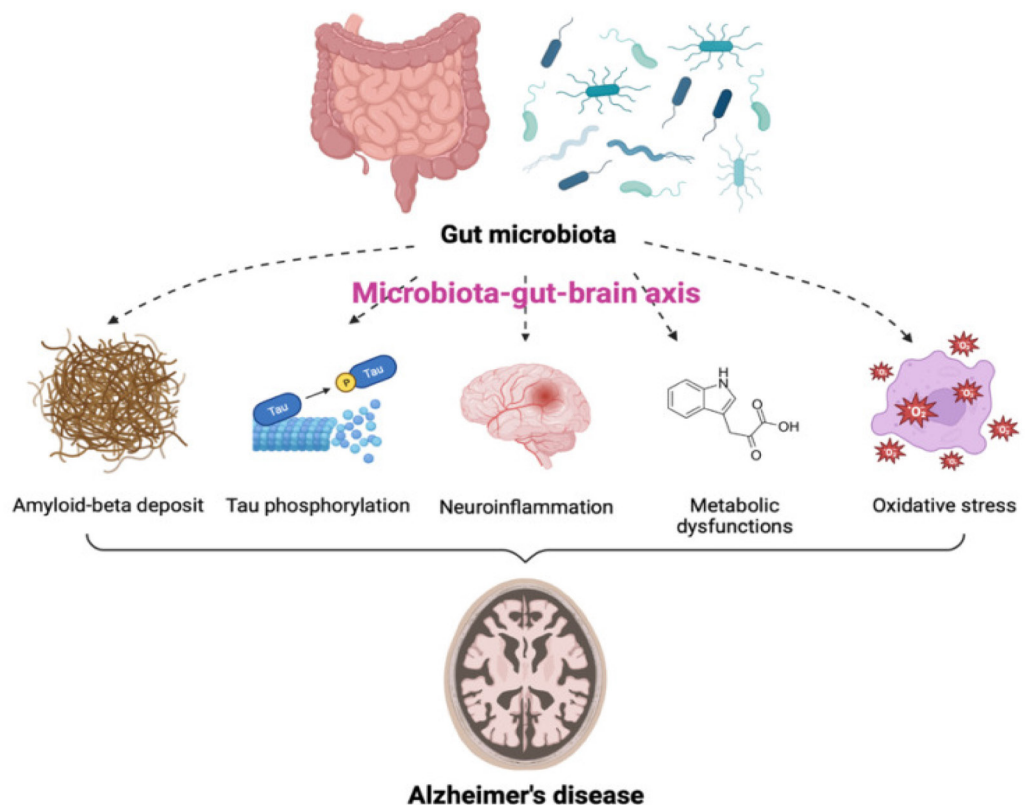


Fig 1 | Dysbiosis involvement in AD pathogenesis. Adapted from Nguyen et al. (2023) with permission under the Creative Commons Attribution License (CC BY 4.0) [DOI: 10.3390/ijms24044047]

role of the gut-derived neurochemical messenger (dopamine, serotonin, γ -aminobutyric acid [GABA], and butyrate) in regulating BBB integrity.²⁷ However, increased gut permeability due to dysbiosis can differentially impact neuroimmune homeostasis. *Escherichia coli*, a gram-negative bacterium, produces neurotransmitters such as dopamine and serotonin, aggravating neuroinflammation and disruption of the BBB when these microorganisms escape into circulation. In contrast, *Lactobacillus rhamnosus* and *Lactobacillus plantarum* support the integrity of the BBB by producing GABA and SCFAs, especially butyrate, which have shown anti-inflammatory and neuroprotective properties.²⁸ An imbalance in the levels of neurotransmitters influenced by dysbiosis and increased gut permeability may have direct effects on neuroinflammation and BBB integrity. While certain neurotransmitters such as GABA and serotonin do not efficiently cross the BBB, their dysregulation may indirectly influence neuroimmune processes by promoting cognitive decline in AD. Recent studies have shown GABA levels were lower in the cerebrospinal fluid and brain of AD patients compared to healthy patients, suggesting the GABAergic system impairment in AD.²⁹ The mechanistic effect of the specific microbiota strains on GABAergic systems in dementia needs further investigation (Figure 2).

Further supporting the link between dysbiosis and BBB integrity, animal studies have demonstrated the impact of gut microbiome manipulation on the BBB. A study involving a transgenic mice model of AD (App/PS1 mice) showed a shift in the microglia inflammatory

response and increased BBB disruption.³⁰ Notably, restoration of the healthy gut flora, particularly from beneficial species such as *Lactobacillus* and *Bifidobacterium*, was associated with decreased A β burden and reduction in BBB leakage.²⁶ Another interesting study was done to explore the effect of gut microbiota on germ-free mice (intrauterine life to adulthood) tight junction proteins occludin and claudin-5, which are key for BBB maintenance.³¹ Results showed that germ-free mice exhibited increased BBB and reduction in expression of tight junctional molecules. However, when germ-free mice were recolonized with pathogen-free gut microbiota, BBB permeability was significantly reduced with an increase in occludin and claudin-5 levels, indicating dysbiosis could potentially impact BBB function and homeostasis throughout life.^{9,32} Nevertheless, the precise mechanisms by which gut microbiota-derived signals influence BBB through immune modulation in AD remain uncertain.

The Microbiome Influence on A β and Tau Pathology in AD Microbial Modulation of A β and Tau Pathology

A β plaques and tau tangles accumulation in the brain are directly correlated with the severity of dementia.³⁰ Recent studies suggest microbiomes and their metabolite's potential role in regulating the production and deposition of these pathological proteins.³³ A study was done on gut microbiota-derived metabolites, phenyl- γ -valerolactones, which significantly inhibited proteasome activity and enhanced autophagy by decreasing levels of intra and extracellular A β (1-42) peptides in cultured neuronal cells.³⁴ Another study showed a shift in gut microbiota composition and diversity and a reduction in A β plaque deposition after long-term broad-spectrum antibiotic treatment in the APP_{SWE}/PS1_{ΔE9} mouse model of AD. Furthermore, microbiome changes were linked with altered levels of pro-inflammatory cytokines, including TNF- α , IL-1 β , and IL-6, as well as chemokines such as C-C motif chemokine ligand 2 and C-X-C motif chemokine ligand 10 and reduced glial reactivity, suggesting dysbiosis can impact A β amyloidosis and neuroinflammation by regulating host immunity.³⁵ It supports the notion that frequent antibiotic usage may increase the risk of AD development. SCFAs (butyrate, acetate, and propionate) are produced by gut bacteria during the metabolism of dietary fibers such as inulin, resistant starch, and pectin. These SCFAs have been shown to have neuroprotective effects against AD by interfering with the formation of soluble toxic A β aggregates in vitro.³⁶

Similarly, in rTg4510 mice (expressing the TauP301L mutation), LPS significantly ameliorated tau phosphorylation at Ser 199/202 and Ser396 but did not affect mature tangle formation and simultaneously cleared pre-existing A β deposits.³⁷ The dual effect of LPS could explain the limited efficacy of anti-inflammatory therapies in treating dementia.³⁸ A recent study highlighted a relationship between specific gut metabolites and tau pathology by employing advanced system biology to analyze 1.09 million metabolite protein pairs involving 408 human G-protein-coupled receptors (GPCRs)

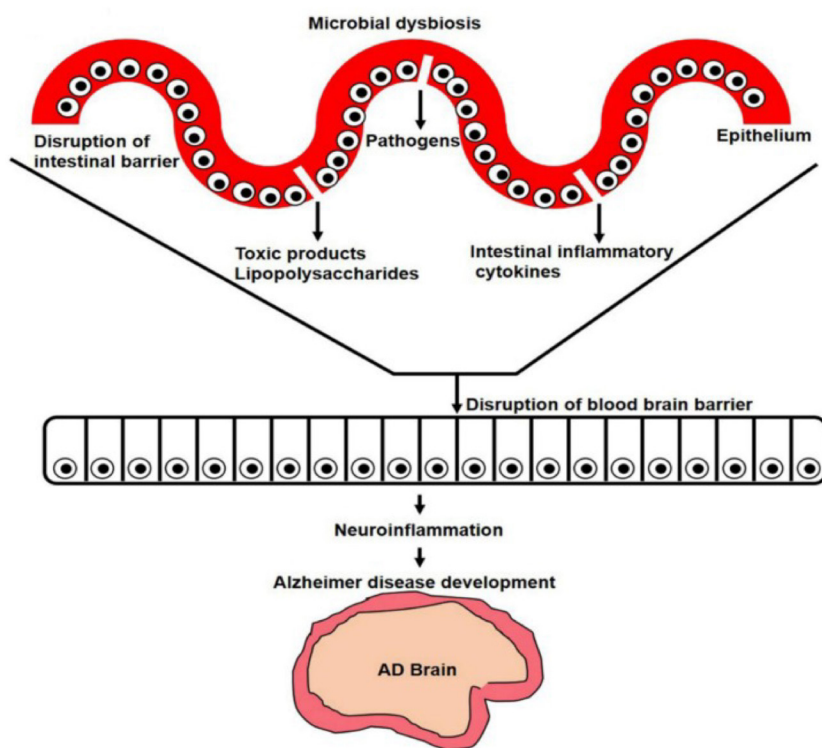


Fig 2 | Influence of gut microbiota on BBB integrity in AD. Dysbiosis augments gut permeability, permitting microbial components and neurotoxic molecules to disturb BBB integrity through enhanced neuroinflammation. Adapted from Khan et al. (2020) [DOI: 10.3390/cells9040853] under CC BY 4.0 license

and 335 metabolites.³⁹ Results demonstrated that gut microbial metabolites phenethylamine and agmatine are potential modulators of tau pathology via GPCR interaction, reducing tau hyperphosphorylation in AD-derived neurons.⁴⁰ Agmatine has also been shown to have neuroprotective effects through NOS inhibition and NMDA receptor modulation, reducing oxidative stress and neuroinflammation associated with tau aggregation.⁴¹ As a neuromodulator, it is believed that PEA interacts with TAAR1 receptors, modulating dopaminergic and serotonergic pathways to regulate tau phosphorylation through a cAMP/PKA pathway.⁴² Though these findings suggest a gut-brain connection with tau accumulation, the exact molecular mechanisms of neuronal damage connecting dysbiosis to tau-related neurodegeneration remain underexplored.

Therapeutic Strategies Targeting Gut Dysbiosis in AD Probiotics and Prebiotics Interventions

Probiotics are live-active organisms that maintain or restore the natural balance of the gut microbiome when consumed in adequate amounts. Prebiotics, on the other hand, are non-digestible fibers or oligosaccharide substrates that promote the growth, survival, and function of beneficial gut bacteria.⁴³ Probiotics such as *Lactobacillus rhamnosus* GG and *Bifidobacterium breve* and prebiotics like fructooligosaccharides (FOS) and galactooligosaccharides (GOS) have attracted significant attention as a potent therapeutic tool in AD by suppressing neuroinflammation.⁴⁴ However, evidence demonstrating pro/prebiotics therapeutic efficacy in mitigating AD symptoms is not widely available.

Over the years, the gut-resorting neuroprotective effects of numerous probiotics have been investigated. A multi-strain probiotic, VSL#3 is composed of a mix of eight species of bacteria—*Lactobacillus* species (*Lactobacillus casei*, *Lactobacillus plantarum*, *Lactobacillus acidophilus*), *Bifidobacterium* species (*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*), and *Streptococcus thermophilus*. This particular formulation of seven strains has been shown to restore the balance of gut microbiota, maintain the integrity of the intestinal barrier, and also decrease systemic inflammation.⁴⁵ The different strains in VSL#3 are believed to synergistically enhance the gut-brain interaction, providing a therapeutic advantage for neurodegenerative diseases such as AD.⁴⁶

SLAB51, one specific strain of probiotics, has been explored for its potential neuroprotective effects in models of AD. It is a strain of *Lactobacillus* that was originally isolated from human gut microbiota and has been shown to impact the balance of the gut microbiome. SLAB51 can also affect neuroimmune interactions that play a central role in AD pathology.⁴⁷ Previous studies showed the utility of SLAB51 probiotics in reducing brain damage in 3xTg-AD mice by increasing gut microbiota homeostasis, lowering A β plaque, and enhancing cognitive symptoms.⁴⁸

A systematic review of the role of *Lactiplantibacillus plantarum* in AD animal models and its use in humans showed a limited number of studies.⁴⁹ Overall,

L. plantarum supplementation attenuated neuroinflammation, influenced gut microbiota composition with a rise in numerous beneficial *Lactobacillus* and *Bifidobacterium* populations, increased beneficial gut bacteria, restored balance of gut microbiota, and decreased *Escherichia coli* and *Clostridium perfringens*. This microbial shift resulted in lesser production of LPS along with enhancements in memory and learning abilities.⁵⁰ Multiple studies found that *Bifidobacterium longum* breve A1 probiotic consumption is useful for ameliorating AD symptoms. A clinical study of elderly patients with mild cognitive impairment showed that memory function, especially immediate and delayed recalling of tasks, significantly improved after *Bifidobacterium longum* breve A1 supplementation (12 weeks) compared with the placebo group. Further, supplementation was linked to decreased amounts of inflammatory cytokines, indicating a neuroprotective function in AD pathology.⁵¹

Many prebiotic dietary fibers, such as FOS, inulin, GOS, and resistant starches, have been shown to produce neuroprotective effects in AD.⁵² In pre-clinical AD models, the administration of inulin—a prebiotic mediator for beneficial bacteria such as *Bifidobacteria* and *Lactobacilli*—in female APOE4 mice showed a decrease in *Escherichia coli* and inflammation pathways by restoring alpha diversity. Contrarily, male APOE4 mice showed less pronounced improvement in SCFAs-producing bacteria, suggesting a sex-specific dietary response to inulin.⁵³ Additionally, studies found the positive effect of synbiotic treatment (a combination of *Lactiplantibacillus plantarum* and inulin) in the AD model by improving A β clearance, reducing tau proteins, and boosting cognitive functions (Figure 3).⁵⁴

Building on these findings, researchers are now exploring advanced genetic approaches to enhance gut microbiome modulation. Furthermore, investigations are also in progress for applying CRISPR-Cas9 technology to edit specific bacterial species of the microbiome to combat dysbiosis in AD.⁵⁵ Future studies should employ CRISPR-Cas9 to enhance the production of beneficial microbes, improve gut integrity, and possibly reduce neuroinflammation.⁵⁶ Such genetic modification also has the potential as an adjunct-based non-drug therapeutic approach to restore microbiome balance in the gut that can help effectively alleviate AD symptoms.^{57,58}

Fecal Microbiota Transplant (FMT)

FMT is an ancient treatment method that involves transferring fecal material from a healthy donor into the GI tract of a recipient in order to restore dysbiosis.⁵⁹ Since 1958, after the application of FMT in treating *Clostridioides difficile* infection-associated enterocolitis, researchers are increasingly investigating its potential in AD therapeutics.^{60,61}

Pre-clinical studies have demonstrated that FMT done from healthy wild-type mice into ADLP^{APT} transgenic models showed restoration of gut homeostasis and reduction in the formation of A β plaques and neurofibrillary tangles, leading to cognitive improvement.³³ Mechanistically, this was associated

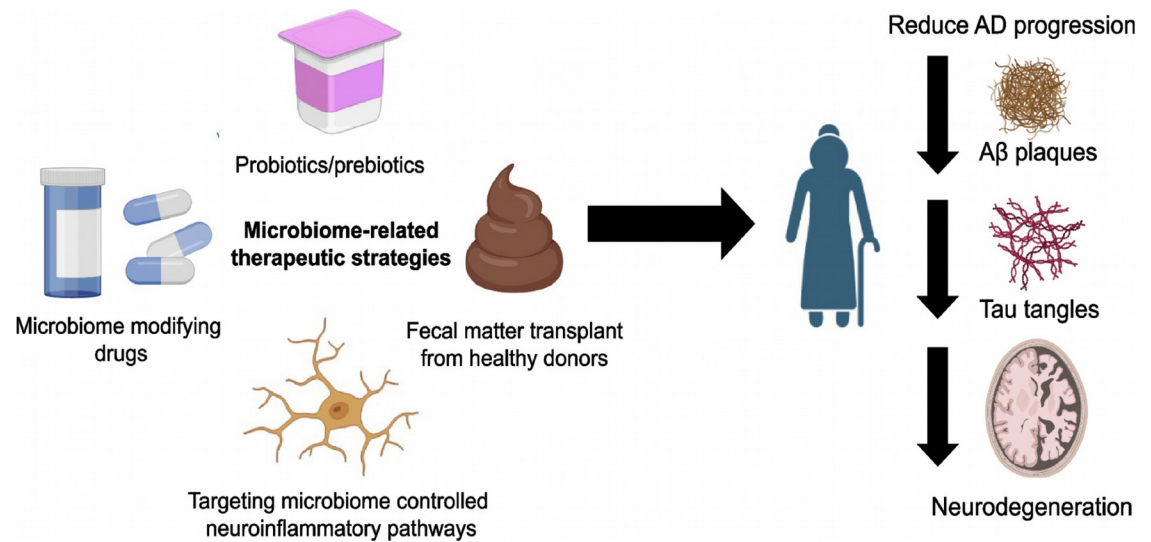


Fig 3 | Microbiome-related therapeutic benefits targeting gut dysbiosis in AD. Adapted from Chandra et al. (2023) under the terms of the Creative Commons Attribution License (CC BY 4.0) [DOI: 10.1186/s13024-023-00595-7]

with upregulation of tight junction proteins (e.g., occludin and claudin-5), reduced expression of pro-inflammatory cytokines (e.g., TNF- α , IL-1 β), and modulation of microglial activation. A pilot study of human patients with cognitive decline showed that FMT normalized gut microbial composition with a decrease in *Proteobacteria* and *Bacteroidetes* and an increase in protective bacteria such as *Firmicutes* and *Actinobacteria*. These changes were associated with lower levels of systemic inflammation, lower pro-inflammation cytokines (TNF- α , IL-6), and improved cognition and quality of life.⁶² Clinical trials exploring the effectiveness of FMT, particularly targeting AD dysbiosis, are in the early stages, but preliminary data is encouraging.

Conclusion and Prospects

AD is a complex, multifactorial neurological disorder with diverse pathological and molecular mechanisms. Although the amyloid cascade hypothesis has been prevailing in the field for several decades, increasing evidence indicates that gut dysbiosis plays a significant role in the progression of AD and is associated with neuroinflammation, impaired BBB integrity, and A β and tau pathology. Dysbiosis-induced changes in microbial metabolites, immune responses, and neurotransmitter production highlight the relevance of interactions through the GBA in neurodegeneration.

Thus, targeting gut microbiota is a viable strategy for the development of new AD treatments. Microbial-based metabolites and neurotransmitters have the capacity to be used as biomarkers for early diagnosis. Additionally, the therapeutic promise of hacking dysbiosis with the use of probiotics, prebiotics, and fecal microbiota transplantation in AD is encouraging, but these results need to be verified by large-scale studies. Nonetheless, future studies are still needed to identify specific microbial strains and/or metabolic pathways that impact AD pathology—whether directly or indirectly.

Studies examining microbiome-based precision therapies are under consideration to explore novel avenues

for therapeutic utility. Future studies need to employ cutting-edge microbiome editing using CRISPR-Cas9 techniques to selectively eliminate pathogenic strains and enhance beneficial bacteria. It will help to target specific gut bacteria imbalances and uncover their metabolite's role in neuroprotection and disease progression. Integrating gut microbiome research with neurodegenerative disease models could open the door for effective treatment strategies to halt the progression of AD and potentially delay the onset of AD.

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