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Navigating the Role and Approach of Gut Microbiota in Addressing Alzheimer's Disease Pathogenesis

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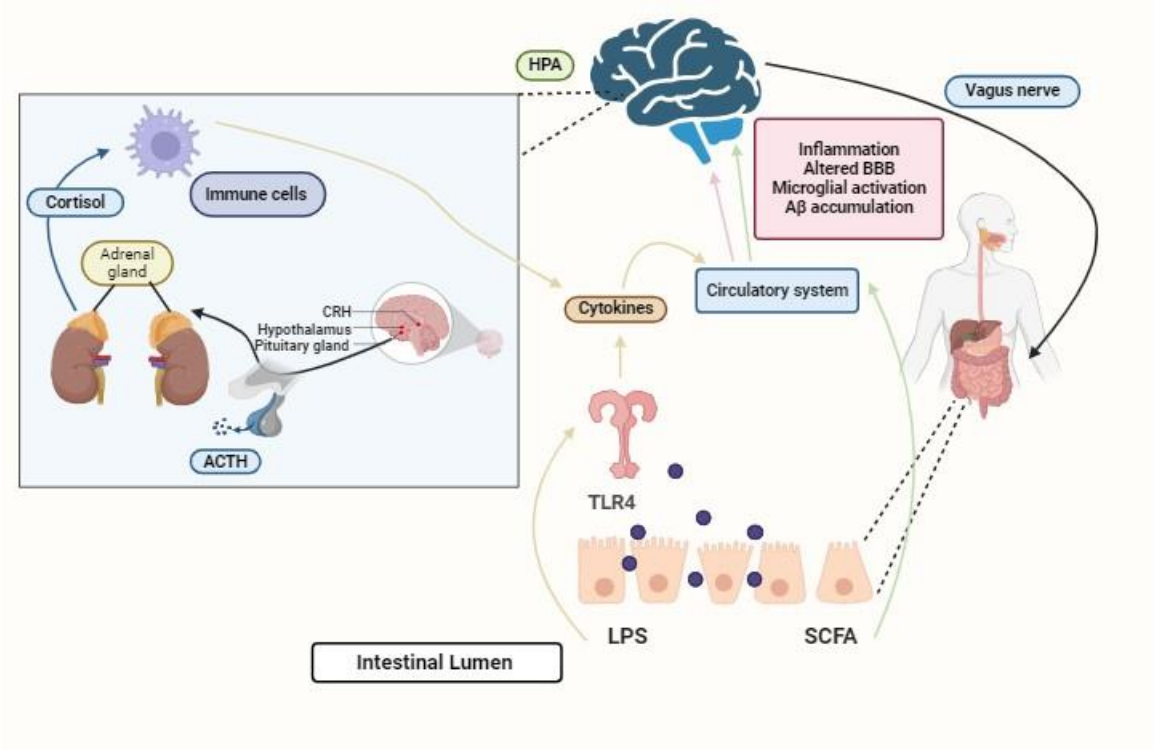
Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid beta plaques and tau protein neurofibrillary tangles, leading to cognitive decline. The lack of effective treatments compounds the significant human and financial burdens AD poses. Despite extensive research, the exact mechanisms of the disease remain elusive. Recent studies have shown promise in using anti-Aβ antibodies to reduce amyloid accumulation and slow dementia progression. However, diversifying therapeutic strategies is crucial for making meaningful progress. In recent years, research has increasingly focused on the microbiota-gut-brain axis in AD. Mounting evidence suggests that changes in gut microbiota composition are linked to AD progression, implicating various pathways. Dysregulation of microbiota taxa can trigger systemic inflammation by increasing gut permeability, ultimately leading to neural damage and neurodegeneration. Poor dietary habits and aging exacerbate gut dysbiosis, worsening AD pathology. However, investigations in this area are still in their early stages, with many aspects awaiting exploration and understanding. A thorough comprehension of the complex interactions within the microbiota-AD relationship is essential for refining therapeutic approaches. Interventions targeting gut microbiota, such as dietary adjustments, probiotics, and faecal microbiota transplantation, offer potential as therapeutics. This review highlights the detrimental role of gut dysbiosis in AD, offering insights into enhancing therapeutic avenues for the disease.



Graphical abstract: The bidirectional interaction between the brain and the gut through neuroendocrine, immune, and metabolic pathways. Created with BioRender.com.

Keywords: Alzheimer's disease; gut microbiota; dysbiosis; gut-brain axis; inflammation; SDG 3 Good health and well-being

1. Introduction

Alzheimer's Disease (AD) accounts for more than half of dementia cases worldwide (up to 60-80% of dementia) [1]. In AD, there is profound memory loss and impairment, eventually leading to disturbed behavior and inability to carry out daily functions [2, 3]. This uncertainty in behavioral representation is due to shrinkage of the cortex, enlarged ventricles, and loss of neurons in the brain's hippocampus and cerebral cortex region [3]. With dementia being a multifactorial complex clinical syndrome characterized by deterioration in cognitive functioning beyond the usual consequences of biological aging, it is significant enough to hinder a fruitful social life in individuals affected through means of disability and premature death [4, 5]. As of 2020, over 55 million cases have been reported, and numbers in the next twenty years are expected to double to 78 million by 2030 and 139 million by 2050. This growing prevalence poses a serious public health concern worldwide [6-8]. Dementia and its rising prevalence could affect and lead to the financial burden in arenas of care provided by family informally, direct social care provided by professionals, and medical costs of treating symptoms along with primary and secondary care. In 2019, the worldwide costs amounted

to US$ 1.3 trillion and is expected to hit US$ 2.8 trillion by 2050 [9-12]. AD remains a condition that has persisted throughout the years and is a disease that is especially prevalent among the elderly. With the rise of the aging society, it is considered one of the most significant health threats worldwide; however, there is no cure for it, except for certain drugs providing temporary improvement in cognitive functioning depending on the severity of the disease [3, 13-15]. This suggests an urgent need to identify those at risk and the need for novel research on the mechanisms of AD and its development, potentially resulting in newer frontiers in treatments and newer avenues that would serve as therapeutic options for the disease.

1.1. Pathogenesis of AD

AD is a brain disease that can be picked up years before clinical onset due to its pathological hallmarks of atrophy of the hippocampus, extracellular amyloid beta plaques, and intracellular neurofibrillary tangles of hyperphosphorylated tau protein [16-19]. Neuropathologically, one consequence of depositions is the activation of an immune response triggering neuroinflammation, which results in synapse loss and neuronal death [7, 20], causing activation of microglia, eventually leading to a Central Nervous System inflammatory response [7, 21]. While a self-limiting neuroinflammatory response can lead to amyloid beta plaque clearance [22-24], the aging process impairs this mechanism due to changes in the immune system and microglia [25-27]. Amyloid deposition alone is not the sole culprit; another hypothesis is the tau hypothesis, which contributes to neurodegeneration through modulation of the axonal microtubules by altered and aggravated forms of highly soluble protein that act as toxic stimuli [25, 28]. The abnormal cleavage of Amyloid precursor protein (APP) by β-secretases and γ-secretases generates $A\beta_{40}$ and $A\beta_{42}$ monomers. $A\beta_{42}$, due to its hydrophobic properties, tends to misfold and clump together. Initially, Aβ peptides exist as single units (monomers) but begin to combine into toxic, forming oligomers that eventually accumulate into senile plaques [29]. Aβ aggregates enhance tau hyperphosphorylation. Tau is a microtubule-binding protein whose phosphorylation at multiple sites regulates its function; moreover, hyperphosphorylation, driven by kinases like Glycogen Synthase Kinase 3 Beta and Cyclin-Dependent Kinase 5 (CDK-5), leads to tau detachment from microtubules and the formation of neurofibrillary tangles, contributing to AD [30, 31]. AD can be categorized into late onset (sporadic) or early onset. The former is present in elderly individuals over the age of 65, cases that occur at a younger age termed early-onset AD and makeup 1-5% of all cases, with its majority being associated with an autosomal dominant inheritance of (APP), Presenilin-1 (PSEN 1) and Presenilin-2 (PSEN 2) mutations [32]. Missense mutations in PSEN1 alter amino acids in the protein, increasing the $A\beta_{42}$ to $A\beta_{40}$ ratio through changes in peptide production [33]. For example, the PSEN1-L166P

mutation triggers very high $A\beta_{42}$ levels, leading to AD's onset in adolescence [34]. Conflicting results of genetics and environment plague the pathogenesis of the disease. Associated genetic components typically allow for the designation of familial AD due to gene mutations for APP or proteins whose products take part in processing APP and presenilin genes [32, 35]. Other genetic factors that play a contributory role include E4 of alloprotein E, which is an established risk factor increasing the risk of acquiring AD by 2-3 times along with an influence on the age of onset in a dose-dependent manner [36]. Additional genes such as Clusterin (CLU), Sortilin-related receptor-1 (SORL1), ATP-binding cassette subfamily A member 7 (ABCA7), Bridging integrator 1 (BIN1), phosphatidylinositol binding clathrin assembly protein (PICALM), CD2 associated protein (CD2AP), Complement component (3b/4b) receptor 1 (CR1), CD33, triggering receptor expressed on myeloid cells 2 (TREM2), and phospholipase D3 (PLD3) too have been implicated in studies as variants that contribute to disease onset or risk [32, 37]. Environmental factors such as human symbiotic microbes influencing host health have also been implicated in many studies, with the majority located in the gut playing a vital role in nutrition, neurotrophy, growth, and influencing brain function and behaviour through the microbiota gut axis [36, 38]. Individuals with AD show reduced gut microbial diversity and altered composition, marked by increased *Fusobacterium* and decreased beneficial bacteria like *Bifidobacteria* and *Lactobacillus*. This alteration is linked to elevated inflammatory markers, such as *Escherichia coli*, indicating a connection between gut microbiota and neuroinflammation. Additionally, decreased short-chain fatty acids (SCFAs) production, particularly butyrate, adversely affects gut health and neuroprotection. These changes contribute to dysbiosis, disrupting the gut-brain axis and leading to systemic inflammation, oxidative stress, and cognitive dysfunction[39, 40].

1.2. Overview of the Gut Microbiota

The human body hosts millions of symbiotic microorganisms, including fungi, archaea, viruses, and bacteria [41-43]. Moreover, they play homeostatic functions in times of health and disease, with their roles varying from beneficial to neutral and detrimental [44]. The gut hosts the vast majority of these microorganisms, with iatrical ecological colonies of microorganisms that dwell in the gastrointestinal tract termed gut microbiota. Gut microbiota plays a pivotal role in synthesizing amino acids and vitamins and metabolizing steroid molecules and bioactive compounds, thus resulting in a strengthened immune system [41, 45]. Much of the gut's microbiota taxa composition belongs to the Gram-negative phylum group, *Bacteroides*, and the Gram-positive phylum group, *Firmicutes*. A smaller portion comprises Gram-positive – *Actinobacteria* and Gram-negative *Proteobacteria* [45, 46]. Despite certain variations, similarities in microbiota taxa exist across individuals. Differences are attributed to the influence of several factors, including diet, environment, Body Mass Index (BMI),

cholesterol, lifestyle, drug use, and ethnicity; thus, gut microbiota composition varies per person and at different stages of life [47, 48]. Studies report that even though homeostatic, at the age of 65, microbiota begins altering, leading to gut microbiota and its diversity being affected by age-related processors, causing metabolic alterations with potentially deleterious effects, thus leading to an increased number of *Bacteroides* and fewer *Firmicutes*. A misbalance such as this can introduce toxic metabolites into the circulation through gut inflammation, affecting the gut barrier's functioning and increasing its permeability for bacteria [47, 49]. It is not only gastrointestinal physiology that is affected by gut microbiota; mounting evidence suggests the integrity of the blood-brain barrier (BBB), whose function is to regulate the migration of immune cells into the brain, can too be affected thus, brain function and behaviour are affected by the role gut microbiota plays [45, 50]. In AD, the BBB becomes less effective, allowing harmful gut microbiota and their by-products to enter the brain; products from gut microbiota, like lipopolysaccharides ([51], which are components of the outer membrane of Gram-negative bacteria, can adversely affect the integrity of the BBB[52]. The migration of immune cells into the brain can lead to neuroinflammation, exacerbating neuronal damage and contributing to AD. These cells release pro-inflammatory cytokines that disrupt neuronal function and can affect synaptic activity and cognitive functions. While immune cells can promote tissue repair initially, their activity may also compromise BBB integrity, increasing vulnerability to harmful substances[53, 54].

1.3. Bidirectional Connection of the Gut-Brain Axis

A hotspot for clinical research in recent years has included the concept of an interconnection between the gut and the brain. Dysbiosis, a term explained as the alteration in the gut microbiota community, has been considered the basis of many psychiatric and neurodegenerative disorders (NDDs) due to the presence of a microbiota-gut-brain axis [44, 52, 55-57]. The gut-brain axis serves as a bidirectional connection between the brain and the gut. Moreover, it gives an insight into how gut dysbiosis may influence brain function and behaviour [58, 59]. This two-way communication system, with neuronal, endocrine, metabolic, and immune pathway involvement, currently serves as a focus of intensive research due to hints of the roles it plays in NDDs such as AD [58, 60, 61]. The role of gut microbiota in the pathogenesis of AD is studied through animal models exposed to pathogenic microbial infections, faecal microbiota transplantation, or antibiotics [58, 62]. After this continuous study of the gut-brain connection, bidirectional communication routes along the axis between the gut microbiota and brain have been summed into three parallel pathways.

1. Neural pathway – through means of a connection within the enteric nervous system
2. Endocrine pathway - through hormone signalling by use of the Hypothalamic pituitary – adrenal system

3. Immune pathway – through modulation of mucosal and systemic immunity and microbial release of inflammatory factors [50, 61].

All these mechanisms—along with other pathways such as the vagus nerve, tryptophan metabolism, neurotransmitters, microbial metabolites, and short-chain fatty acids that influence the gut microbiota—contribute to the development of various brain and mental disorders, including depression, autism, Parkinson's disease, and AD [59, 63-65]. Investigating this microbiota-gut-brain axis and its signaling pathways has unveiled new directions in neurodegenerative disease research, reinforcing the idea that AD pathology is linked to gut microbiota and suggesting that the gut may play a role in the disease's onset[58, 66]. Figure 1 illustrates the bidirectional interaction between the brain and the gut through neuroendocrine, immune, and metabolic pathways.

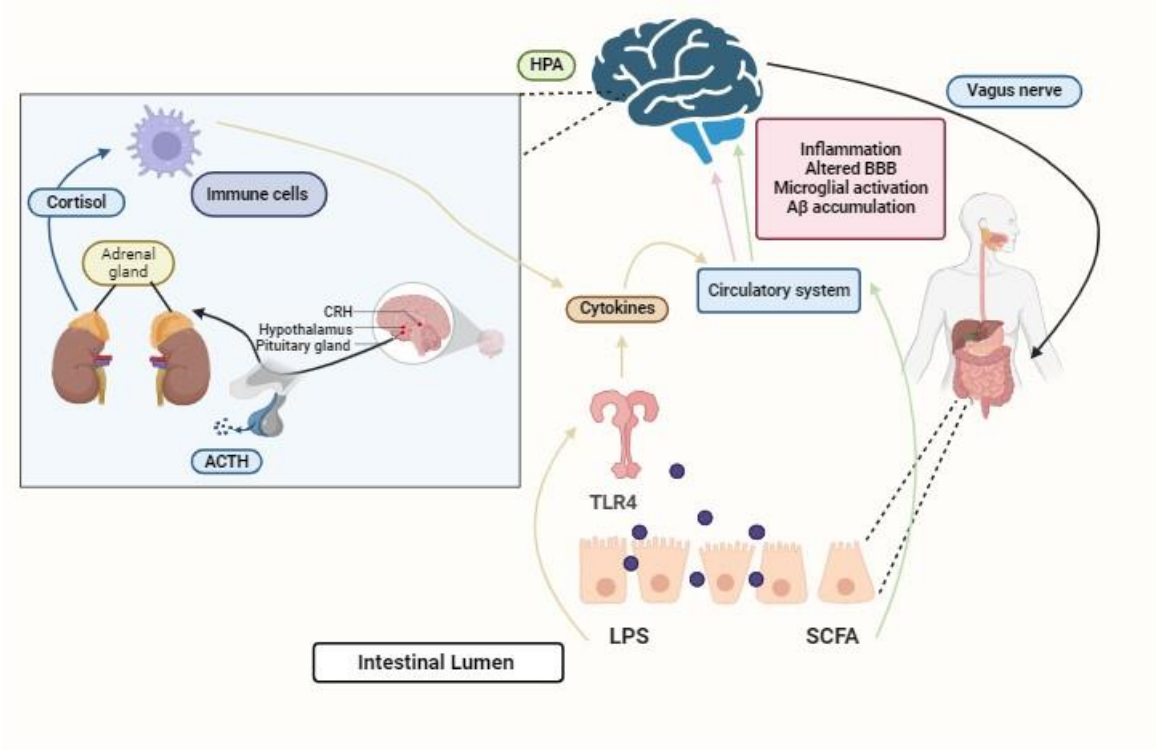


Figure 1. Summary of the bidirectional interactions between the brain and the gut microbiota via neuroendocrine, immune, and metabolic pathways. HPA: hypothalamic-pituitary axis, BBB: blood-brain barrier, ACTH: adrenocorticotropic hormone, CRH: corticotropin-releasing hormone, TRL4: toll-like-receptor-4, LPS: lipopolysaccharides, SCFA: Short chain fatty acids [45]. Created with BioRender.com.

2. Gut Microbiota in Alzheimer's Disease

In cognitively impaired individuals, changes in microbiota taxa have been documented. These include a higher number of proinflammatory bacteria and a lower number of neuroprotective short-chain fatty acids (SCFA) butyrate and bacteria synthesizing anti-inflammatory [3, 67, 68]. Changes in gut microbiota caused by aging and NDDs like AD can affect the permeability of the blood-brain barrier (BBB) through the gut-brain axis. This

allows the gut microbiota to influence brain activity[45]. *Peptostreptococcaceae, Clostridiaceae, Bifidobacteriaceae, Turicibacteraceae, Mogibacteriaceae,* and *Ruminococcaceae* are among some of the bacterial families found in abundance in individuals with AD [45, 69]. Studies done using mice models compared gut microbiota in mice with AD and controls to find a decreased microbial diversity in the diseased mice and decreased numbers of *Bacteroidaceae, Gemellaceae,* and *Rikenellaceae* families [70]. Emerging data from these studies reveal alterations in the microbial diversity in individuals with AD compared to healthy controls. These studies reported an increase in glycan biosynthesis and metabolism and a reduction in major SCFA producers, such as *Lachnospiraceae, Clostridiaceae,* and *Ruminococcaceae*. In contrast, healthy controls had higher *Gammaproteobacteria, Enterobacteriales,* and *Enterobacteriaceae* levels [67, 68, 70]. Additional research has picked up a difference in microbial taxa correlating with CSF biomarkers of AD pathology. It was picked up by Brandscheild et al. that in mice with severe amyloid pathology [5xFAD], there was a higher number of *Firmicutes* and a significant lowering in *Bacteroides* numbers [71]. Vog et al.'s study showed an increase in *Bacteroides* and a decrease in *Firmicutes* and *Bifidobacteria* in the microbiome of individuals with AD [3, 72]. Moreover, altered microbiota taxa mentioned in the previous studies can be linked to AD; additionally, Zhang revealed in his study on APPSwe/PS1E9 transgenic mice; hence, a descriptive correlation in mice with important metabolic pathway alterations was a result of changes in diversity and composition of faecal microbiota associated with amyloid deposition in the intestines of mice with AD [61]. In a bidirectional Mendelian randomization study, Chen et al. revealed that they had identified potential causal relationships between seven gut microbiota species and AD. The identified species include Order *Selenomonadales*, Family *Pasteurellaceae*, and Genus *Methanobrevibacter*, which may increase the prospect of developing AD. Conversely, the Class *Mollicutes*, Genus *Ruminiclostridium9,* Genus *Clostridiuminnocuum* group, and Genus *Eggerthella* offer a protective effect against the onset of AD [73].

2.1. Alteration of Gut Microbiota and Effects on Alzheimer's Disease

The gut microbiota holds multiple inflammatory and metabolic pathway links through its composition, thus promoting AD development. Collective data suggests microbiota play a role in the aggravation of AD features through the deposition of amyloid beta and tau hyperphosphorylation, which leads to tissue destruction and inflammation and further triggers inflammatory responses [61, 74, 75].

2.1.1. Bacterial Amyloids

The gut houses several amyloids, one of which is bacterial amyloids due to *Escherichia coli* production. While sharing similar tertiary structures, these bacterial amyloids differ from their central nervous system counterparts in the primary structure. Chen et. al. conducted a study where rats were exposed to curli-producing *E. coli,* which showed an increased gut and brain deposition of neuronal alpha-synuclein. Exposed rats also reported enhanced microgliosis and astrogliosis compared to the unexposed. An increase of TLR2-II6 and TNF was also found in exposed mice, leading to Friedland and Chapman proposing the term "Mapranosis," describing the process of proteopathy and neuroinflammation linked to microbiota [32, 76, 77]. Excreting immunogenic mixtures of amyloids and lipopolysaccharides [51], among other microbial exudates, into their immediate surroundings is carried out by bacteria residing in the gut microbiome. These bacterial amyloids together with other gut microbiota, are known to play a role in neurodegeneration and the pathogenesis of AD through their activation of signaling pathways [76, 78]. A study by Asadifard et al. highlighted a reduction in gut microbes like *Clostridia, Firmicutes,* and *Faecalibacterium*. This analysis gives an insight into signalling pathways affected by disruption of the gut microbiome involved in AD progression: The Axon guidance pathway (genes FZD3, BMPR2, MAPK1), critical for synaptic connectivity and cognitive function; the ErbB pathway, essential for neuronal survival and plasticity, with disruptions linked to neuroinflammation; and MAPK signalling, involved in cellular stress responses. Additionally, processes like peptidyl-lysine acetylation and mast cell degranulation were identified as disrupted, further contributing to AD pathology[79]. Bacterial strains that produce functional extracellular amyloid fibers include *E. coli*, *Salmonella enterica*, *Salmonella typhimurium*, *Bacillus subtilis*, *Mycobacterium tuberculosis*, and *Staphylococcus aureus*, and they interact with their host in multiple ways [80-82]. *E. Coli* (Strain K12) extracellular bacterial amyloid or curli fibers contribute to the pathogenesis of AD due to their potentiating the formation of amyloid beta fibrils, which has been the interest of many studies [83, 84]. This bacterial strain is made up of the subunit CsgA. It is a common secretory unit involved in structural material facilitation, surface attachment, adhesion, biofilm development, and protection against host defenses. Various structural forms of LPS, along with other complex lipoproteins and a matrix of extracellular polymeric amyloids, is represented by the biofilm formed by curli fibers engulfing surrounding bacteria, thus clumping many bacteria together. Toll- like receptor 2 recognizes these pathogen-associated molecular patterns exhibited by extracellular CsgA amyloid precursor [85]. Other bacterial amyloid systems also exhibit functional amyloids, a widespread phenomenon extensively generated by a wide range of microbiome bacteria and recognized by TLR2 [86]. In patients with AD, transportation mechanisms that involve the receptor for advanced glycosylation production (RAGE), which mediates the amyloid brain

influx through the BBB, are disrupted. This barrier usually depends on amyloid chaperones, apoproteins E and J, with amyloid clearance controlled by low-density lipoprotein receptor-related protein 1. Therefore, as a consequence, bacterial amyloids accumulate in the systemic and brain levels due to leakage from the gastrointestinal tract, thus activating nuclear factor signalling due to increased reactive oxygen species. This causes an upregulation of microRNA34a and a downregulation of TREM2, leading to phagocytosis impairment contributing to Aβ42 peptide accumulation, recognized by TLR2 [84]. Additionally, while exacerbating gut leakiness, amyloidal bacteria increase levels of cytokines (IL 17A, 22), which are directly associated with AD. These cytokines transit through the GI tract and BBB, further triggering immunogenic reactions, reactive oxygen species, and signals the TLR2, CD14, nuclear factor kappa light chain enhancer of activated B cells (NF- κB), all known to play a role in neurodegeneration as can be found in Figure 2 [84, 87]. As we age, the role of gut microbiota in amyloid formation becomes more prominent. With advancing age, the GI tract epithelium and the BBB undergo structural changes, becoming more permeable. This increased permeability allows microbial amyloids to influence various processes, such as molecular and cellular adaptation, stimulation of adhesion, aggregation, biofilm formation, tissue invasion, bacterial colonization, and pathogen infectivity.[84].

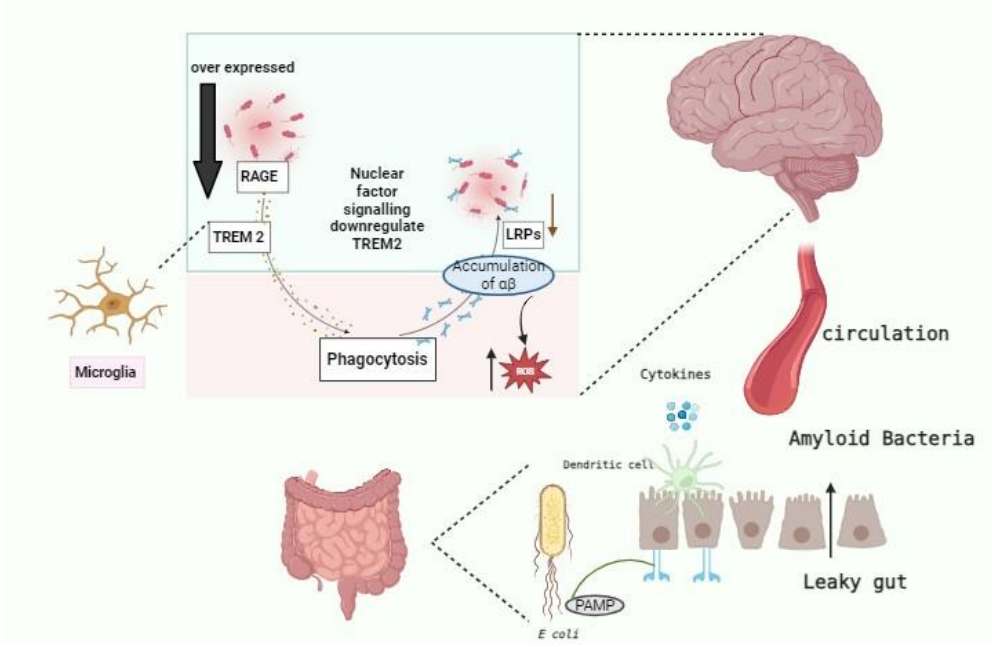


Figure 2. Amyloid beta peptide (Aβ) is transported to the brain by the receptor for advanced glycosylation products (RAGE) and cleared from the brain to the blood by LDL-Receptor-Proteins (LRPs) transport systems; however, in Alzheimer's disease, these are impaired. RAGE is overexpressed, and the expression of LRPs is decreased, leading to the accumulation of Aβ in the brain. This increases reactive oxygen species, and hence, nuclear factor signaling is activated to downregulate TREM2, impairing phagocytosis and further contributing to Aβ accumulation, which TLR2 picks up. In the gut, *E. Coli* (Strain K12), an extracellular bacterial amyloid, plays its role in pathogenesis by exposing its pathogen-associated molecular patterns in its subunit CsgA. This is recognized by TLR2, thus triggering neuroinflammatory activation through an increment of cytokines (IL-17A, IL-22) traveling through the circulation to the brain, further triggering immunogenic reactions [32, 76, 80, 81, 84]. Created with BioRender.com.

2.1.2. Lipopolysaccharides

Many inflammatory and pathological features noticed in AD were reproduced when animal models were injected with bacterial LPS into their brains. This also led to cognitive defects in test subjects due to prolonged amyloid elevation in the hippocampus; thus, studies confirm that bacterial LPS promotes amyloid fibrogenesis [32]. Interestingly, the nature and magnitude of neuroinflammation determine if it results in benefit or harm, bearing this in mind higher numbers of proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-12, IL-18, tumour necrosis factor (TNF)-α, TNF-β, interferon (INF)-γ and LPS have been sourced from the brains of those with AD [32, 88, 89]. Activation of the Toll-like receptor 4 (TLR4) by LPS, through the induction of neuronal autophagy and interactions with Cluster of differentiation 14 [51], is crucial for the biological processes involved. Thus, an inflammatory response is promoted, and this extensive inflammatory status can significantly promote AD [61, 88, 90]. Dysbiosis intensifies the production of pro-inflammatory bacteria such as *Verrucomicrobia*, *Escherichia/Shigella*, *Proteobacteria*, and *Pseudomonas aeruginosa*. It may contort the levels of anti-inflammatory bacteria comprising *Eubacterium hallii*, *Bacteroides fragilis*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Bifidobacterium.* It can be concluded that dysbiosis aggravates neuroinflammation, which in turn leads to more production of Aβ plaques [45, 91]. Figure 3 describes the role of LPS associated with the pathological conditions induced in AD.

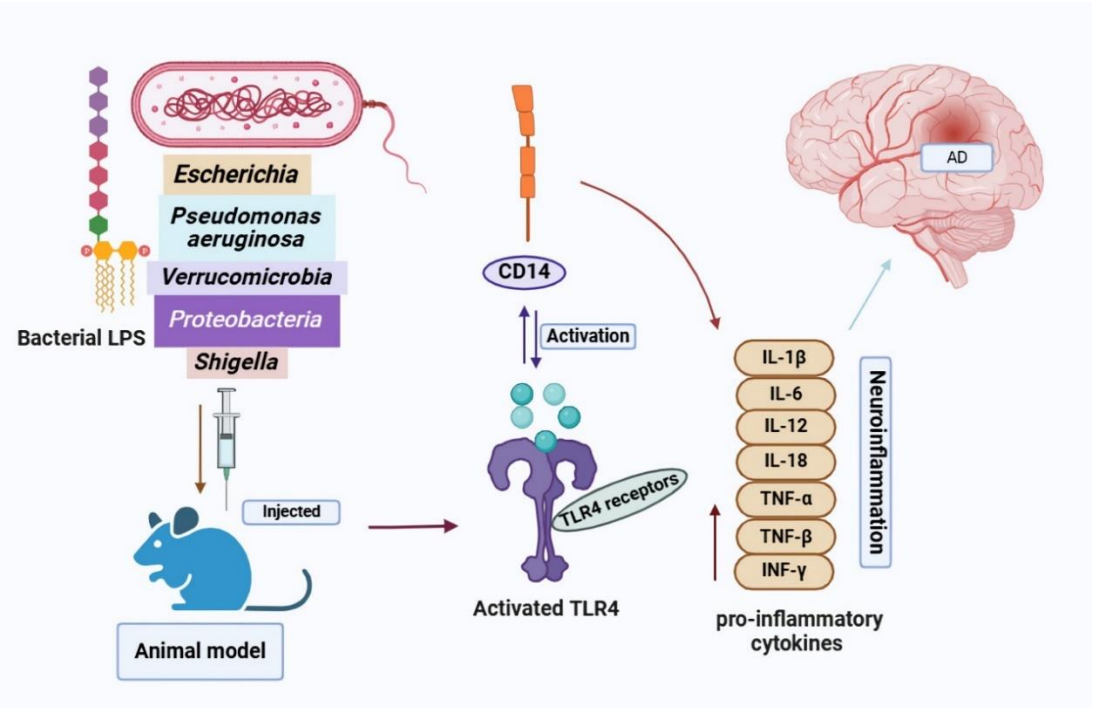


Figure 3. Illustration of pathological features noticed in AD production in animal models when injected with bacterial lipopolysaccharides. AD: Alzheimer's Disease, LPS: Lipopolysaccharides, CD14: Cluster of differentiation 14, TLR4: Toll-like receptor 4, IL1-4: Interleukin 1-4, TNF-α, β: tumour necrosis factor alpha and beta, INF-γ: interferon gamma [28, 61, 88, 90]. Created with BioRender.com.

2.1.3. Gut Dysbiosis and the Blood-Brain Barrier Permeability

The BBB strictly regulates and restricts the diffusion of harmful substances while allowing essential nutrients to pass through to perform brain functions. Significant changes in the gut microbiota complex can adversely affect the BBB, thus allowing the entry of harmful toxins into the brain, leading to neurological perturbations. Animal studies report that the permeability of the BBB is affected in mice who lack gut microbiota that modulate the expression of claudin-5, occluding, and zona occludens, which are proteins that modulate the expression of tight junctions in the BBB [63, 92]. Most LPS-producing Gram-negative bacteria, such as *Proteobacteria* and *Bacteroides*, are solely responsible for inflammation, typically deranging the BBB activity [93]. BBB disruption due to the pose of bacteria is pictorially represented in Figure 4.

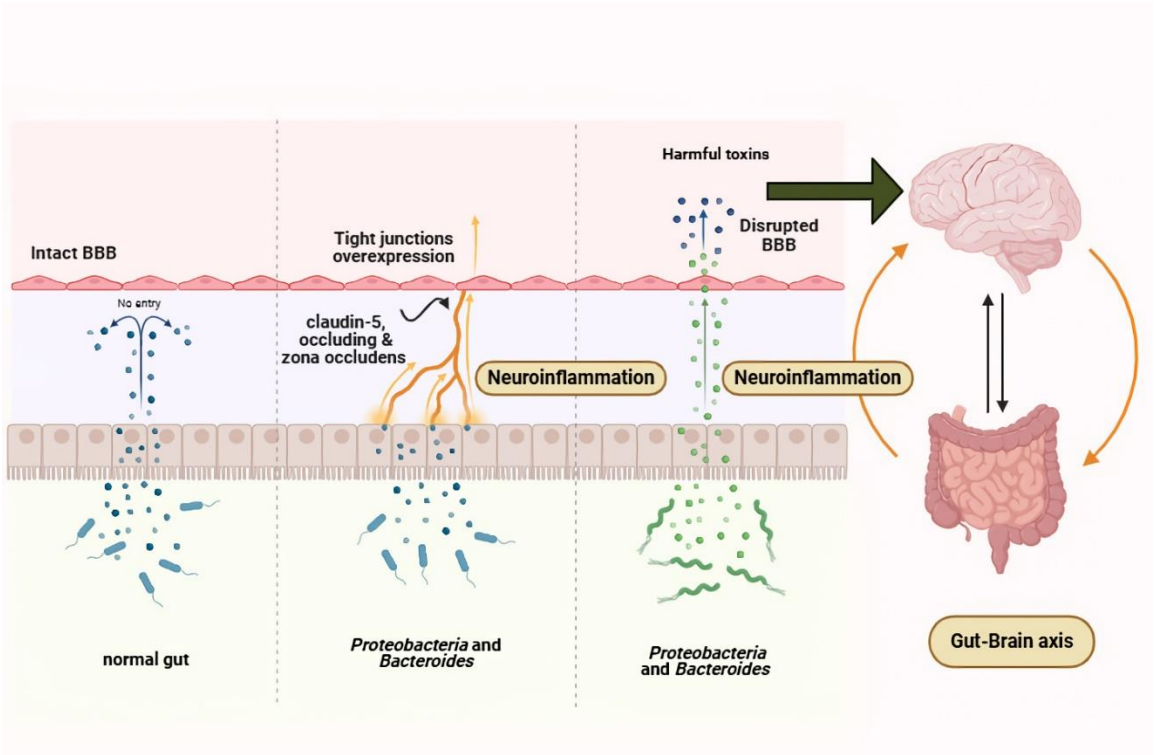


Figure 4. Illustration of normal gut and significant changes in gut microbiota complex can adversely affect the blood-brain barrier, thus allowing the entry of harmful toxins into the brain, leading to neurological perturbations. The adverse effect is the loosening of BBB due to the expression of claudin-5, occluding, and zona occludens, which are proteins that modulate the expression of tight junctions in the BBB [63, 92, 93]. Created with BioRender.com.

3. Therapeutic Strategies Targeting Gut Microbiota in Alzheimer's disease

In NDDs like AD, microbial changes are likely to occur, presenting a potential therapeutic avenue to halt the disease progression. However, further understanding is needed to identify specific gut-related targets linked to these disruptions in AD. The possible targets

include probiotics, antibiotics, diet-based interventions, and faecal microbiota transplantation.

3.1. Probiotics

Probiotics are defined as bacteria in the gut of humans and, when in the right amounts, can benefit their recipients. They are quite famously used in treating gastrointestinal diseases; however, research has been done to include them as a therapeutic option for other pathologies [52, 75, 83, 94-96]. Probiotics and prebiotics have been introduced as methods to suppress neuroinflammation, which is significant because neuroinflammation is a key factor in amyloid accumulation and AD progression [83, 97, 98]. A study by Bonfili et al. described the effects of the probiotic SLAB51 on the AD model using a transgenic mouse model. The researchers found that oral supplementation with SLAB51 led to significant changes in the gut microflora, suggesting a potential role of probiotics in modulating microbial composition in the context of AD [3]. Probiotics have shown promising effects in attenuating cognitive decline by reducing amyloid aggregation and restoring neuronal pathways [52, 76, 97]. There are also existing laboratory studies that demonstrate the function of a novel probiotic formulation (BIOCG), which plays a role in several pathways, such as the attenuation of microglial activation, reduction in amyloid load, and preservation of dendritic spine structure and function to exert neuroprotective effects on transgenic mice with AD. This study could prove that alteration in microbial composition through probiotics results in the preservation of synaptic spine morphology through altering neuronal physiology and improves long-term potentiation [99]. Other studies on this concept report better cognitive performance upon introducing probiotics to transgenic AD mice with reduced amyloid plaques in the hippocampus region [100]. This cognitive performance was further consistent with results reported in the Chen et al. study [101]. A randomized, double-blind, controlled trial study by Akbari et al. assessed the effects of probiotic supplementation on cognitive function and metabolic status in 60 AD patients. Patients were divided into two groups, one receiving probiotic milk and the other regular milk (control) for 12 weeks. The probiotic group showed a significant improvement in Mini-Mental State Examination (MMSE) scores (+27.90% vs. -5.03% in controls, $P < 0.001$). The study suggests probiotics may benefit cognitive function and certain metabolic parameters in AD patients [102]. Additionally, probiotics may be beneficial in counteracting cognitive decline based on the aforementioned studies. As observed in this study, the inclusion of probiotics may improve cognitive function, and further studies may help to calibrate the findings positively.

3.2. Antibiotics

Antibiotics are generally used to remove or prevent bacterial colonization, but their effectiveness may vary based on whether they are broad-spectrum or narrow-spectrum. Given this broad spectrum, antibiotics can greatly affect the composition of the gut microbiota, reduce its biodiversity, and delay colonization for a long period after administration [103]. Some studies report the benefit of antibiotics as they can lead to gut microbiota composition alterations and serve a function in ameliorating neuroinflammation along with other aspects of the pathology of AD pathology, such as amyloid beta and tau accumulation. However, there still exists the need for future research to discover if antibiotic treatment effects are truly mediated via changes in microbiota composition or other host pathways [47, 104]. Furthermore, it is categorically stated that Aβ results from the activity of immune cells due to detrimental bacteria. Initially, Aβ may act as an antimicrobial agent, but its effectiveness is overwhelmed as AD develops, driven by the neuroinflammation induced by gut microbiome bacteria. This process eventually leads to an accumulation of Aβ in the brain [105]. Similarly, gut microbiota plays a crucial role in gut health; arresting the bacterial flora with antibiotics in the gut may reduce Aβ deposition, as demonstrated in animal studies. In contrast, inflammatory cytokines and chemokines may abruptly activate the microglia [103]. A blind approach to decreasing gut microbiota may be fallacious; therefore, a proper guide and specific targets need to be considered [103, 106]. Some of the findings highlighted the beneficial effects of antibiotics in AD. A study by Bello-Medina et al. investigated the effects of an antibiotic cocktail comprising ampicillin, vancomycin, metronidazole, and neomycin on gut microbiota. It showed that this treatment led to dysbiosis. Notably, in a 3xTg AD model, the researchers found that antibiotic-induced dysbiosis significantly influenced spatial memory impairment. Specifically, it was noted that the dysbiosis delayed or attenuated both the spatial memory decline and the total levels of Aβ and $A\beta_{1-42}$ aggregates [107].

3.3. Diet-Based interventions

Diet and lifestyle play a role in the variation of microbial composition, and these effects can be exerted due to changes in bacterial metabolite production (LPS, SCFA) [52, 108]. Saturated fats, carbohydrates, and highly processed food may have disastrous consequences on health due to reduced microbiota diversity, neuroinflammation, and cognitive impairment. With neuroprotective effects being reported through healthy dietary patterns, one such studied diet is the Mediterranean diet, rich in various components of vegetables, legumes, cereals, and polyphenols, which could be helpful for patients with AD [3, 109, 110]. An appropriate intake of flavonoids (flavones, flavanones, and isoflavones) rich diets such as fruits (berries, citrus fruits), nuts, omega-3 fatty acids, vegetables (broccoli, parsley, and

celery), tomatoes, and whole grains was associated with a reduced risk of AD [111-113]. In most studies, adherence to the Mediterranean diet correlated with better cognitive scores and a lower risk of AD. One such study is Mediterranean-DASH Intervention for Neurodegenerative Delay, which also indicated positive effects on cognitive function, with olive oil potentially linked to improved cognition [114].Diet-based interventional therapies can be summed up into probiotic-enriched foods, polyphenol supplementation, calorie restriction, and digestion-resistant fiber consumption [3, 109].

3.4. Faecal Microbiota Transplantation

A well-used approach and treatment option in gastrointestinal conditions such as inflammatory bowel disease, diarrhoea, and irritable bowel syndrome is faecal microbiota transplantation [67]. This therapeutic approach is currently being researched for its potential in NDDs [115]. Faecal microbiota transplantation involves restoring the diversity and function of gut microbiota through transplanting stool from a healthy donor to a patient's gastrointestinal tract, thus combating diseases associated with microbiota imbalance. However, studies investigating it as a potential intervention need to be interpreted with caution due to the limitations of rodent models [116, 117]. Studies show that treating AD mice through faecal microbiota transplantation (FMT) can reverse microbiota alteration, improve cognition and synaptic plasticity, decrease amyloid beta and tau pathology, and reduce neuroinflammation [47, 117]. This method is expected to lessen dysbiosis and its negative effects on the gut and brain while restoring intestinal microflora [7]. Table 1 summarises the studies on therapeutic options targeting gut microbiota on AD.

Table 1. Summary of the list of studies conducted on therapeutic options targeting gut microbiota in Alzheimer's disease.

Therapeutic option	Study description	Results	Study
Probiotics			
SLAB51 (*Streptococcus thermophilus*, *Bifidobacteria*) at 200bn bacteria/kg/day for 4 months	Transgenic AD mice were given SLAB51, focusing on the role of SIRT1-related pathways.	Reduction in oxidative stress through the activation of SIRT-1-dependent mechanisms.	[118]
FRAMELIM® (*Bifidobacterium longum* and *Lactobacillus acidophilus* lysates) at 120 mg/day for 20 weeks	Mice underwent exercise training and probiotic treatments.	Mice showed reduced hippocampal amyloid and beta plaques and improved cognition	[100]

Fructooligosaccharides from *Morinda officinalis (OMO)*	*OMO* administered in AD-like rats	*OMO* improved AD-like symptoms and stability of the gut microbiome.	[101]
Antibiotics			
Rifampicin	Review of rifampicin's mechanisms related to neuroprotection through anti-inflammation, anti-tau, anti-amyloid, and cholinergic effects.	Rifampicin demonstrates neuroprotective and cognitive-enhancing potential in AD through its anti-inflammatory, anti-tau, anti-amyloid, and cholinergic actions.	[104]
Diet			
Mediterranean diet	Association of Mediterranean diet and AD risk through a cross-sectional study in elderly individuals.	Low Mediterranean diet adherence linked to cognitive impairment.	[110]
Faecal microbiota			
Faecal microbiota transplant	The ability of mice to transfer behavioral traits through FMT and their resulting interactions	FMT in germ-free mice resulted in changes in brain chemistry, including altered neurotransmitter levels, reduced inflammation, and improved social and cognitive behaviour.	[117]

Abbreviations: SIRT-1: Sirtuin 1; OMO: *Morinda officinalis*; FMT: Faecal microbiota transplant; COX-2: Cyclooxygenase-2.

4. Knowledge Gaps and Future Research Potentials

Posing a serious threat to health and quality of life, NDDs require intensified research heralding renewed hope for more effective treatments [61]. Gut dysbiosis and its role in the gut microbiota axis, thus contributing to the pathogenesis of AD, is one with very little doubt around it [58]. However, few studies have confirmed a clear association between cognitive impairment and gut microbiota changes. While these findings have paved the way for potential therapeutic interventions, a significant knowledge gap remains regarding the precise mechanisms underlying this connection [61]. Literature has identified key functional bacteria associated with AD pathology. While this can be used as targets for therapeutic interventions and diagnostics for AD, the exact role microbiota plays in the development of AD remains elusive, with most studies only shining a spotlight on the association between gut microbiota and the disease, the causal relationship between bacteria and brain functions about the disease cannot be illustrated. Therefore, it is important to shift the narrative from microbiome studies conducted to identify associations to ones that demonstrate causality [58, 119]. This is especially important as an overlap in gut microbiota composition exists between the elderly with and

without cognitive impairment. Therefore, further research is required to identify the AD microbial biomarkers for diagnosis and treatment [61]. Utilizing sequencing methods such as 16S rRNA gene sequencing, shotgun metagenomic sequencing, and metatranscriptomics [120, 121] to detect AD-related alterations in the gut microbiome offers valuable insights into the underlying mechanisms. It could serve as a potential therapeutic target for future treatments [52, 122]. Animal model studies have demonstrated the therapeutic effects of antibiotics, probiotics, prebiotics, and faecal microbiota transplants on AD by influencing gut microbiota composition. However, there remains significant potential for further research to explore the connection between these therapies and the simultaneous assessment of gut microbiota metabolites. This could be done by investigating various pathways, neuroinflammatory mechanisms, and changes in amyloid deposition associated with AD pathology [36, 123-125]. The majority of studies have been done on animal models. While these preclinical findings can be utilized to indicate the development of AD, caution must be exercised in extrapolating data as diets and microbiota composition tend to vary between species, leading to the need for human trials to explore treatments aimed at gut microbiota manipulation [36, 126, 127].

Dietary-based intervention strategies are another avenue with promising therapeutic potential, and certain dietary patterns may lower the risk of acquiring AD and show a link to the regulation and function of gut microbiota. Therefore, clinical studies focusing on therapeutic interventions regarding diet can be conducted in humans targeting gut microbiota modulation to help decipher the mechanism of gut dysbiosis influenced by diet and disease development [120, 128-130]. Despite ongoing clinical trials investigating the modulation of gut microbiota in AD, they are still in preliminary stages, requiring more evidence to determine their effectiveness. Longitudinal studies are crucial to assessing microbiota modulation's long-term effects and impact on AD progression. Recent discoveries in gut microbiota and AD include signalling pathways implicated in neuroinflammation, brain amyloid deposition, AD pathogenesis and the role of microbiota-generated lipopolysaccharides and amyloids. This signifies a need for therapeutic strategies to alter amyloids produced by bacteria [70, 131-134].

5. Conclusion

In conclusion, recent advancements in microbiome AD research indicate that altering the gut microbiome might offer a promising approach to decelerate AD progression. However, navigating this path is riddled with challenges, including the intricate nature of gut microbiota interactions, individual variabilities, and the absence of standardized protocols. To surmount these challenges, it is imperative to delve deeper into understanding the bidirectional communication between the gut and the brain to facilitate the development of more precise interventions.

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