Exploring the effect of gut microbiome on Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most widespread and irreversible form of dementia and accounts for more than half of dementia cases. The most significant risk factors for AD are aging-related exacerbations, degradation of anatomical pathways, environmental variables and mitochondrial dysfunction. Finding a decisive therapeutic solution is a major current issue. Nuanced interactions between major neuropathological mechanisms in AD in patients and microbiome have recently gained rising attention. The presence of bacterial amyloid in the gut triggers the immune system, resulting in increased immune feedbacks and endogenous neuronal amyloid within the CNS. Also, early clinical research revealed that changing the microbiome with beneficial bacteria or probiotics could affect brain function in AD. New approaches focus on the possible neuroprotective action of disease-modifying medications in AD. In the present review, we discuss the impact of the gut microbiota on the brain and review emerging research that suggests a disruption in the microbiota-brain axis can affect AD by mediating neuroinflammation. Such novel methods could help the development of novel therapeutics for AD.

1. Introduction

The most prevalent neurodegenerative illness is Alzheimer's disease (AD), accounting for more than half of all dementia cases and half of all dementia deaths in those aged 85 and over [1,2]. AD affects more women than men [3]. AD is a very incapacitating condition that progresses from minor memory problems to complete mental function loss, eventually leading to death [4]. Some of the most common warning signs are depression, memory loss, difficulty organizing and solving problems, challenges in recognizing time, personality changes, problems with motor function, and difficulty recalling literature [5,6]. Even though both genetic factors and environmental factors contribute to the pathogenesis of AD, the most significant risk factors have been determined to be aging-related exacerbations [7,8], degradation of anatomical pathways [9], environmental variables [10,11], mitochondrial dysfunction [12], and hereditary components counting changes of amyloid precursor proteins (APP) [13]. Amyloid-beta (Aβ) peptide aggregation and hyperphosphorylated tau tangles are the most apparent histopathological clues. Other theories on the pathophysiology of AD point to neuroinflammation, calcium imbalances, and energy metabolism problems, as well as degeneration of the blood vessels, but therapeutic attempts based on these current theories and ideas haven't worked in the past few years. Several studies have shown that the gut and central nervous system (CNS) communicate and that controlling gut microbiota could be a promising therapeutic approach for neurodegenerative diseases such as Parkinson's disease (PD) and AD [14,15]. In this review, we will be focusing on the role of the gut microbiota on the brain and discussing the new evidence that indicates that a disturbance in the microbiota-brain axis can lead to neuroinflammation giving rise to AD.

2. Alzheimer's disease pathophysiology

Amyloid-beta plaques and neurofibrillary tangles (NFTs) are two well-established markers that contribute to the advancement of AD [16]. Patients with AD show low levels of the 42-aminoacid form of amyloid beta (Aβ42) due to amyloid deposition in the cortex. High total tau (T-tau) levels are found due to cortical neuronal loss. Furthermore, high phosphorylated tau (P-tau) levels are detected, indicating the development of cortical tangles [17,18].

The excessive production of Aβ peptide originates from the transmembrane amyloid precursor protein (APP) due to the sequential action of beta and gamma secretases. As a result, Aβ plaques are formed. According to a recent study, the pathogenesis of amyloid starts with the abnormal breakdown of APP by γ- and β-secretases, which leads to the formation of insoluble Aβ fibrils [19]. Afterward, Aβ oligomerizes, spreads into clefts in synapses, and prevents synaptic signaling. Plaques are created when they polymerize into insoluble amyloid fibrils that group together. This polymerization activates kinases, which can expedite the hyperphosphorylation of tau protein linked with microtubules and the polymerization of tau into insoluble NFTs [20–22].

Two pioneering research studies in 2001 demonstrated that Aβ load in the AD brain causes tau accumulation by increasing tau phosphorylation [23,24]. It was discovered that Aβ oligomers might cause tau phosphorylation by primarily stimulating the AKT-GSK3beta signaling pathway as part of the process [25,26]. Tau phosphorylation at ser-202 and ser-396 (or ser-404) amino acids was demonstrated to be soluble or amorphous-aggregated in rodent hippocampus and human cortical nerve cells formed by Aβ, supporting the in vivo observation [27].

Hyperphosphorylation of serine or threonine residues in the microtubule-associated protein Tau, on the other hand, promotes its intracellular deposition, resulting in the formation of neurofibrillary tangle (NFT), a protein that is extremely soluble, required for the integrity of microtubules in axons. NFTs cause damage to the microtubule structure of neurons, resulting in an insoluble material found in the locus coeruleus, as well as the transentorhinal and entorhinal sections of the brain [28,29]. Even if the Aβ load stays the same or increases, the elimination of tau can help augmentation of the cognitive function. As a result, tau aggregation is thought to be a more important causal mediator of cognitive decline than Aβ [30–32]. Aβ has been established as an antimicrobial peptide that triggers neuroinflammation by stimulating immunological pathways that toll-like receptor 2 recognizes (TLR2) [21]. It is important to note that, in addition to classical immunoinflammatory pathways, discovery of new inflammation markers which may regulate gut microbiota in AD is recommended. A good example is Fas ligand (FasL) molecular which is widely known as an apoptotic factor but recent research showed it could mount inflammatory response in infectious conditions [33]. Hence, FasL-mediated degeneration of the brain and its expression in inflamed brain areas is interesting and deserves further study [34]. Enhanced CSF Fas (Apo-1) levels in AD and associations with IL-6 levels has been explored [35]. However, these data need in-depth investigation to be useful for therapeutic targeting.

3. Microbiota-gut-brain (MGB) axis mediates the development of AD

3.1. Gut microbiota

At the level of individual bacterial strains, the gut microbiota exhibits significant individual variation and variety. Approximately 10^3–10^4 bacteria live in the human gut flora [36]. *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* are the most numerous species in healthy gut flora, respectively. Firmicutes and Bacteroidetes are the two main phyla of gut flora in humans. Presvotella, Bacteroides, and Ruminococcus species presence has been suggested as a means of classifying populations [37]. Human microbial colonization is thought to begin at birth. *Lactobacillus* and *Prevotella* spp., which are found in the mother's gut, colonize the newborn infant initially [38]. Diet may have a big role in age-related changes in the elderly microbiota; if it's not good enough, it can lead to a significant decline in microbial diversity, which has been associated to inflammation ("inflammaging") in the elderly [39]. It is still unclear if aging affects the microbiota by itself, regardless of environmental effects. Obesity, colorectal cancer, inflammatory bowel disease, heart failure, type 2 diabetes, and neurological disorders can all be exacerbated by changes in the composition of bacteria caused by dietary changes [40–42] (Fig. 1).

3.2. Gut-brain axis

The idea of the microbiota-gut-brain axis is not a recent concept. Over 60 years ago, researchers discovered a connection between gut bacteria, their byproducts, and hepatic coma. They also found that antibiotic therapy can alleviate the syndrome of hepatic encephalopathy. This was a significant breakthrough [43,44]. An extensive body of research implies that the microbiota influences brain function and behavior, and that the microbiota-gut-brain axis is set to become a bidirectional communication network [45,46]. Since the ENS and the CNS share many morphological, physiological, and pharmacological characteristics, bacteria that can affect the ENS can also affect the CNS if they or their messengers can get there [47,48].

Experiments in germ-free animals have yielded a lot of information about the role of the gut microbiota in neurodevelopment [49,50]. These studies have demonstrated that the microbiome influences behavioral changes as well as the morphological and functional progression of multiple brain regions [51,52]. In the cortex, hippocampus, and amygdala, germ-free animals had reduced expression of the key neurotrophic factor, brain-derived neurotrophic factor (BDNF) [51]. Others have found decreased neurogenesis in the hippocampus [53] and changed neuronal architecture in the amygdala in germ-free mice [54], which supports our declaration. Another experimental technique, reducing the microbiota using broad-spectrum antibiotics, has shown similar results [55].

The transmission of important central neurotransmitters is also influenced by the gut flora, which modifies precursor levels; *Bifidobacterium infantis*, for example, has demonstrated to increase plasma tryptophan levels and alter central 5-HT transmission, which results in influencing cognitive function, and reducing depression-related behaviors [56]. Furthermore, bacteria can produce and release neurotransmitters. Certain species of Lactobacillus and Bifidobacterium can produce the inhibitory neurotransmitter γ-aminobutyric acid (GABA). This neurotransmitter is known to alleviate anxiety, stress, and fear and improve symptoms of ADHD [41,57], whereas noradrenaline can be produced by *Escherichia*, *Bacillus*, and *Saccharomyces* spp., which improves memory formation and retrieval [58]. Serotonin production has been recorded in *Candida*, *Streptococcus*, *Escherichia*, and *Enterococcus* spp. [59,60], dopamine production has been documented in *Bacillus*, and acetylcholine production has been observed in *Lactobacillus* [61]. These microbiologically generated neurotransmitters can permeate through the intestinal mucosal layer and might be involved in brain physiological events [62,63].

3.3. Neuroinflammation and AD

According to a number of recent studies, neuroinflammation is a key factor in the development of the neuropathological changes linked to AD. Many cellular and molecular mechanisms are now recognized to be silent key factors that contribute to neuroinflammation in aging and long-term metabolic conditions like high blood pressure, diabetes, metabolic syndrome, memory loss, and depression [64]. Innate immune cells in the CNS produce pro-inflammatory cytokines such as IL-1, IL-6, IL-18, and tumor necrosis factor (TNF) (Fig. 2). Innate immune cells also produce chemokines including C-C motif chemokine ligand 1 (CCL1), CCL5, and C-X-C motif chemokine ligand 1 (CXCL1), as well as
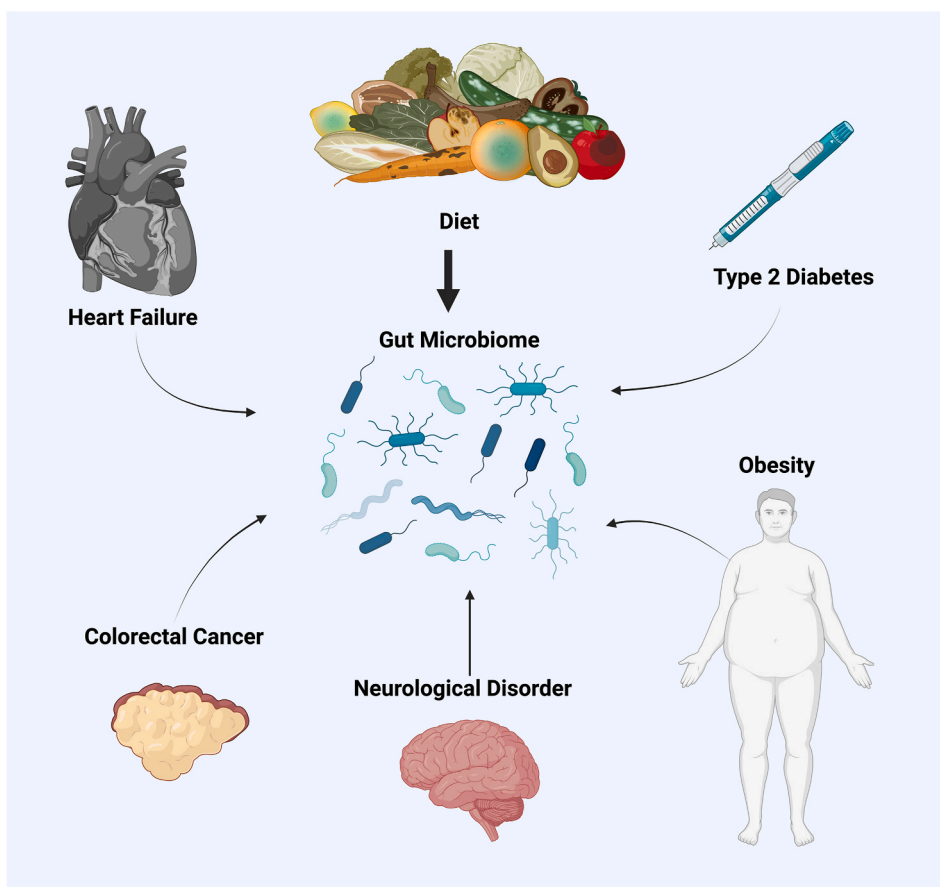
Fig. 1. In the realm of gut-brain-microbiome interaction, various impacts stemming from the gut microbiome can exert a significant influence on a wide array of diseases, with dietary choices potentially exacerbating certain conditions such as diabetes, obesity, heart failure, colorectal cancer, and neurological disorders. These effects underscore the intricate interplay between the gut, brain, and microbiome, highlighting the multifaceted nature of the gut-brain axis and its implications for overall health outcomes. Understanding the nuanced relationships between the gut microbiome and disease pathogenesis is crucial for developing targeted interventions that can modulate these interactions and potentially mitigate the risk of developing associated health conditions.
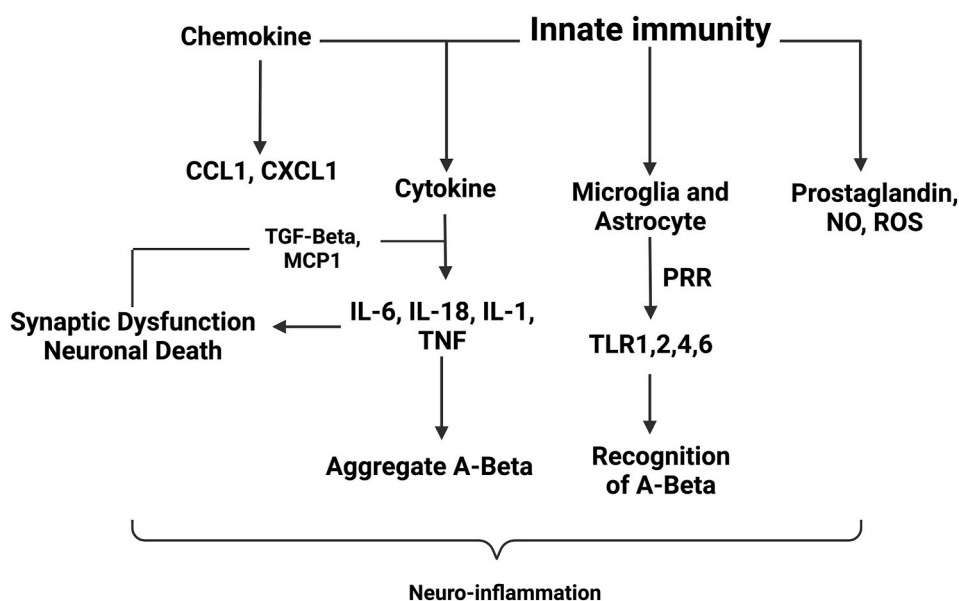

Fig. 2. Innate immune cells in the CNS, primarily microglia and astrocytes, produce various pro-inflammatory cytokines such as IL-1, IL-6, IL-18, and TNF. These cells also release chemokines, including CCL1, CCL5, and CXCL1, along with small-molecule messengers like prostaglandins, nitric oxide (NO), and reactive oxygen species. Reactive microglia have been shown to internalize amyloid plaques, linking them to Alzheimer's disease. Various species of Aβ aggregates can induce glial activation and the production of pro-inflammatory cytokines IL-1, IL-6, IL-8, and TNF. Additionally, TGF-β, an anti-inflammatory cytokine, and chemokines such as MCP1 and macrophage inflammatory protein 1, may contribute to neuronal death and dysfunction.

small-molecule messengers like prostaglandins and nitric oxide (NO), and reactive oxygen species [65]. Microglia and astrocytes are the main innate immune cells engaged in this process [66]. Reactive microglia have been demonstrated to internalize amyloid plaques in AD patients' brains, establishing a link between these two clinical markers of the disease. Glial activation and the generation of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF were discovered to be caused by different species of Aβ aggregates. TGF-β, an anti-inflammatory cytokine, and chemokines including MCP1 and macrophage inflammatory protein 1 may cause neuronal death and dysfunction [67]. Other contributors to neuroinflammation comprise vascular endothelium and invading blood cells, especially when the blood-brain barrier (BBB) is disrupted biochemically or mechanically [68,69]. Microglia and astrocytes have a wide spectrum of innate immunological receptors on their membranes, including pattern recognition receptors [66]. When pattern recognition receptors on microglia are engaged, a unique signaling cascade is activated, resulting in cell activation and the generation of inflammatory mediators [70,71]. Microglia use pattern recognition receptors such as TLR1, TLR2, TLR4, and TLR6, as well as CD14, CD47, and scavenger receptors such as CD36, to recognize Aβ species. These receptors then trigger molecular pathways that cause phenotypic alterations in microglia [72–74].

Synaptic dysfunction, neuronal death, and neurogenesis suppression are all possible outcomes of pro-inflammatory chemical release [75]. When the nuclear factor-B (NF-B) pathway is blocked, TNF triggers neuronal death by activating TNF receptor 1 (TNFR1) and recruiting caspase 8, while IL-1 causes synaptic loss by causing presynaptic glutamate release and postsynaptic N-methyl-D-aspartate (NMDA) receptor activation via increasing prostaglandin E2 synthesis [76]. Numerous clinical approaches, including histological assessment, neuroimaging, and the analysis of proteomic and other biomarker signatures in blood and CSF, have been utilized to comprehend the role of neuroinflammation in AD [77,78]. IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-18, interferon-γ (IFN-γ), TNF, and transforming growth factor (TGF) have all been studied in the blood and CSF of AD individuals. A previous meta-analysis reported that AD is often associated with an inflammatory response, resulting in elevated levels of various cytokines such as IL-6, TNF-α, IL-1, TGF-β, IL-12, and IL-18 in the peripheral blood. Additionally, levels of TGF-β are also higher in the CSF of AD patients [77]. Therefore, we can observe an overall increase in inflammatory responses in the blood and cerebrospinal fluid of AD patients [79]. The elimination of Aβ in the body is quite efficient. Low Aβ concentrations stimulate microglia through CD14 and TLR in the early stages of AD, increasing phagocytosis and amyloid clearance [80].

3.4. Gut microbiota affects the development of AD

The MGB axis reflects the ongoing relationship between CNS and the gastrointestinal tract (GIT). Important pathways in MGB are thought to include the neuroendocrine, neuroimmune, and sympathetic and
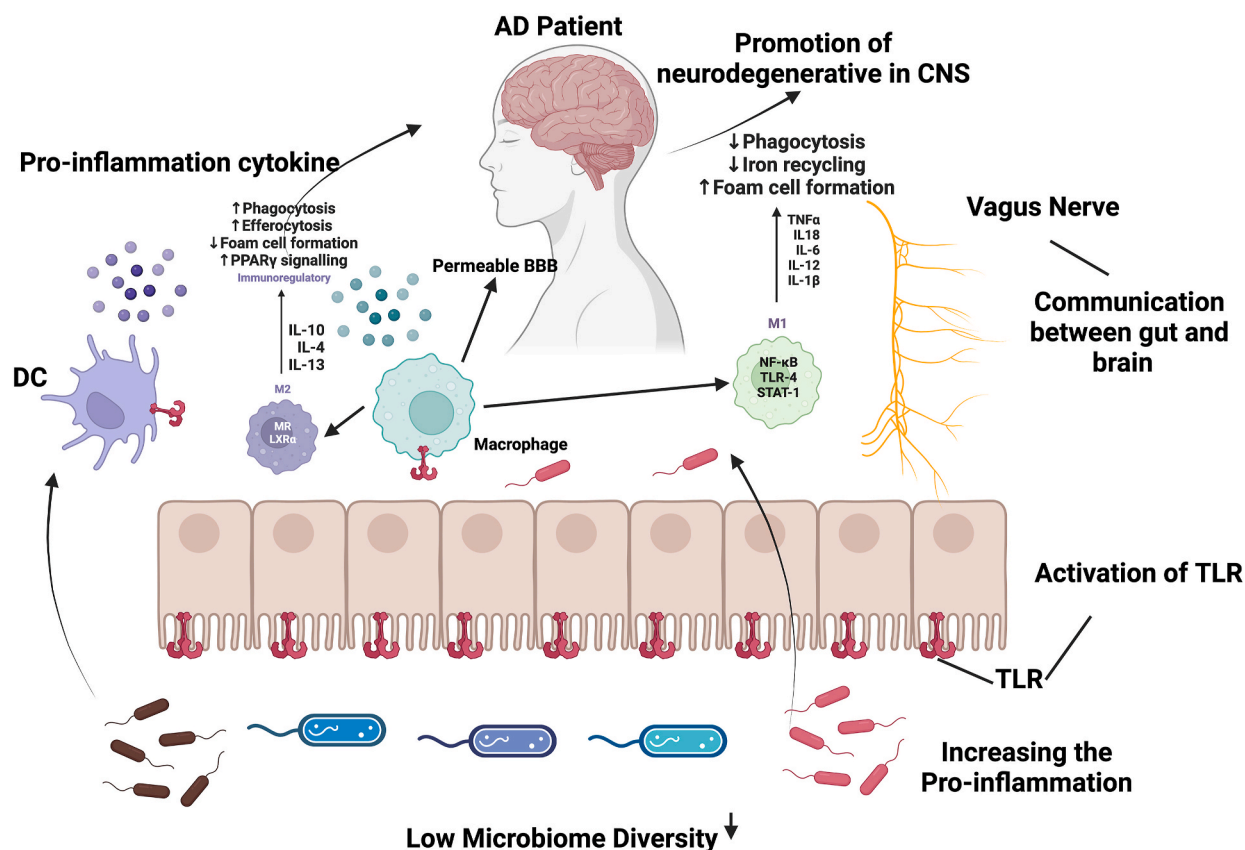

Fig. 3. TLRs are crucial components of the innate immune system as they are responsible for recognizing pathogens derived from microbes and triggering the inflammatory cascade, thereby playing a significant role in immune responses. Additionally, these TLRs have been identified in the brain, particularly in microglial cells, and have been implicated in the pathogenesis of Alzheimer's disease. The immunological implications of TLR activation include a reduction in microbiome diversity, which in turn leads to an increase in pro-inflammatory cytokines through the activation of macrophage and dendritic cells. The interplay between the innate immune responses and the microbiome's side effects via TLR activation in Alzheimer's disease underscores the complexity of the immune system's involvement in neurodegenerative disorders. Understanding the mechanisms by which TLRs contribute to the development and progression of AD is essential for the development of targeted therapies that can modulate immune responses without compromising the delicate balance of the microbiome. Further research into the intricate interactions between TLRs, the microbiome, and neuroinflammation may provide valuable insights into potential therapeutic strategies for Alzheimer's disease.

parasympathetic autonomic nervous systems [81,82]. Proinflammatory cytokines are activated, and intestinal permeability is increased due to gut flora alterations, resulting in insulin resistance, which is linked to AD [83]. Intestinal inflammation is exacerbated by gut microbiota dysfunction, which in colon epithelial cells diminishes the expression of tight junction proteins. When connections are lost, microbial metabolic residues permeate the circulatory system, causing an inflammatory response (Fig. 3). A high quantity of pro-inflammatory cytokines in plasma penetrates the BBB and induces inflammation via changing microglial maturation and astrocyte activation [84].

Although most studies were post-mortem, multiple human studies linked microbial existence in the brain to the pathogenesis of AD, lessening the proof of their causative involvement in AD pathophysiology [85–87]. Recent studies have revealed that AD development may initiate in the gut and then progress to the brain. A prior study investigated whether intra-GI delivery of Aβ may cause central nervous system (CNS) amyloidosis and AD-related diseases like dementia. Mice's stomach walls were injected with Aβ-42 oligomers. Over the course of a year, the amyloid moved from the colon to the brain. As a result, oligomer translocation from the gut to the brain may play an important role in AD and neuroinflammation development [88].

Gut microbes are critical for the development of microglia and the control of inflammation in the central nervous system, according to new findings, which are backed up by epigenetic studies looking into the impact of short chain fatty acids (SCFAs) on AD [89,90]. Bacterial metabolites, such as SCFAs, were previously assumed to be important in the interplay between the microbiota and the microglia. These chemicals have the ability to pass the blood-brain barrier and translocate from the mucosa to the systemic circulation, influencing the CNS and its function [91]. Gut metabolites have been shown in a meta-analysis to promote inflammation, tau, and Aβ aggregations in the CNS [92]. As a result, when the gut microbiota is compromised, microglia maturation and phagocytosis capacity for tau and Aβ is reduced. Some bacterial species that can form functional extracellular amyloid fibers include *Escherichia coli*, *Salmonella enterica*, Bacillus subtilis, *Mycobacterium tuberculosis*, and *Staphylococcus aureus* [68]. Amyloid proteins aid bacterial strains in developing biofilms and creating robust connections with each other to endure physical and immune pressures [93]. The main structure of bacteria-produced amyloids differs from that of CNS amyloids, although their tertiary structure is similar [94]. Briefly, the immune system may be activated by bacterial amyloid aggregates seen in the gastrointestinal tract, resulting in enhanced immune responses and endogenous amyloid formation in the nerve cells of the brain. When compared to healthy adults, research on the blood and CSF fluid of AD patients showed an elevated inflammatory response [68]. As reported previously, neurotransmitters are another microbial secretion that has lately been speculated to regulate brain activities but has yet to be proven [95]. This field of research is intriguing, because it will help to explain the interplay of bacterial neurotransmitters with neurodegeneration and AD.

According to a prior study, the quantity of Firmicutes increased significantly in 5xFAD mice (a model with extensive amyloid pathology); however, a considerable decline in Bacteroidetes was seen, which is consistent with other AD models [96]. Since the digestive tracts of these animals are extremely inflammatory, Bacteroidetes should normally grow unitedly with Firmicutes in 5xFAD rodents, allowing only inflammatory bacteria to endure. Additional pathogenic bacteria's metabolites, whose quantity in the gut grew proportionately, may be the reason for the drop in Bacteroidetes species in the bacterial flora in 5xFAD mice, although it is still unknown if commensal bacteria might reduce each other's chances of survival [97].

The number of B. fragilis and Escherichia (or Shigella) in the bacterial categorization increased dramatically in individuals with amyloidosis. However, E. rectale significantly decreased, according to a study examining the correlations between gut bacteria, systemic inflammation, and AD. The study also found that the levels of NLRP3, CXCL2, IL-6, and IL-1b increased significantly in the plasma of amyloidosis patients [68]. When these cytokines were tested to see if they had a relationship with the bacteria genus in the gut, it was discovered that the prevalence of pro-inflammatory bacteria Escherichia/Shigella was favorably connected with IL-1b, NLRP3, and CXCL2, but negatively correlated with the presence of anti-inflammatory bacteria E. rectale [68].

The most crucial characteristics of AD pathogenesis are undoubtedly Aβ and tau aggregations. By regulating glucose homeostasis, host immunological response, inflammatory pathways, and tumor suppression, metabolic byproducts such as short-chain fatty acids (SCFAs) play a critical role in human health and illness [90]. Both in vitro and in vivo studies were conducted to examine the impact of SCFAs on Aβ aggregation. In an earlier study, Ho et al. used an in vitro method called photoinduced crosslinking of unmodified proteins to find that butyric acid, propionic acid, and valeric acid inhibited Aβ-40 oligomerization in a dose-dependent manner [95]. A spectroscopic experiment revealed that valeric and butyric acids dose-dependently prevented the generation of Aβ fibrils from Aβ-40 monomers [95].

Numerous obstacles will need to be overcome in the future for gut microbiota studies on AD. Understanding what constitutes a normal or healthy microbiome is essential to comprehending the connection between AD and gut bacteria. Variables such as medication, food, and health can pose difficulties in this research field. It is necessary to conduct longitudinal investigations that include metagenomics sequencing, phylogenetic analysis, and thorough phenotypic characterization. It is better to support causal and functional investigations rather than observational ones. Optimizing basic research focuses on the microbiota-gut-brain axis in AD while taking host-specific interactions, environmental variations, and the complexity of the brain's structure into account. It's also crucial to translate basic research findings into real clinical outcomes. Owing to the considerable variations in human gut microbiota makeup, future therapeutic approaches might be predicated on these individual distinctions [3].

4. Microbiota modulation influences molecular mechanisms through the gut-brain axis

Improved comprehension of the gut microbiota's function in AD progression and the significant correlation between intestinal permeability, disruption of average bacterial balance, and brain impairment open new therapeutic avenues [98]. Probiotics improve intestinal epithelium health, protect against the disruption of barriers, reduce proinflammatory responses, and limit the beginning or propagation of neuroinflammation and neurodegeneration, according to the findings of various studies [99,100]. LPS and amyloid peptides are abundant in the gut microbiome. TLR4 is activated by LPS through CD14. Bacterial amyloid proteins assist bacteria in forming biofilms and resisting removal by physical or immunological stimuli, as well as causing CNS inflammation in a variety of ways (Fig. 4) [93].

Microglial activation is a multifaceted process that results in a variety of phenotypes. Outside of the CNS, activated macrophages are classified as either a classical, proinflammatory (M1) phenotype linked with cytotoxic gene expression or a non-inflammatory, alternate activation (M2) phenotype [101,102]. Increased pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin IL-1, IL-6, IL-12, and IL-18, as well as reduced phagocytic ability, characterize classic M1 activation. MHC-II, integrins (CD11b, CD11c), costimulatory molecules (CD36, CD45, CD47), and Fc receptors are all present in M1 microglia [103]. Differently, the anti-inflammatory cytokines IL-4, IL-10, IL-13, and transforming growth factor-beta (TGF-β) are secreted in the M2 state, as is increased phagocytic capacity without toxic NO generation [104,105].

SCFAs have an impact on a variety of GI functions, including electrolyte and water absorption, in addition to their crucial role as fuel for intestinal epithelial cells. SCFAs have at least two modes of action on leukocytes and endothelial cells: stimulation of GPCRs and inhibition of
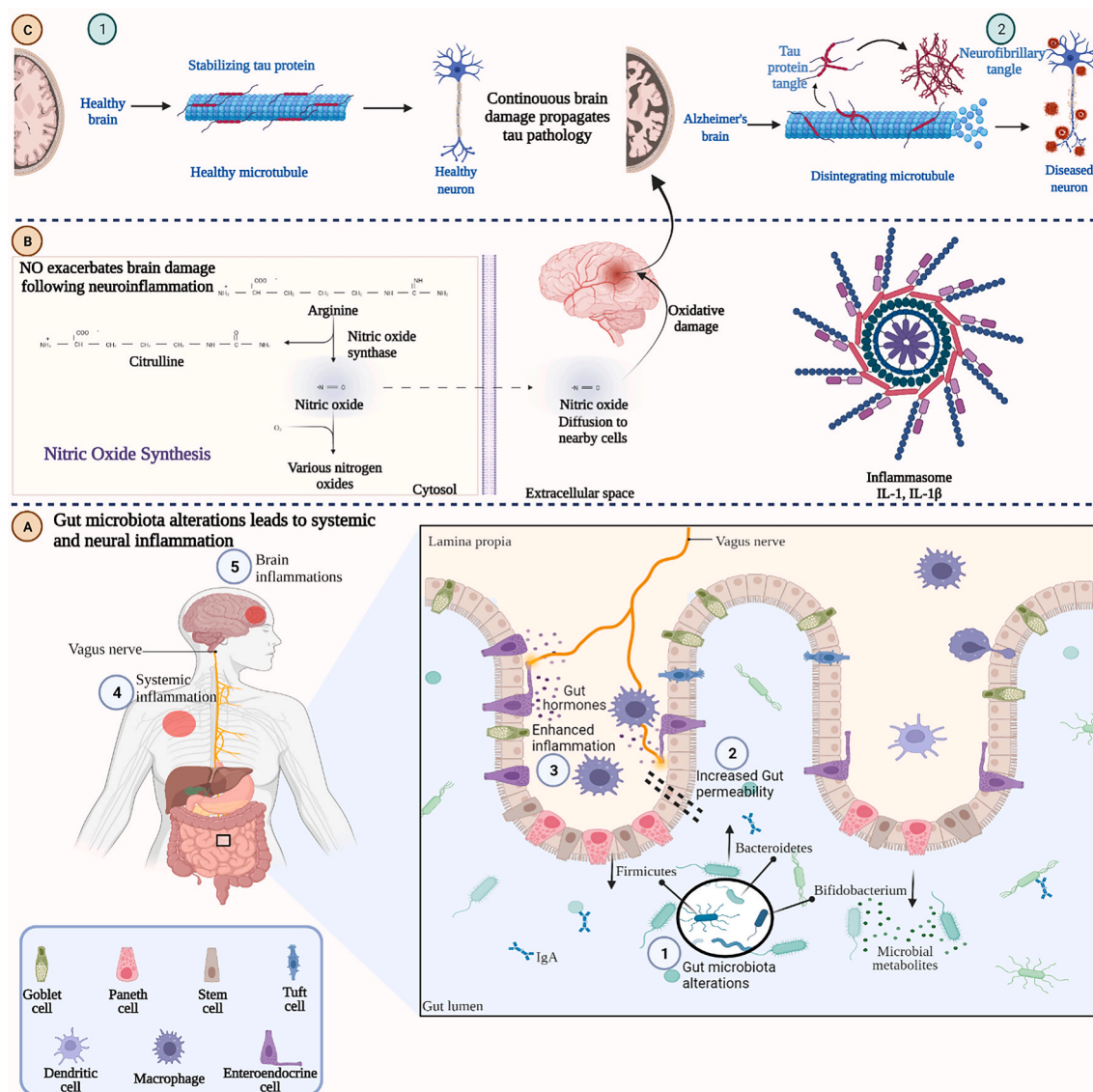
Fig. 4. An overview of tauopathy modulation via gut-brain-axis. A) The induction of neuroinflammation by the gut microbiota. 1) diminished *Firmicutes* and *Bifidobacterium* in line with increased *Bacteroidetes* levels are examples of gut microbiota alterations. 2) gut microbiota alterations lead to enhanced permeability of gut lining. 3,4) The enhanced permeability ends in enhanced gut and systemic inflammation. 5) Systemic inflammation causes brain inflammation. B) Nitric oxide pathway is a key regulator of brain damage following inflammation. C) The mentioned damages could end in tauopathy.

histone deacetylase (HDAC) [106,107]. SCFAs also have a crucial neuromodulatory function. Bioactive bacterial metabolites with anti-inflammatory properties are known to affect the intracellular potassium content in cell signaling systems. These metabolites can also directly affect the neurochemistry of the brain by controlling the expression of the tryptophan hydroxylase gene [108]. SCFAs have the ability to activate gastrointestinal endocrine cells to synthesize neuroactive substances such as histamine, serotonin, γ-aminobutyric acid, β-alanine, leptin, and glucagonlike peptide-1 (GLP-1) [109]. Using SCFAs or their derivatives therapeutically in inflammatory in vivo settings has been the goal of multiple studies. In an earlier study on inflammatory bowel disease (IBD), intestinal bacterial growth, laminin restoration, epithelial cell proliferation, and IBD symptoms were all improved by introducing SCFAs in a diet, including resistant starch (1.53 kg/10 kg of food) [110]. Another study on IBD model rats represented that the activities of Myeloperoxidase (MPO) and NO synthase were reduced, colonic glutathione levels were restored, and TNF-α concentrations were reduced [111]. The majority of human clinical investigations on microbiome modification have recruited healthy volunteers and elderly adults with cognitive deficits, given that AD, insulin resistance, diabetes, overweight, and cardiovascular disease are all closely connected and that preventative strategies are urgently needed [112]. Significant differences between the gut microbiota of people with mental illness (MCI) and cognitively normal persons have previously been found. These differences have unveiled the distinct gut microbiome patterns associated with MCI, which correlate with Aβ, total tau, and phosphorylated tau levels in the CSF fluid [113]. Within the same research, a modified Mediterranean ketogenic diet improved AD biomarker in the CSF of patients receiving treatment for mild cognitive impairment by altering the abundance of Enterobacteriaceae, Akkermansia, Slackia, Christensenellaceae, and Erysipelotriaceae and decreasing Bifidobacterium and Lachnobacterium [113]. Probiotics have been suggested to suppress acetylcholinesterase and antioxidant activity, hence reducing LPS-induced neuroinflammation and memory impairments [114]. As reported previously, supplementation with Lactobacilli and Bifidobacteria-based probiotics also enhanced Mini-Mental State Examination (MMSE) scores in AD patients in a clinical investigation [86]. According to another study, B. longum probiotic

supplementation decreased stress and enhanced cognitive function in healthy adult participants [115]. In this regard, utilizing probiotics, prebiotics, and other dietary interventions to change the composition of the gut microbiota is a promising and long-term strategy. Considering that probiotics, prebiotics, and synbiotics are relatively cheap and easy to administer, dietary interventions are often safer and more efficient than drug-based regimens.

Fecal microbiota transplantation is commonly used in animal models to study the pathogenic mechanisms of neurodegenerative diseases. Several cases of individuals with PD, multiple sclerosis, and autism spectrum disorders have demonstrated the therapeutic potential of fecal microbiota transplantation as an innovative approach to treating these diseases. However, the efficacy of this approach in treating AD has yet to be established [116]. On the other hand, antibiotic treatment is another approach for gut microbiota regulation, and it can be used to treat small intestinal bacterial overgrowth (SIBO) and pathogenic strain colonization. As represented in a previous prospective controlled study, the increased prevalence of SIBO in PD patients was confirmed, and an interplay between SIBO and motor instability was established, which also showed that SIBO elimination reveals a meaningful clinical impact [117].

The present study could not provide insights on specific molecular and immunology-therapeutics to target microbiota. It is recommended that future research utilizes new drug design techniques such as in silico design of candidates to target key microorganisms. This could boost the emergence of clinically efficient drugs for AD management in the long term [118,119]. Finally, we believe it is important to implement novel concepts in AD research to classical university teaching with good support system. E-learning technologies in this regard are vital. A good learning system could be used to increase patient compliance AD clinical trials as well. There are numerous examples for utility of these elements in other fields [120–123]. Another creative question could be "Do internet-delivered methods of cognitive enhancement influence the gut-brain axis?". While this is not evidence for this and it is far-fetched to estimate if there is any relationship in this regard, it could be interesting to study for future research as the role of virtual technology in modifying cognition is prominent in the present century.

5. Conclusion

AD is the most widespread and irreversible form of dementia, and finding a decisive therapeutic solution is a major current issue. There is mounting evidence that the gut microbiota might play a significant role in the pathogenesis of AD. The gut microbiota, which produces a lot of amyloids, LPS, and other toxins, may play a role in systemic inflammation and the breakdown of physiological barriers. Dysbiosis, or changes in the volume and composition of the microbiome, has been related to immunological, endocrine, and neurological system diseases, including mood swings, sadness, increased vulnerability to stress, and autistic tendencies. It has been shown that an imbalance in the gut microbiota, known as dysbiosis, can increase the risk of developing AD. Various factors, including lifestyle, geography, medication use, and dietary choices, can cause this imbalance. Meanwhile, an increasing number of research papers emphasize the critical involvement of peripheral infections and intestinal bacterial flora in the microbiome-gut-brain axis' physiological function. In both health and disease, the microbiome regulates the CNS's basic functions, immunity, and behavior. Early human research revealed that changing the microbiome with beneficial bacteria or probiotics could affect brain function, particularly cognitive abilities. Identifying gastrointestinal microbes through metagenomics and metabolomics approaches has enabled a more nuanced exploration of the interactions between host and microbiome. Developing functional diets and leveraging the intestinal microbiome to enhance the results of pharmaceutical therapy for a range of illnesses will be made possible by a deeper comprehension of the reciprocal communication between the brain and microbiota, as well as

the function of particular probiotic bacteria. Finally, the focus of new approaches appears to be on studying the potential neuroprotective effects of disease-modifying medications during the presymptomatic stages of AD, using biomarkers to predict disease progression before overt dementia occurs.

Availability of data and materials

Not applicable.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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