Journal of Medical Bacteriology

# The Role and Relationship of Different Bacteria in Alzheimer's Disease: Effects; Pathogenesis; Complication

*Mahdi Bozorgi [1#], Mohana Heydari [2#], Mobina Niknian [3], Atefeh Khodayar [4], Yeganeh Ghafarli [5], Forozan Chamani [6], Fatemeh Mahdavinasab [7], Najmeh Yazdekhasti [8], Roya Haghighatjo [9*], Yalda Malekzadegan [10], Reza Yekani [11], Mohammad Ebrahim Karimbakhsh [12*], Saina Najafi [6*], Delaram Jafari [13*]*

*1 Kashan University of Medical Sciences.*

*2 Microbiology Department, Faculty of cellular and Molecular Biology, Islamic Azad University of Hamedan, Hamedan, Iran.*

*3 Student Research Committee, Kurdistan University of Medical Science, Sanandaj, Iran.*

*4 Department of Microbiology Tehran Medical Sciences Islamic Azad University, Tehran, Iran.*

*5 Department of Biology, Central Tehran Branch, Islamic Azad University, Tehran, Iran.*

*6 Department of Microbiology, Faculty of Medicine, Ahvaz Jundishapur university of Medical Science, Ahvaz, Iran.*

*7 Department of Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.*

*8 Department of Physical education, Esfahan branch, Islamic azad University, Esfahan, Iran.*

*9 Nursing and Midwifery Sciences, Najafabad Branch, Islamic Azad University, Najafabad, Iran.*

*10 Department of Microbiology and Parasitology, School of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran.*

*11 Department of Biochemistry and Biophysics, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.*

*12 Department of Medical Microbiology and Virology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.*

*13 Department of Cell and Molecular Biology, Faculty of Advanced Science and Technology, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.*

**ARTICLE INFO**

***Article type:***
Review Article

***Article history:***
Received 01 Feb 2025
Revised 28 Feb 2025

**ABSTRACT**

***Background:*** The Alzheimer's association restated the necessity of the brain gut axis within the context of studying the disease. With its broad-spectrum impact cutting across mnemonics, degeneration of cortex, and neurology, Alzheimer's disease is known as a neurodegenerative disease. Rising gudiance implicate AD as a progressive disease of the Gut microbe dysbiosis with the gut ecosystem destruction resulting in the cascade of neuroinconsistency, accumulation of amyloid-β,

| | | | |
|---|---|---|---|
| Accepted | 26 | Mar | 2025 |
| Published | 05 | May | 2025 |

***Keywords:***
*Alzheimer's disease, Bacteria, Gut Microbiota*.

*Corresponding Authors:
Saina Najafi: Department of Microbiology, Faculty of Medicine, Ahvaz Jundishapur university of Medical Science, Ahvaz, Iran.. *Tel*: +98-61-32215689, *E-mail:* najafsaina4@yahoo.com
Mohammad Ebrahim Karimbakhsh: Department of Medical Microbiology and Virology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran. *Tel*: +98-15-13452387, *E-mail:* mohammadkarimbakhsh1@gmail.com
Delaram Jafari: Tehran Medical Sciences Azad University Cell and Molecular Biology. *Tel*: +98-21-235257186, *E-mail:* university.ac66@gmail.com
± Mahdi Bozorgi, Mohana Heydari are co-first authors.

compromise of blood brain barrier, and the impairment. Metabolic aberration along with the inflammation caused by microbes such as *Chlamydia pneumoniae*, *Helicobacter pylori* and *Porphyromonas gingivalis* have advanced the degeneration of the Alzhemers patient. The cyclic attack set forth by the bacterials in the brain together with the systemic cytokine secretion creates an inflammation and neurodegeneration enhancing loop which cannot be broken. Such potential microb target therapies which aim not on the total elimination of the disease but on its on-going replacement are being later on presented within this review alongside with detailed explanation of the above mechanism.

***Conclusion***: Alzheimer's disease relates to gut-brain axis; gut issues can cause inflammation and cognitive problems. Certain bacteria may worsen AD. Microbiome therapies could help; future research should target key microbial strains and conduct clinical trials for treatments.

- ***Please cite this paper as:*** Bozorgi M, Heydari M, Niknian M, Khodayar A, Ghafarli Y, Chamani F, Mahdavinasab F, Yazdekhasti N, Haghighatjo R, Malekzadegan Y, Yekani R, Karimbakhsh ME, Najafi S, Jafari D. The Role and Relationship of Different Bacteria in Alzheimer's Disease: Effects; Pathogenesis; Complication. *J Med Bacteriol.* 2025; **13** (2): pp.108-117. DOI: 10.18502/jmb.v13i2.18662

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the early extracellular deposition of diffuse and neuritic plaques (composed of amyloid-β peptides) followed by the intracellular formation of neurofibrillary tangles (formed by hyperphosphorylated tau protein) in the brain (1). While these aggregates represent the main pathological hallmarks of AD, the disease involves various other pathophysiological changes and processes, such as neuroinflammation, synaptic dysfunction, and metabolic dysregulation. Despite tremendous research efforts to understand the pathogenesis of the disease, the cause-and-effect relationships of the complex biological processes involved in AD are not fully understood. The lack of clarity poses significant challenges for developing effective treatments, highlighting the need for a comprehensive and multidimensional approach to tackle the disease (2).

AD is an age-associated neurodegenerative disorder characterized by loss of cognitive function. The cognitive functions include behavioral changes, reduced mental capacity to learn, and memory deficit leading to dementia. AD is caused by the accumulation of beta-amyloid (Aβ) fibrils, oligomers, and neurofibrillary tangles (NFTs) in the hippocampus, cerebral cortex, and other areas of the brain (3).

Probiotics are living microorganisms that promote health benefits when consumed in adequate quantity. They regulate the level of pH in the body, help preserve the integrity of the intestinal lining, act as antibiotics, and enhance the brain-derived neurotrophic factor (3). These neurotrophic factors are made up of a type of protein in the brain that facilitates the survival and differentiation of neurons. Hence, it plays a crucial role in neurological development. Learning disabilities and memory impairments are some of the common issues that tend to arise if these factors are missing from the brain (4).

The effects of probiotics on the central nervous system (CNS) are achieved by alteration of gut microbiota, by increasing the diversity of the good bacterial composition, thereby boosting CNS

functions. Apart from brain neurotrophic factor, probiotics tend to provide good prognosis in curing memory deficits and psychiatric disorders by directly modifying brain biochemical components such as serotonin, γ-aminobutyric acid (GABA) and dopamine (5).

General discussions about the relationship between the gut microbiota and AD have already been reviewed in our previous review article. In this narrative review, we will briefly summarize and update the recent progress in the field and discuss emerging questions from the new observations that need further elucidation. Finally, we will discuss possibilities for disease modification by leveraging the capabilities of the gut microbiota. The presence of lipopolysaccharide (LPS) by gram-negative bacteria and the increased buildup of amyloids in the human gut are critical in the etiopathogenesis of neurological disorders characterized by amyloidogenic features (6, 7).

*Alzheimer's disease*

AD presents with diverse symptoms and progression patterns. Early stages often include amnestic mild cognitive impairment (MCI), strongly linked to underlying AD pathology, which significantly raises the risk of progressing to dementia. Biomarkers such as amyloid PET, CSF (cerebrospinal fluid) analysis, and neuroimaging help predict progression risks. Early signs of AD, often appearing years before diagnosis, include mood changes, anxiety, apathy, and sleep disturbances. In later stages, symptoms like impaired judgment, confusion, aggression, and neuropsychiatric issues emerge. Recognizing these signs early and conducting appropriate evaluations are essential for effective management (8).

AD is strongly linked to aging, with about 90% of cases occurring in individuals aged 65 and older. Its prevalence doubles every five years, highlighting a time-dependent, exponential increase. This association suggests that as people age, they face a significantly higher risk of developing AD, alongside other neurodegenerative diseases like Parkinson's. Theories of aging provide a framework to understand how biological changes with age increase susceptibility to such conditions. These findings emphasize the broader vulnerability of the elderly to age-related diseases, even if not all individuals manifest them. The rising prevalence of AD and other dementias in aging populations calls for intensified research and healthcare strategies to address these challenges. Understanding the mechanisms of aging and their relationship with neurodegeneration is critical for developing preventative and therapeutic interventions to improve the health and quality of life of older adults (9).

AD is the most prevalent form of dementia, characterized as a progressively worsening neurodegenerative disorder. It is marked by the presence of neurotic plaques and neurofibrillary tangles caused by the accumulation of Aβ in brain regions most affected by the disease, including the medial temporal lobe and neocortical structures (10).

Two distinct neuropathological changes are associated with AD progression and symptomatology. The first category, termed positive lesions, arises from the accumulation of pathological structures such as neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads, and other deposits found in the brains of individuals with AD. The second category, negative lesions, is characterized by significant brain atrophy resulting from the loss of neurons, neuropil, and synapses. Additional contributors to neurodegeneration include neuroinflammation, oxidative stress, and damage to cholinergic neurons (11).

AD is recognized as a multifactorial disease linked to various risk factors, including advancing age, genetic predisposition, head trauma, vascular conditions, infections, and environmental exposures (e.g., heavy metals and trace metals). Despite extensive research, the primary cause of the pathological changes in AD—such as Aβ accumulation, neurofibrillary tangles, and synaptic loss—remains unclear. While several hypotheses have been proposed, two are considered

predominant: one attributes the disease to impairments in cholinergic function as a key risk factor, while the other suggests that disruptions in amyloid-protein production and processing act as the primary triggers. However, no universally accepted theory currently explains the pathogenesis of Alzheimer's disease (11).

*Related and effective bacteria in Alzheimer's disease*

AD, which affects approximately 50,000,000 people worldwide, is the most frequent cause of dementia, constituting a real global health problem (12). The disease is characterized by the progressive deposition of Aβ plaques and tangles of hyperphosphorylated tau neurofibrils, leading to neuroinflammation and progressive cognitive decline (13). Synaptic dysfunction and neuronal death are at least in part due to the excessive or non-resolving activation of the immune response and any infections or traumatic events affecting the brain (traumatic brain injury) can interfere with central immune homeostasis and accelerate the progression of the disease (14). Although several hypotheses have been formulated about the causes of AD pathogenesis and progression, both the onset and the evolution of the disease remain not entirely clear. Therefore, although different therapeutic options have been proposed, many have failed in clinical trials and have not been found to produce significant benefits (15-17). It is widely thought that an early diagnosis could be essential to act at the earliest disease stages, but effective and reproducible biomarkers are still far from clinical application (18, 19).

AD is a deadly neurodegenerative illness that mostly impacts the elderly and is a major health concern for the geriatric population worldwide. AD prevalence increases substantially with age, reaching 50% in 85-year-olds (12). AD is expected to become significantly more common in the geriatric population as the median life expectancy grows. The worldwide incidence of dementia is about 24 million, and it is estimated to surge fourfold by the year 2050 (13). As such, there is a need for modern treatment options given the probable risk factors for AD and treatments that can delay AD onset and occurrence (14). About 5000 species of gut microorganisms, notably Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, have been reported in the human intestinal lumen. These microbes play crucial roles in gut digestion and absorption functions (15). Among these microorganisms, in particular, Chlamydia pneumoniae and Spirochetes have multiple research findings pointing to their significance in the pathogenesis of AD (16).

According to the AD pathogen hypothesis, pathogens operate as triggers, in conjunction with genetic variables, in starting the accumulation and/or processing of Aβ, hyperphosphorylated tau proteins, and inflammation in the brains of AD patients (17). HSV1 and other pathogens, such as C. pneumoniae and Spirochetes, are commonly found in the brains of AD patients, as these may evade the host immune response and infect the brain (18, 19). In vitro and animal studies have demonstrated that pathogens facilitate amyloid plaque formation and increased levels of hyperphosphorylated tau (20, 21). Such pathogens induce a glial inflammatory response, damaging and killing neurons directly and indirectly (22). In the brains of AD patients, there are major inflammatory cascades (23, 24), and these pathways combine to cause further neurodegeneration and disease progression. Neurodegenerative illnesses occur and progress due to genetic and lifestyle factors and are significantly influenced by gene–environment interactions (25). The human gut is a reservoir of several bacterial species, and the human body is home to a variety of microorganisms, including bacteria, viruses, archaea, and microeukaryotes (26, 27).

Interestingly, patients with neurological, autoimmune, metabolic, and cancer illnesses have distinct gut microbiota compared with healthy individuals. The enteric nervous system (ENS) and central nervous system (CNS) communicate bidirectionally through the gut–brain axis(27, 28).

*Role and relationship of different bacteria in Alzheimer's Disease*

Alzheimer's Disease and Bacterial Infection

Bacteria, particularly Porphyromonas gingivalis (P. gingivalis), which is known for causing gum disease, have been proposed as possible contributors to Alzheimer's disease. Research indicates that infection with P. gingivalis in mice leads to higher levels of Aβ in peripheral macrophages, and this bacterium has also been detected in postmortem brain tissues of AD patients (29). Research suggests that individuals with AD have approximately seven times more oral bacteria in their brains compared to those who are cognitively healthy. Despite this, there is still ongoing debate regarding whether these microbes simply invade the brain or establish an ecosystem, as the concept of microbes existing within the brain remains controversial (30).

The influence of *P. gingivalis* on AD is thought to involve the production of toxic enzymes called gingipains, which have been found to correlate with tau pathology in AD patients (31). Furthermore, inhibiting gingipains has demonstrated neuroprotective effects in mice infected with *P. gingivalis* by reducing Aβ levels and markers of neuroinflammation. However, clinical trials of a drug targeting *P. gingivalis* did not yield significant benefits and were stopped due to concerns about liver toxicity (32).

Other bacterial species are also considered potential contributors to AD. For instance, the DNA of *Chlamydia pneumoniae*, a common respiratory bacterium in the elderly, has been discovered in the brain tissue of 80% of AD patients (33). Recent studies in mice have demonstrated that *Chlamydia pneumoniae* can infect the central nervous system, potentially traveling along the olfactory and trigeminal nerves (34).

In addition, *Borrelia burgdorferi*, the bacterium that causes Lyme disease, has been proposed as a contributor to the development of AD. This bacterium has been found in association with plaques in AD patients, and studies have shown that its infection of mammalian cells in vitro results in elevated levels of beta-amyloid (Aβ) and phosphorylated tau (35).

*Fusobacterium nucleatum*, a prevalent bacterium associated with periodontitis, has been linked to AD. Importantly, this causal relationship is supported by evidence demonstrating worsened cognitive symptoms, increased Aβ accumulation, and tau phosphorylation in 5XFAD mice that were topically infected with F. nucleatum to induce periodontitis (36).

Gut Microbiota

Recent research indicates that gastrointestinal bacteria could influence the development of AD (37). The gut microbiome is mainly composed of various bacterial species, including *Lactobacillus*, Bifidobacteria, Verrucomicrobia, Spirochetes, Proteobacteria, Fusobacteria, Firmicutes, and Cyanobacteria. Evidence suggests that bacterial infections may initiate pathological processes linked to AD (38).

Bacteria such as *Helicobacter pylori*, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Escherichia coli* (*E. coli*), *Shigella*, *E. rectale*, and *Bacteroides fragilis* have been linked to AD (39). These bacterial species can work together to heighten the infection burden in AD patients. One way these bacteria may cause pathological changes is through the release of neurotoxic substances (40).

*Lactobacillus* and actinobacteria can convert glutamate into gamma-aminobutyric acid (GABA) in the central nervous system. Elevated GABA levels in the gut can lead to higher GABA levels in the central nervous system, which might cause memory issues, depression, and problems with synapse formation (41).

Gut bacteria release inflammatory agents, beta-amyloid protein, and neurotoxic substances that disrupt the immune system. These bacteria produce endotoxins called lipopolysaccharides (LPS), found in the outer membrane of Gram-negative bacteria, which are common in the gut and other parts of the body. An imbalance in gut

microbiota is linked to diseases like AD. This imbalance weakens gut barrier function and increases intestinal permeability. When the gut barrier is compromised, microbial metabolites can enter the bloodstream. If the blood-brain barrier (BBB) is also compromised, proinflammatory cytokines can reach the central nervous system, causing neuroinflammation by activating microglia and astrocytes (40).

Role of Gut Microbiota in Alzheimer's Disease (AD) Pathogenesis

Studies have shown that the gut microbiome plays a role in the development of AD in both animals and humans. Research has found connections between specific microbial organisms and CSF biomarkers related to AD. For example, lower levels of biomarkers such as the Aβ42/Aβ40 ratio and phosphorylated tau (p-tau) are linked to Clostridiaceae and Erysipelotrichaceae, whereas higher levels of these biomarkers are associated with *Blautia* and *Bacteroides* species (42).

Changes in gut microbiota at the phylum level, including variations in Firmicutes, Proteobacteria, and Bacteroidetes, have been observed in AD patients and animal models. Clinical studies have shown that individuals with amyloidosis have distinct gut microbiota compositions compared to those without the condition. Additionally, higher levels of proinflammatory cytokines such as IL-6, CXCL2, NLRP3, and IL1β have been found in amyloid-positive patients (42).

Role of gram-negative bacteria in Alzheimer's Disease (AD) Pathogenesis

Gram-negative bacteria release outer membrane vesicles (OMVs) during both planktonic growth and in surface-attached biofilm communities. These small, spherical vesicles detach from the outer cell membrane and contain LPS, peptidoglycan (PG), proteins, DNA, RNA, and various virulence factors like enzymes and toxins (43, 44). OMVs are nanosized and carry higher concentrations of toxins and virulence factors compared to their parent bacteria (45). During infection, these vesicles deliver pathogenic factors to host cells and can bypass direct cell-to-cell contact (46). As a result, OMVs enable bacteria-

**Table 1.** Role of gram-negative bacteria in Alzheimer's Disease (AD) Pathogenesis.

| Bacteria | Effects on Alzheimer's Disease (AD) | Mechanism | References |
|---|---|---|---|
| *Porphyromonas gingivalis* | - Increased Aβ levels - Neuroinflammation | Production of toxic gingipains correlated with tau pathology | (1) |
| *Chlamydia pneumoniae* | - Cognitive decline - Infection of central nervous system | - Invasion through olfactory and trigeminal nerves | (2) |
| *Borrelia burgdorferi* | - Elevated Aβ and phosphorylated tau levels | - Association with amyloid plaques | (3) |
| *Fusobacterium nucleatum* | - Increased Aβ accumulation<br>- Worsened cognitive symptoms | - Induction of periodontitis | (4) |
| *Gut Microbiota* | - Memory issues<br>- Depression<br>- Disruption of immune system | - Production of inflammatory agents, beta-amyloid protein, and neurotoxic substances | (5-7) |
| *Helicobacter pylori* | - Increased intestinal permeability<br>-Neuroinflammation | - Production of endotoxins (LPS) | (8) |
| *Escherichia coli* | - Increased proinflammatory cytokines | - Production of LPS | (9) |
| *Bacteroides fragilis* | - Disruption of blood-brain barrier (BBB) | - Release of microbial metabolites | (10) |

host communication and can trigger disease processes even in the absence of live bacteria. Recent studies have associated OMVs with a variety of inflammatory diseases, including chronic inflammatory conditions, autoimmune disorders, and inflammation-related tumors. OMVs have been thoroughly studied for their roles in diseases such as periodontal disease, gastrointestinal inflammation (including inflammatory bowel disease), pulmonary inflammation, sepsis, and inflammation-related tumors. For instance, *F. nucleatum* OMVs increase osteoclast numbers and inflammatory cytokine production in gingival connective tissues, exacerbating periodontitis symptoms (47).

*Helicobacter pylori* (*H. pylori*) OMVs, containing virulence factors, are rapidly internalized by gastric epithelial cells, contributing to mucin barrier destruction and bacterial colonization in gastric diseases (43). OMVs from *P. gingivalis* significantly disrupt tight junction proteins in lung epithelial cells, causing cytotoxic effects and pulmonary inflammation(48, 49). *E. coli* OMVs increase the expression of IL-6, P-selectin, and intercellular adhesion molecules while significantly decreasing thrombomodulin, triggering the coagulation cascade. Additionally, small RNA23392 (sRNA-23392) packed in *P. gingivalis* OMVs promotes the migration and invasion of oral squamous cell carcinoma cells by targeting desmocollin-2 (50).

## Conclusion

Alzheimer's disease (AD) pathogenesis is strongly associated with the gut-brain axis, and gut microbiome dysbiosis is causative of neuroinflammation and cognitive impairment. The literature indicates that integrity compromise of this axis in association with inflammation, endothelial dysfunction, and amyloid β deposition propels neurodegeneration (51, 52). Certain bacterial infections, such as Chlamydia pneumoniae, Helicobacter pylori, and Porphyromonas gingivalis, have been seen to be involved in the aggravation of AD through chronically promoting inflammation and sustaining neuroinflammatory reactions (53). This indicates the involvement of microbial imbalance in AD development and onset. Precision microbiome therapies, such as probiotics, prebiotics, and antimicrobials, are promising in the restoration of microbial balance, the alleviation of inflammation, and the maintenance of cognitive health (54, 55). But there would need to be accurate application of antimicrobials to prevent disturbance of gut homeostasis that has an effect on disease outcome. The key focus for future studies would be to determine the most significant microbial strains, their metabolites, and their involvement in AD pathology. Clinical trials of microbiome-guided treatments will be vital in taking lab-based findings to clinic-based treatments. Because the gut-brain interaction is so pivotal in AD, microbiome-targeted strategies offer an intriguing avenue for the creation of new therapies.

## Acknowledegements

None.

## Funding Information

None.

## Ethics approval and consent to participate

None.

## Conflict of interest

None.

## References

1. Seo D-o, Holtzman DM. Current understanding of the Alzheimer’s disease-associated microbiome and therapeutic strategies. *Exper Mol Med* 2024; **56**(1):86-94.
2. Agirman G, Yu KB, Hsiao EY. Signaling inflammation across the gut-brain axis. *Science*

2021; **374**(6571):1087-92.
3. Fang Z, Li L, Zhao J, et al. Bifidobacteria adolescentis regulated immune responses and gut microbial composition to alleviate DNFB-induced atopic dermatitis in mice. *Eur J Nutr* 2020; **59**(7):3069-81.
4. Larroya-García A, Navas-Carrillo D, Orenes-Piñero E. Impact of gut microbiota on neurological diseases: Diet composition and novel treatments. *Crit Rev Food Sci Nutr* 2019; **59**(19):3102-16.
5. Wang H, Lee IS, Braun C, et al. Effect of probiotics on central nervous system functions in animals and humans: a systematic review. *J Neurogastroenterol Motil* 2016; **22**(4):589-605.
6. Seo DO, Holtzman DM. Gut microbiota: from the forgotten organ to a potential key player in the pathology of Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* 2020; **75**(7):1232-41.
7. Shoemark DK, Allen SJ. The microbiome and disease: reviewing the links between the oral microbiome, aging, and Alzheimer's disease. *J Alzheimers Dis* 2015; **43**(3):725-38.
8. Atri A. The Alzheimer's disease clinical spectrum: diagnosis and management. *Med Clin North Am* 2019; **103**(2):263-93.
9. Trevisan K, Cristina-Pereira R, Silva-Amaral D, et al. theories of aging and the prevalence of Alzheimer's disease. *Biomed Res Int* 2019; **2019**:9171424.
10. Harris JR. Protein aggregation and fibrillogenesis in cerebral and systemic amyloid disease: Springer Science & Business Media; 2012.
11. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules* 2020; **25**(24).
12. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; **366**(9503):2112-7.
13. Garbuz DG, Zatsepina OG, Evgen'ev MB. Beta amyloid, tau protein, and neuroinflammation: an attempt to integrate different hypotheses of Alzheimer's disease pathogenesis. *Mol Bio* 2021; 55:670-82.
14. Kamer AR, Craig RG, Dasanayake AP, et al. Inflammation and Alzheimer's disease: possible role of periodontal diseases. *Alzheimer's & Dementia* 2008; **4**(4):242-50.
15. Sochocka M, Donskow-Łysoniewska K, Diniz BS, et al. The gut microbiome alterations and inflammation-driven pathogenesis of Alzheimer's disease—a critical review. *Mol Neurobiol* 2019; **56**:1841-51.
16. Landry RL, Embers ME. Does dementia have a microbial cause? *NeuroSci* 2022; **3**(2):262-83.
17. Sait A, Angeli C, Doig AJ, et al. Viral involvement in Alzheimer's disease. *ACS Chem Neurosci* 2021; **12**(7):1049-60.
18. Wozniak M, Mee A, Itzhaki R. Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. *J Pathology* 2009; **217**(1):131-8.
19. Ashraf GM, Tarasov VV, Makhmutova A, et al. The possibility of an infectious etiology of alzheimer disease. *Mol Neurobiol* 2019; **56**(6):4479-91.
20. Miklossy J, Kis A, Radenovic A, et al. Beta-amyloid deposition and Alzheimer's type changes induced by *Borrelia spirochetes*. *Neurobiol Aging* 2006; **27**(2):228-36.
21. Wozniak MA, Itzhaki RF, Shipley SJ, et al. Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. *Neurosci Lett* 2007; **429**(2-3):95-100.
22. Ramesh G, Alvarez AL, Roberts ED, et al. Pathogenesis of lyme neuroborreliosis: *Borrelia burgdorferi* lipoproteins induce both proliferation and apoptosis in rhesus monkey astrocytes. *Eur J Immunol* 2003; **33**(9):2539-50.
23. Ho GJ, Drego R, Hakimian E, et al. Mechanisms of cell signaling and inflammation in Alzheimer's disease. *Curr Drug Targets Inflamm Allergy* 2005; **4**(2):247-56.
24. Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. *Cold Spring Harb Perspect Med* 2012; **2**(1):a006346.
25. Ajayi A, Jolaiya T, Smith S. Evolving technologies in gastrointestinal microbiome era and their potential clinical applications. *J Clin*

*Med* 2020; **9**(8):2565.
26. Kho ZY, Lal SK. The human gut microbiome - a potential controller of wellness and disease. *Front Microbiol* 2018; **9**:1835.
27. Khaledi M, Sameni F, Gholipour A, et al. Potential role of gut microbiota in major depressive disorder: A review. *Heliyon* 2024; **10**(12):e33157.
28. Singh R, Zogg H, Wei L, et al. Gut microbial dysbiosis in the pathogenesis of gastrointestinal dysmotility and metabolic disorders. *J Neurogastroenterol Motil* 2021; **27**(1):19-34.
29. Beydoun MA, Beydoun HA, Hossain S, et al. Clinical and bacterial markers of periodontitis and their association with incident all-cause and alzheimer's disease dementia in a large national survey. *J Alzheimers Dis* 2020; **75**(1):157-72.
30. Nie R, Wu Z, Ni J, et al. *Porphyromonas gingivalis* infection induces amyloid-β accumulation in monocytes/macrophages. *J Alzheimers Dis* 2019; **72**(2):479-94.
31. Kennedy KM, de Goffau MC, Perez-Muñoz ME, et al. Questioning the fetal microbiome illustrates pitfalls of low-biomass microbial studies. *Nature* 2023; **613**(7945):639-49.
32. Dodiya HB, Kuntz T, Shaik SM, et al. Sex-specific effects of microbiome perturbations on cerebral Aβ amyloidosis and microglia phenotypes. *J Exp Med* 2019; **216**(7):1542-60.
33. Chacko A, Delbaz A, Walkden H, et al. *Chlamydia pneumoniae* can infect the central nervous system via the olfactory and trigeminal nerves and contributes to Alzheimer's disease risk. *Sci Rep* 2022; **12**(1):2759.
34. Gérard HC, Dreses-Werringloer U, Wildt KS, et al. *Chlamydophila* (*Chlamydia*) *pneumoniae* in the Alzheimer's brain. *FEMS Immunol Med Microbiol* 2006; **48**(3):355-66.
35. Senejani AG, Maghsoudlou J, El-Zohiry D, et al. *Borrelia burgdorferi* co-localizing with amyloid markers in alzheimer's disease brain tissues. *J Alzheimers Dis* 2022; **85**(2):889-903.
36. Williams ZAP, Lang L, Nicolas S, et al. Do microbes play a role in Alzheimer's disease? *Microb Biotechnol* 2024; **17**(4):e14462.
37. Faruqui NA, Prium DH, Mowna SA, et al. Gut microorganisms and neurological disease perspectives. *Future Neurology* 2021; **16**(1):FNL53.
38. Dalile B, Van Oudenhove L, Vervliet B, et al. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepatol* 2019; **16**(8):461-78.
39. Tang W, Zhu H, Feng Y, et al. The impact of gut microbiota disorders on the blood-brain barrier. *Infect Drug Resist* 2020; **13**:3351-63.
40. Rutsch A, Kantsjö JB, Ronchi F. The gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology. *Front Immunol* 2020; **11**:604179.
41. Dissanayaka DMS, Jayasena V, Rainey-Smith SR, et al. The role of diet and gut microbiota in alzheimer's disease. *Nutrients* 2024; **16**(3).
42. Cattaneo A, Cattane N, Galluzzi S, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging* 2017; **49**:60-8.
43. González MF, Díaz P, Sandoval-Bórquez A, et al. *Helicobacter pylori* outer membrane vesicles and extracellular vesicles from *Helicobacter pylori*-infected cells in gastric disease development. *Int J Mol Sci* 2021; **22**(9).
44. Furuyama N, Sircili MP. Outer membrane vesicles (omvs) produced by gram-negative bacteria: structure, functions, biogenesis, and vaccine application. *Biomed Res Int* 2021; **2021**:1490732.
45. Zhang Z, Liu D, Liu S, et al. The role of *Porphyromonas gingivalis* outer membrane vesicles in periodontal disease and related systemic diseases. *Front Cell Infect Microbiol* 2020; **10**:585917.
46. Behrouzi A, Vaziri F, Riazi Rad F, et al. Comparative study of pathogenic and non-pathogenic *Escherichia coli* outer membrane vesicles and prediction of host-interactions with TLR signaling pathways. *BMC Res Notes* 2018; **11**(1):539.
47. Chen G, Sun Q, Cai Q, et al. Outer membrane vesicles from fusobacterium nucleatum switch m0-like macrophages toward the m1 phenotype

to destroy periodontal tissues in mice. *Front Microbiol* 2022; **13**:815638.
48. Ho MH, Chen CH, Goodwin JS, et al. Functional advantages of *Porphyromonas gingivalis* vesicles. *PLoS One* 2015; **10**(4):e0123448.
49. He Y, Shiotsu N, Uchida-Fukuhara Y, et al. Outer membrane vesicles derived from *Porphyromonas gingivalis* induced cell death with disruption of tight junctions in human lung epithelial cells. *Arch Oral Biol* 2020; **118**:104841.
50. Chen S, Lei Q, Zou X, et al. The role and mechanisms of gram-negative bacterial outer membrane vesicles in inflammatory diseases. *Front Immunol* 2023; **14**:1157813.
51. Yang J, Liang J, Hu N, et al. The gut microbiota modulates neuroinflammation in alzheimer's disease: elucidating crucial factors and mechanistic underpinnings. *CNS Neurosci Ther* 2024; **30**(10):e70091.
52. Sochocka M, Donskow-Łysoniewska K, Diniz BS, et al. The gut microbiome alterations and inflammation-driven pathogenesis of alzheimer's disease-a critical review. *Mol Neurobiol* 2019; **56**(3):1841-51.
53. Park G, Kadyan S, Nagpal R, editors. 2960. A Gut Pathobiont Triggers Neuroinflammation and Neurocognitive Impairment via Breaching the Gut-Brain Axis in a Preclinical Model of Alzheimer's Disease: From Microbial Pathogenesis to Neuropathogenesis. Open Forum Infectious Diseases; 2023: Oxford University Press US.
54. Bedon JCR, Altamirano MBA, Lasluiza MWC, et al. The relationship between the gut microbiome and the development of Alzheimer's disease: a review. *Inter J Health Sci* 2024; **4**:90.
55. Wojtuś M, Tomaszuk S, Wąsik K. pathogenesis and treatment of Alzheimer The role of the gut microbiota in the disease–review. *J Edu Health Sport* 2024; **51**:11-20.
56. Beydoun MA, Beydoun HA, Hossain S, et al. Clinical and bacterial markers of periodontitis and their association with incident all-cause and alzheimer's disease dementia in a large national survey. *J Alzheimers Dis* 2020; **75**(1):157-72.
57. Gérard HC, Dreses-Werringloer U, Wildt KS, et al. *Chlamydophila* (*Chlamydia*) *pneumoniae* in the Alzheimer's brain. *FEMS Immunol Med Microbiol* 2006; **48**(3):355-66.
58. Senejani AG, Maghsoudlou J, El-Zohiry D, et al. *Borrelia burgdorferi* co-localizing with amyloid markers in alzheimer's disease brain tissues. *J Alzheimers Dis* 2022; **85**(2):889-903.
59. Williams ZAP, Lang L, Nicolas S, et al. Do microbes play a role in Alzheimer's disease? *Microb Biotechnol* 2024; **17**(4):e14462.
60. Faruqui NA, Prium DH, Mowna SA, et al. Gut microorganisms and neurological disease perspectives. *Future Neurology* 2021; **16**(1):FNL53.
61. Dalile B, Van Oudenhove L, Vervliet B, et al. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat Rev Gastroenterol Hepato*l 2019; **16**(8):461-78.
62. Tang W, Zhu H, Feng Y, et al. The Impact of gut microbiota disorders on the blood-brain barrier. *Infect Drug Resi*st 2020; **13**:3351-63.
63. González MF, Díaz P, Sandoval-Bórquez A, et al. *Helicobacter pylori* outer membrane vesicles and extracellular vesicles from *Helicobacter pylori*-infected cells in gastric disease development. *Int J Mol Sci* 2021; **22**(9).
64. Chen S, Lei Q, Zou X, et al. The role and mechanisms of gram-negative bacterial outer membrane vesicles in inflammatory diseases. *Front Immunol* 2023; **14**:1157813.
65. Rutsch A, Kantsjö JB, Ronchi F. The Gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology. *Front Immuno*l 2020; **11**:604179.