



# Neuromicrobiology: Alzheimer's Disease and Gut Microflora

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**ABSTRACT:** Alzheimer's disease (AD) is a neurodegenerative condition related with ageing and marked by cognitive decline. The cognitive functions include altered behavior, a diminished ability to learn, and memory loss that results in dementia. The hippocampus, cerebral cortex, and other parts of the brain develop beta-amyloid (A) fibrils, oligomers, and neurofibrillary tangles (NFTs), which are the root cause of AD. Studies that are now available indicate that gene mutation, protein aggregation, excitotoxicity, protein aggregates, oxidative stress, and mitochondrial dysfunction are the main mechanisms contributing to the pathogenesis of AD. A collection of microorganisms needed to support the digestive system makes up the gut microbiota. The microbiota-gut-brain axis is a dynamic, bidirectional communication system that connects the functions of the peripheral intestine with cognitive and emotional awareness. This chapter encompasses around the role of gut microflora in Alzheimer's Disease and also the role of probiotics, prebiotics and synbiotics in AD.

**Keywords:** Alzheimer's disease (AD), beta-amyloid, oxidative stress, microbiota-gut-brain axis, Probiotics.

## INTRODUCTION

According to Deture and Dickson (2019), Alzheimer's disease (AD) is a progressive neurological disorder characterised by neuronal degeneration, memory loss, learning disabilities, and major changes in personality and behavioural activities. Although there aren't many cases of AD in young people, it is an age-related disease that has been reported to affect 10% of people between the ages of 65 and 75 and about 32% of people over the age of 80 (Alzheimer's Association, 2016). Due to the complexity of AD's pathogenesis, no treatment has yet been found to stop the disease's progression. One of the causes of cholinergic dysfunction has been linked to increased acetylcholinesterase activity and decreased levels of the neurotransmitter acetylcholine [1]. According to Selkoe

and Hardy (2016), intracellular neurofibrillary tangles (NFTs) containing hyperphosphorylated tau (tubulin associated unit) protein and extracellular b-amyloid senile plaques composed of amyloid b (Ab) peptides are pathological features of Alzheimer's disease (AD), a complex neurodegenerative condition. According to Chakrabarti (2015), sporadic AD is thought to be the main cause of dementia in people. The "infection" hypothesis of AD aetiology postulates that infection by bacteria, fungi, and viruses may cause the beginning of sporadic AD, perhaps leading to systemic inflammation. The most common pathogenic potential microorganisms mentioned include *Chlamydia pneumoniae* (pulmonary bacteria), *Porphyromonas gingivalis* (periodontal bacteria), *Helicobacter pylori* (gut bacteria), as well as spirochaetes, fungi, viruses, and protozoa. According to Dando *et al.* (2014), these bacteria can enter the CNS directly through the trigeminal nerve, the oral-olfactory system, or the systemic circulation [2].

### **Alzheimer's disease and the microbiota-gut-brain axis**

Extracellular amyloid-beta (A $\beta$ ) plaques made of amyloid and intracellular neurofibrillary tangles made of hyperphosphorylated tau contribute to the progression of AD, which is a neurodegenerative condition. It is believed that as people age, genetic and environmental variables start to play a bigger role in the onset of AD. The notion that AD is a "systemic disease" has significantly gained ground, especially recently. One of the most significant research areas at the moment is the impact of the gut microbiota on human health. The microbiota-gut-brain axis and cognitive processes are significantly correlated, according to recent studies. The impact of the gut microbiota on the progression of the illness has gained widespread interest because AD is a condition marked by cognitive impairment. In addition, a number of recent investigations have demonstrated that AD is intimately linked to dysbiosis in the gut microbiota and can begin in the gut (Fig.1). The microbiota, gut, and brain are connected by a complex, multidirectional interconnection system that allows for bidirectional communication between them. This system consists of the neuroendocrine (hypothalamus-pituitary-adrenal axis (HPA)), immune (gastrointestinal and neural-immune system), neuroendocrine (sympathetic and parasympathetic nervous system), and metabolic systems. The brain is reached by cytokines and other immunological signals as well as metabolites, neurotransmitters, and hormones produced by the microbiota through neurological and humoral routes. Some significant metabolites produced by the microbiota are linked to alterations. Neurotransmitters as serotonin, dopamine, -aminobutyric acid (GABA), and short-chain fatty acids (SCFAs) are produced by the microbiota and are linked to changes in brain activities. Additionally, it has been claimed that the microbiota plays a role in the development and operation of microglia. It has been noticed that the production of amyloid plaques and the activation of neuroinflammation are both influenced by oxidative stress, certain microbiome alterations, and AD. The ability of the microorganisms is related to how the microbiota affects the pathogenesis of AD. It contains metabolites, amyloid, and high concentrations of lipopolysaccharides (LPS), which cause cerebrovascular degeneration and inflammation in the central nervous system (CNS). The viable count of intestinal Bifidobacterium, which maintains the integrity of the intestinal barrier and exhibits anti-inflammatory effects by blocking bacterial/endotoxin translocation, was also found to be negatively linked with plasma LPS levels. It was

further claimed that pro-inflammatory gut microorganisms (such protozoa) and the development of amyloid plaques were related. By creating large levels of amyloid, these bacterial species trigger the release of proinflammatory cytokines, which may impair cognitive abilities. A neuroprotective function is performed by the brain-derived neurotrophic factor (BDNF), which is controlled by the microbiota. In AD patients, oxidative stress alters intestinal homeostasis, and BDNF levels are found to be significantly decreased. This is thought to have a role in the gradual neurodegeneration of hippocampus neurons and the decline in cognitive function. These factors have made research on the connection between the microbiota, gut, and brain axis and the development of AD increasingly interesting [3].

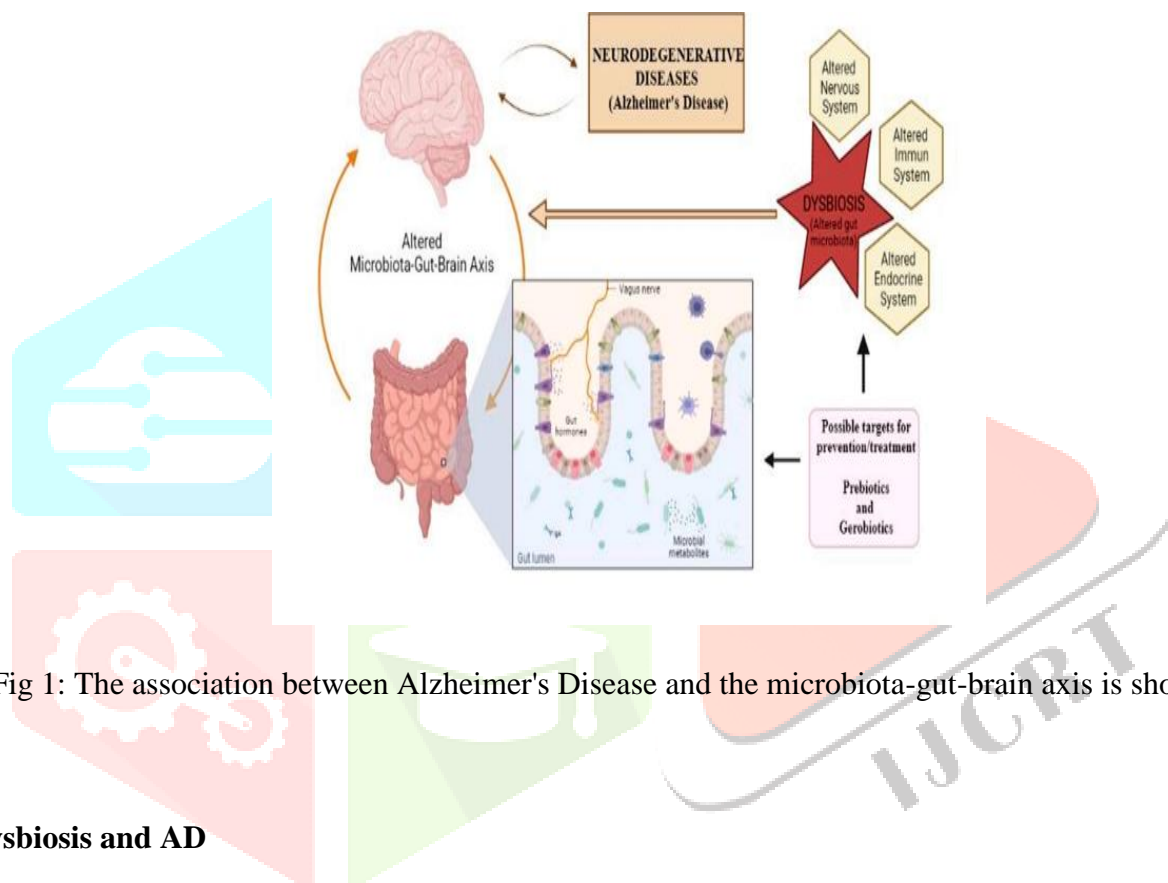


Fig 1: The association between Alzheimer's Disease and the microbiota-gut-brain axis is shown [3].

## Gut Dysbiosis and AD

Microorganisms of a vast variety and high level of activity live in the human gut. These intestinal microorganisms coexist with the host in a symbiotic relationship and have developed to coordinate conserved metabolic signalling, regulate homeostasis, and enhance immunity, ensuring the host's survival. The gut microbiota has a wider range of functions than is generally recognised, including those that go beyond homeostasis maintenance, the production of bioactive molecules like enzymes that actively participate in the biotransformation of ingested food, and the metabolism of xenobiotics. Recent studies has indicated that the microbiome is crucial in controlling neurological processes, behaviour, and brain development. Researchers are constantly examining the unique function of the gut microbiota and how changes to it may have an impact on chronic neuroinflammation and cognitive decline in AD (Fig. 2). According to several studies the gut microbiota plays a major and crucial role in the regulation of the MGB axis. According to various studies specific phyla like Firmicutes and Bacteroidetes dominate the bacterial population in the gut. The diversity and composition of this population are also spatially distinct among

individuals. In addition to neurological illnesses, changes or dysbiosis in the complex microbial ecology are linked to the emergence of a number of conditions, including gastrointestinal disorders, metabolic diseases, cardiovascular disturbances, obesity, and diabetes. Recent research suggests that gut dysbiosis is linked to a wide range of neurodegenerative disorders, including mental conditions, autism, depression, multiple sclerosis, Parkinson's disease, and Alzheimer's disease (AD). As a result, it is believed that the widespread use of antibacterial agents, non-steroidal anti-inflammatory medicines, changes in lifestyle, and dietary patterns are at least partially to blame for these myriad defects. In a transgenic mouse model of AD and the gut of human AD patients, Puig (2015) previously showed the over-expression of amyloid-protein precursors, dispersed immunoreactivity of A $\beta$  plaques, and phospho-tau. These alterations were discovered to be connected to the alterations in brain tissue. According to Saiyasit (2020), a prolonged high-fat diet (HFD) caused considerable gut dysbiosis, triggered systemic inflammation, and resulted in hyperactivated microglia and dysplastic hippocampi. This showed that nutrition significantly affects the growth of cognitive abilities. The finding that long-term antibiotic (ABX) treatment causes persistent gut dysbiosis and changes peripheral inflammatory components affecting cognitive function was undoubtedly the most convincing argument [4].

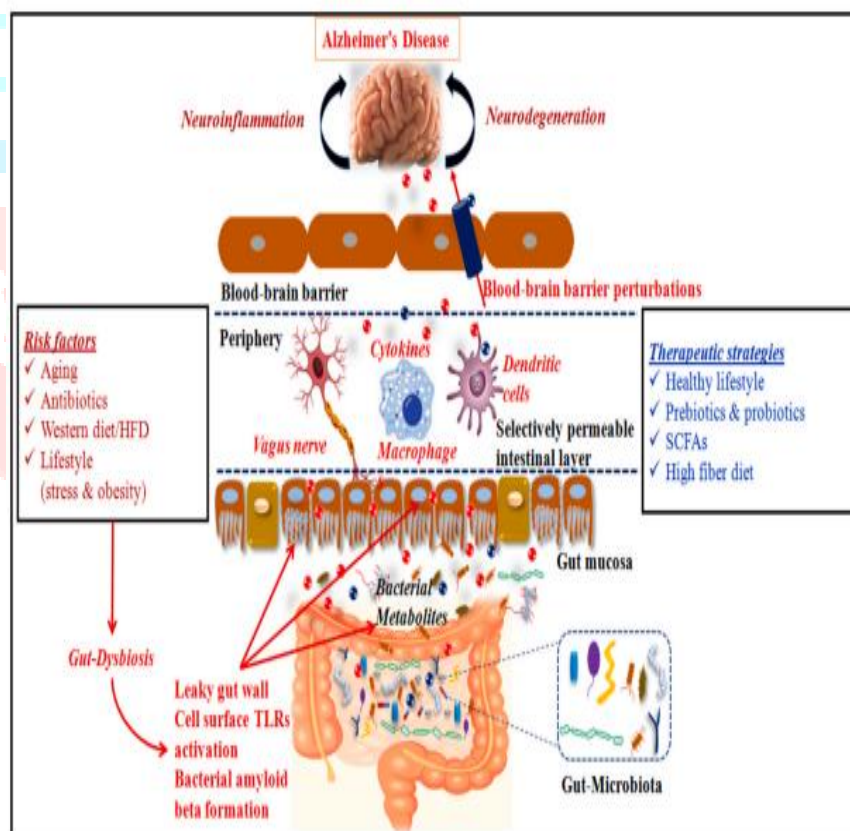


Figure 2: Through manipulation of the enteric nervous system, production of bacterial metabolites, and accumulation of amyloid in the gut, gut dysbiosis may help to start the pathogenesis. Through the stimulation of immune cells and TLRs, these pathogenic characteristics cause local and systemic inflammation. These inflammatory characteristics result in increased intestine and blood-brain barrier permeability, which ultimately aids in the aetiology of Alzheimer's disease [4].

## Role of gut bacterial amyloid in AD

The growth of amyloid protein is expected when gut bacteria are present. Curli, a functional extracellular amyloid protein, is produced by *Escherichia coli*. Certain bacterial amyloid causes the production of biofilms or other population activities where cells interact with a surface or another cell. Although the fundamental structures of bacterial and CNS amyloid differ, their tertiary structures are comparable. The immune system is boosted by bacterial amyloid protein, which also increases the brain's endogenous production of amyloid protein. In a rat experiment, animals exposed to *E. coli*-producing curli accumulated more neuronal alpha-synuclein (-syn) in the stomach and hippocampus. Additionally, increased expression of TLR2, IL-6, and microgliosis and astrogliosis markers were observed in exposed rats. The terms "mapranosis" and "-osis" have been used by Friedland and Chapman to describe the proteinopathy and neuroinflammation caused by the microbiota. Bacterial amyloid can function as a protein that is misfolding and can enhance the production of an amyloidogenic protein that facilitates the formation of pathogenic  $\beta$ -sheets [5].

## Relation of Age with gut microbiota and AD

One of the main risk factors for AD is age. An significant in vivo biomarker of AD is the progression of A deposition, which increases with age. A causes a number of metabolic reactions that result in tau accumulation, neuronal damage, and neuronal death, all of which are symptoms of AD. According to recent studies, ageing has a deleterious effect on the variety, function, and composition of the microbiota, and age-related gut dysbiosis triggers the development and progression of numerous metabolic disorders. Probiotic diet supplementation would benefit older people's health and mitigate age-related drawbacks, according to Coman and Vodnar (2020). A growing number of clinical research have looked into the potential health benefits of probiotics [6].

## Probiotics, Prebiotics, Synbiotics and AD

Probiotics are specific microorganisms that when administered in adequate amounts can exert a health benefit on the host by restoring microbiota and maintaining immune homeostasis. The most common probiotic bacteria currently used are representatives of *Lactobacilli*, *Enterococci*, *Bifidobacteria*, yeasts and mixtures of different beneficial bacteria. Various studies have reported the beneficial effects of probiotics by enhancing intestinal epithelial integrity, protecting from barrier disruption, stimulating a healthy homeostasis of the mucosal immune system and suppressing pathogenic bacterial growth. Moreover, different strains of probiotic bacteria have been shown to be effective in stimulating intestinal motility and reducing GI dysbiosis. According to Gibson and Roberfroid (1995), prebiotics are non-digestible oligosaccharides that have a positive effect on the host by selectively promoting the proliferation and/or activity of a specific type of bacteria in the gut. Prebiotic fibres have been shown to improve immune function; bowel motility and constipation; effects that may be particularly important for inflammation and GI-related symptoms in AD. Synbiotics are a combination of both probiotics and prebiotics, The term only applies to goods where a prebiotic ingredient favours a probiotic ingredient specifically [7]. Recent studies have looked at probiotics positive benefits on cognitive disorders like AD. Probiotics could

reduce AD through a variety of mechanisms. Recent research has established that probiotics, especially *L. plantarum*, can enhance mice's capacity for learning and memory. These bacteria may have these effects in a number of different ways. Indeed, the levels of acetylcholine and acetylcholinesterase may benefit from this probiotic strain [8].

## Conclusion

Alzheimer's disease (AD) is a complicated, multifaceted illness that includes neurodegeneration and chronic neuroinflammation. Recent research has shown that the brain and gut microbiome interact, and this interaction is known as microbiota-gut-brain axis. Intestinal permeability might increase and systemic inflammation can result from gut microbial dysbiosis. Through the neurological, immunological, endocrine, and metabolic pathways, this may result in the diseases of AD and cognitive impairment. Consequently, the modification of Gut microbiota may change as a result of a customised diet and oral bacteriotherapy, which may affect the production of amyloid protein. It has been shown that altering the gut microbiome has positive impacts on neural pathways, which slows the progression of Alzheimer's disease. The role of probiotics, prebiotics, synbiotics is a topic of research that can help treating AD to a great extent in near future.

## References

1. Ekundayo, T. C., Olasehinde, T. A., Okaiyeto, K., & Okoh, A. I. (2021). Microbial Pathogenesis and Pathophysiology of Alzheimer's Disease: A Systematic Assessment of Microorganisms' Implications in the Neurodegenerative Disease. *Frontiers in neuroscience*, *15*, 648484.
2. Li, F., Hearn, M., & Bennett, L. E. (2021). The role of microbial infection in the pathogenesis of Alzheimer's disease and the opportunity for protection by anti-microbial peptides. *Critical Reviews in Microbiology*, *47*(2), 240-253.
3. Ağagündüz, D., Kocaadam-Bozkurt, B., Bozkurt, O., Sharma, H., Esposito, R., Özoğul, F., & Capasso, R. (2022). Microbiota alteration and modulation in Alzheimer's disease by gerobiotics: The gut-health axis for a good mind. *Biomedicine & Pharmacotherapy*, *153*, 113430.
4. Goyal, D., Ali, S. A., & Singh, R. K. (2021). Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *106*, 110112.
5. Dhama, M., Raj, K., & Singh, S. (2023). Relevance of Gut Microbiota to Alzheimer's Disease (AD): Potential Effects of Probiotic in Management of AD. *Aging and Health Research*, 100128.

6. Thakkar, A., Vora, A., Kaur, G., & Akhtar, J. (2023). Dysbiosis and Alzheimer's disease: role of probiotics, prebiotics and synbiotics. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 1-13.
7. Salim, S., Banu, A., & Mohammad, F. (2022). Gut microbiome and Parkinson's disease: Perspective on pathogenesis and treatment. *Journal of Advanced Research*.
8. Aghamohammad, S., Hafezi, A., & Rohani, M. (2023). Probiotics as functional foods: How probiotics can alleviate the symptoms of neurological disabilities. *Biomedicine & Pharmacotherapy*, 163, 114816.

