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# Probiotics, Brain Gut Axis as a Therapeutic Target in AD

*corresponding author: **Sandip Kumar Dash**

HOD and Sr. Consultant AMRI Hospital, Mukundapura, Kolkata, India.
Email: drskdash@yahoo.co.in

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## Abstract

Alzheimer's disease is a slowly progressive neurodegenerative disease, leading ultimately to dementia. Despite the most prevalent neurodegenerative disease, among older population, till now no effective treatment nor preventive treatment has been found. It has been found out from various studies, that there is a link between gut micro biota and AD. It is also seen from various studies some probiotics have therapeutic and preventive roles on memory *via* microbiota gut brain axis. In this article the role of probiotic on Alzheimer's disease is discussed.

**Keywords:** Probiotic; Gut micro flora; Alzheimer's disease; Dementia.

**Abbreviations:** Alzheimer's Disease; Aβ: Amyloid Beta; ENS: Enteric Nervous System; SCF: Short Chain Fatty Acid; LPS: Lipo Poly Saccharides; ROS: Reactive Oxygen Species.

## Introduction

It is seen that the intestinal microflora takes part in bidirectional communication between the gut and the brain. Scientists suggest that human gut microflora may even act as the "second brain" and be responsible for neurodegenerative disorders like Alzheimer's Disease (AD) [1]. Enteric bacteria, commensal, and pathogenic microorganisms may have a major impact on immune system, brain development, and behavior, as they are able to produce several neurotransmitters and neuromodulators like serotonin, kynurenine, catecholamine, etc., as well as amyloids. However, brain destructive mechanisms that can lead to dementia and AD start with the intestinal micro biome dysbiosis, development of local and systemic inflammation, and deregulation of the gut-brain axis. It is strongly postulated that AD may begin in the gut and is closely related to the imbalance of gut microbiota. This is promising area for therapeutic intervention.

It is evident from different studies that, intestinal micro biota influences the brain gut interaction from early life to neuro degeneration in different point of time and at different levels [2]. The influence of microbiota on the brain leads to the term "brain gut microbiota axis" [3]. The concept of the MGB axis is well established. The neuro endocrine and neuro immune systems, in addition to the sympathetic and parasympathetic arms of the Autonomic Nervous System (ANS) and the ENS, are key pathways in gut–brain communication. Although the exact mechanisms mediating gut–brain interactions are not fully understood, they were suggested to involve endocrine, immune, and neural pathways (vagus nerve and enteric nervous system, leading to possible alteration in AD patients or aggravating inflammation.[4]. Enteric bacteria, commensals as well as pathogenic microorganism, may have a major impact on immune system, brain development, and behavior, as they are capable of producing several neurotransmitters and neuro modulators, as well as amyloids [5]. It has also been demonstrated that different hormones and neurotransmitters are produced like serotonin from entero chromaffin cells by modulation of gut microbiota signaling path way [6]. Disturbances in brain gut axis may cause the neurodegenerative diseases like AD [7].

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Hyper stimulation of immune system may result in a low grade inflammation [8]. It may be associated with persistent inflammatory state of gut mucosa due age related changes in composition of gut micro biota [2], thereby causing gut barrier breakdown, leading to pro inflammatory cytokines and bacterial derived products in to circulation causing blood brain barrier break down and neuro inflammation.[9], and, ultimately to neurodegeneration [10]. Micro biota influences peripheral immune cell activation and cytokine profile resulting in CNS inflammation and injury [10]. Various studies have suggested that environmental factors affect neurological activities under both physiological and pathological conditions. Although there is anatomical separation, it is seen that there is existence of bidirectional interaction between gut microbiota, i.e., (diverse microorganisms colonizing human intestine), and brain. The crosstalk between gut microbiota and brain may have crucial impact during basic neurogenerative processes, in neurodegenerative disorders [11].

**Gut microbiota and development of AD**

There are various descriptive hypotheses regarding the causes of AD, including the cholinergic hypothesis, amyloid hypothesis, tau propagation hypothesis, mitochondrial cascade hypothesis, calcium homeostasis hypothesis, neurovascular hypothesis, inflammatory hypothesis, metal ion hypothesis, and lymphatic system hypothesis. However, the ultimate etiology of AD remains obscure [12].

Intestinal micro flora forms the micro biome-gut axis that provide two way communications through cytokine, immunological, hormonal, and neuronal signals [13,14]. It is known that bacteria produce and secrete a range of compounds that reduces the intestinal tight junction, allowing the contact of intestinal microbiome with sub mucosal lymphoid tissue [10], thereby causing systemic inflammatory reaction, and impair blood brain barrier and promote neuroinflammation, ultimately results neurodegeneration[2].The human gut microbes induces neuro inflammation in AD by producing proinflammatory cytokines and other metabolites, that enters the circulation and reach the brain [4]. Various pro inflammatory cytokines are also involved in the process. Over expression of IL1is associated with plaque deposition [15]. While up regulation of IL6 is associated with hyper-phosphorelation of tau, causing neuronal damage [15,16]. In addition, bacterial metabolites like short chain fatty acids may play a role in the development or protection of ad pathogenesis [17]. Commensal microbiota also produces neuroactive molecules like serotonin, kynurenine, melatonin, GABA, catecholamines, histamine, and acetylcholine [18].

It was demonstrated that dys-regulation of serotonin and kynurine pathways are responsible for neurodegenerative diseases like AD [19]. Dys-regulation of kynurine route of tryptophan pathway was suggested as a major contributors of AD [20]. The effect of the microbiome on the brain function is not a simple sum of the spectrum of all metabolites produced by bacteria as the different abilities of these metabolites to penetrate the BBB play a key role. A large number of different metabolites produced by gut microbiota may directly or indirectly affect brain functions. Among them are Short Chain Fatty Acids (SCFA) including acetate, bytyrarate, and propionate can modulate peripheral and central nervous system. The restoration of probiotic flora, planned modulation of its composition, and dietary intervention to increase the function of probioticbacteria in SCF as remain a promising intervention that can significantly improve dementia and AD.

A wide variety of microbiome resident bacteria and fungi generate significant amount of LPS, amyloids and various exudates [21,22]. Many bacterial species continuously produce and release extracellular protein fibers to create and maintain a biofilm, as such fibers offer protection from environmental stresses as well as mediate adherence to both biotic and abiotic surfaces [22,23]. Cerebral amyloids are biologically similar. They are recognized by the same TLR2/TLR1 receptor system as Aβ-42, and strongly activate the production of proinflammatory cytokines like IL17.IL22. It is known that man is exposed to large amounts of LPS and amyloid proteins produced by human microbiome [14]. Such exposure may be dangerous to health, specifically in ageing, when gastrointestinal mucosa as well as BBB, became significantly restructured and permeable. [14,24]. So, it is seen that the microbiome derived products constitute to have proinflammatory complement and innate immunity activators, having the potential of produce proinflammatory cytokines, complement activation, and altered immunogenicity in the brain. This ultimately enhances amyloid aggregation and significantly elevated inflammatory reaction. It is seen that both amyloid proteins and LPS are strong activators of the Receptor for Advanced Glycation End Products (RAGE) and TLRs, and co activation of these amplifying inflammatory signaling, the driving force for sustained inflammation [25]. It was demonstrated that gut inflammation and dysbiosis is associated with gut barrier dysfunction and increased intestinal permeability, may contribute to the process of neurodegeneration [26,27].

The intestinal barrier consists of mucus layer, intestinal epithelium, and lamina propria. Dysfunction of this barrier leads to increased permeability causing translocation of bacteria and harmful products into the bloodstream [28,29]. In

the small intestine mucus allows particles to enter to penetrate although but due to high concentration of antibacterial products prevent them to reach the cell surface. It is seen that probiotic strains of lactobacillus plantarum, Ecoli Nussle Bifidobacterium enhances intestinal barrier by increasing expression of proteins forming tight junctions [29]. Other bacterial products, exotoxins, disrupt epithelial cell integrity. Different pathogenic E coli strains, Salmonella, H pylori, Clostridium mediate changes in tight junctions [28]. There is evidence that increased amounts of bacteria in the small intestine influence permeability [30].

Neuro inflammation is a known feature of AD., and the inflammatory response is seen in blood and CSF of Alzheimer's disease patients. [31]. Initially low Aβ concentration activates microglia and causes clearance of amyloid through phagocytosis [9]. Excessive microglia stimulation and increased neuro inflammatory signaling proinflammatory cytokines and reactive oxidative and nitroso active stressors lead to neuronal and glial death [32].

The amyloid protein Alpha syn nuclein may gain access to neuronal cells from the gut lumen, suggesting that misfolded proteins spread *via* gut brain axis [30]. The accumulation of mis-folded protein in neuronal cells and subsequent cell death results in release of the proteins into intracellular space. Again, the living cells may release the proteins *via* exocytosis, which are taken up by other neurons leading to local transmission of misfolded proteins. Propagation of the misfolded tau from outside into the cells, subsequent intracellular protein misfolding, aggregation and transfer to other co cultured cells were observed *in vitro* [33]. In addition to the extra cellular protein Aβ deposition, the protein accumulates inside neurons, which may be observed preceding neurofibrillary tangle formation and extracellular Aβ deposition [34].

In many studies the cause of AD has been implicated to microbiota [35], herpes simplex virustype1 has been associated with AD. In a study it was demonstrated that mice in addition many pathogens like Helicobacter and Odoribacter and a decrease level in Prevotella in APP transgenic mice. [36.] In a study it has been suggested that increased abundance of proinflammatory Escheiria/Shigella and decreased abundance of anti-inflammatory Eubacteriumrectale were possibly associated with peripheral inflammation in patients of cognitive decline and amyloidosis [37]. Similarly in another study, comparing fecal microbiota profile between AD and non-AD patients, it was seen that fecal microbiota profile of AD patients shoed reduced microbial diversity, decreased abundance of Farmicutes and Bifedobacterium and increased abundance of Bacteridetes.,which co related to the increase of CSF fluid markers of AD pathology[38].Gut microbiota composition is influenced by many factors, like poor diet and increased local and systemic inflammation as seen in elderly, accounting for increased incidence of neurodegenerative diseases seen in elderly.

Dietary modification in AD although gut microbiota can be manipulated through many methods including the use of probiotics, prebiotics, synbiotics, and antibiotics or change of diet, diet is the superlative modulator of gut microbiota. Dietary modulations focused on unsaturated fats, fruits and vegetables, and whole grains can confer benefits on AD-related cognitive health. For instance, Mediterranean meal correlates with less brain atrophy in key-AD areas (indicating positive effect on AD pathology [39], besides decreased inflammation, a major symptom of AD, *via* increasing plasma carotenoids and decreasing C-reaction protein levels [40]. Diet strongly modulates the gut microbiota, which might be one of the mechanisms underlying the benefits of these dietary patterns in ameliorating AD-related perturbations in gut-brain axis. Diet strongly modulates the gut microbiota, which might be one of the mechanisms underlying the benefits of these dietary patterns in ameliorating AD-related perturbations in gut-brain axis [41]. Probiotics, prebiotics and synbiotic supplementations have shown the ability to decelerate or potentially reverse the disease's main symptoms through several mechanistic avenues. Whether by alleviating the state of chronic neuroinflammation, scavenging peripheral and cerebral ROS, altering the production and localization of neurotoxic metabolites, or adjusting energy metabolism to serve the vital demands of neurons, modulating the microbiome through these bioactive supplements has shown promising results [42].

**Probiotics as a target for Alzheimer's disease therapy**

The close association between gut dysbiosis and neurological dysfunctions shade a light for the possibility of probiotic may be a therapeutic target for AD, in future [43] It has been seen the beneficial effect of Enterococcus fecium and lactobacillus in animal studies by reducing oxidative stress and induced antioxidant enzymes in the brain [44]. It was seen in a study of gut microbial alteration in Alzheimer's disease, it was shown that the increased Bacteroids and decreased Bbifedobacterium in AD participants, representing a gut microbial phenotype with a propensity for translocation of pro inflammatory bacterial components [38]. Other reports on animal studies have also shown beneficial effect of Lactobacilli and Biofedobacteria [45,46]. Similarly, a clinical study showed Lactobacillus and Biofedobacteria based probiotics improved Mini mental state examination score in AD patients after 12 weeks intervention with probiotics in patients of Alzheimer's

disease [47]. It has also been reported that perturbations of gut micobiota community induced by antibiotic treatment could ameliorate AB deposition and inflammatory response in an aged APP transgenic mice model of AD [48]. It was seen that administration of the probiotic mixture SLAB 51 induced larger shifts in the microbial communities of the 3xTg-AD mice, along with an increase in the proportion of Biofedobacteria, and a reduction in Campylobacterium population, suggesting a possible role of these bacteria in in the regulation of inflammation in AD as shown by a reduction of plasma concentration of proinflammatory cytokines in in AD mice treated with SLAB51 [49]. A high prevalence of Campylobacterales infections were found in patients of Alzheimer's disease, and parameters of cognitive dysfunctions were improved after Helicobacter pylori eradication [50]. Similarly in an explorative intervention study with probiotic supplementation in patients with Alzheimer's disease. It was also seen that species improved neuronal functions and plasticity in young and aged rats. VSL3# altered the expression of genes in the brain tissues such as BDNF and synapsophysin that are associated with inflammation and neuronal plasticity [51]. In a study to find out the effect of probiotic Lactobacillus plantarum mtcc1325, in Alzheimer's disease induced albino rats, it was seen that L.plantarum MTCC1325 might have anti Alzheimer's properties against D-galactose induced Alzheimer's disease [52], it was concluded that further double blind studies are required to see the potential consequences of probiotic treatment with VSL#3 (a probiotic mixture containing eight different gram positive bacteria supplementation in the course of Alzheimer's disease [53].

In a study to find out the effects of prebiotic, probiotics, and synbiotics in male obese rats induced by high fat diet, it was seen that, consumption of prebiotics, probiotics and synbiotics restored cognition in obese insulin resistant subjects through gut brain axis, leading to improved hippocampal plasticity, brain mitochondrial function, and decreased microglia activation, resulting improvement of cognitive function. These neuroprotective effects may be due to attenuation of inflammation, hipocampal oxidative stress, apoptosis, mitochondrial dysfunction along with microglia dysfunction [54]. In a study of scopolamine-induced dementia in mice, to find out assess the effect of probiotic Lactobacillus rhamnosus as a curcumin adjuvant (potentiate the effect of curcumin, it was seen a significant increase in antioxidant enzyme levels in curcumin with a probiotic group compared with curcumin alone, in addition, the histopathology study results showed less neuronal damage of curcumin with probiotics as compared with the curcumin and scopolamine alone groups. Additionally, curcumin with probiotics improved memory and cognitive functions, concluding that curcumin with probiotics has greater activity as compared with curcumin alone and reverses the hallmarks of Alzheimer's disease [55].

Similarly, a patent W02019157585A1 describes the prebiotic formulation for the treatment and alleviation of metabolic and oxidative stress, inflammation, and neurodegeneration. The probiotic formulations consist of any combinations of the three probiotic strains, Lactobacillus fermentum NCIMB 5221, Lactobacillus plantarum NCIMB 8826 and Bifidobacterialongum species infantis NCIMB702255. [56]. In an explorative intervention study it was found that the supplementation of Alzheimer's disease patients with a multiple species probiotic influences gut bacteria composition as well as tryptophan metabolism [53]. However further studies are required to find out the beneficial effect of probiotic supplementation in Alzheimer's patients. A patent WO2018158405A1 [57], relates to a new synbiotic composition comprising a mixture of probiotic and prebiotic ingredients for the prevention and/or treatment of Alzheimer's disease. The new synbiotic composition comprises at least one Roseburia species and at least one Verrucomicrobiale species, in particular an Akkermansia species, in combination with dietary fibers. The invention also relates to the probiotic composition containing at least one Roseburia species and at least one Verrucomicrobiale species. **In another patent, Patent Publication Number**: 20150174177,[58]The inventors found that the probiotic strain *Lactobacillus johnsonii* CNCM I-1225 (La1) in combination with a polyphenol was able to prevent and/or inhibit of Aβ oligomerization and/or fibrillogenesis in a synergistic way, and have hence identified *Lactobacillus johnsonii* CNCM I-1225 (La1) in combination with a polyphenol as a food-grade composition that can inhibit, retard and/or reverse, e.g., AD associated neuropathology, memory loss and/or cognitive decline.

A high prevalence of Campylobacterales were found in AD patients, and it was observed that after eradicating Helicobacter pylori improves cognitive function [59]. These findings suggest that the alteration of gut microbial composition by probiotics could positively modulate the AD-related pathological conditions. High levels of endo toxins in the gut and brain have shown to impair the intestinal barrier and blood brain barrier integrity because of local inflammation and favor accumulations of AB, alpha synuclein and some amino acids [60] Ultimately high levels of endotoxins promote the production or aggregation of AB, tau protein and alpha syn nuclein in the brain [61]. From the various studies it may be assumed that interventions aimed at preventing or treating dysbiosis could interrupt or slowdown the vicious cycle of endotoxins, neuroinflammations and neurodegeneration [61]. However this needs to studied in AD patients, whether it is effective in

preventing the pathogenesis in Alzheimer's disease.

In a study it was seen that ingesting bioactive peptides in dairy products improves cognitive functions [62]. In a study it was seen that dipeptide of tryptophan–tyrosine (WY) and tryptophan–methionine that suppressed the microglial inflammatory response and enhanced the phagocytosis of amyloid-β (Aβ). Intake of the WY peptide prevented microglial inflammation, hippocampal long-term potential deficit, and memory impairment in aged mice. The identified dipeptides regulating microglial activity could potentially be used to prevent cognitive decline and dementia related to inflammation [63]. In a transgenic mice (APP/PS1$^{TG}$) study, treated with exercise and probiotics, it was seen that there was reduced number of amyloid plaques in hippocampus compared to untreated mice, suggesting that exercise and probiotic treatment can decrease the progress of Alzheimer's Disease and the beneficial effects could be partly mediated by alteration of the microbiome [64]. Although there are many studies have shown, the possible mechanisms involved in gut microbiota modulation and the pathophysiology of dementia, the evidence regarding the use of probiotics and symbiotic to improve cognitive function in humans with dementia is insufficient to support their clinical application [65].

## Conclusion

This article describes the results of various studies suggesting the potential role of probiotics in the therapeutic intervention of Alzheimer's disease and could effectively ameliorate the cognitive impairment in Alzheimer's disease and can be a therapeutic target against Alzheimer's disease. Probiotics can influence the pathological factors like inflammation, Aβ deposition and oxidative stress, that are associated with Alzheimer's disease However it needs further studies to prove the scope of probiotics as therapeutic target to ameliorate Alzheimer's disease and the exact mechanism of its action in improving the cognitive decline in Alzheimer's disease.

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