REVIEW ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

The Role of Probiotics in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease that starts slowly and gradually worsens over the time and further leads to cognitive impairment and causes dementia. Since it is the most common neurodegenerative disease in older adults, no successful treatment has been reported. However, many studies in AD are associated with gut microbial alterations. Probiotics are living microorganisms that provide health benefits when consumed in the proper amount. Some probiotic strains provide health benefits such as improving the intestinal environment, immunomodulatory functions, prevention of infections, anti-obesity effects, cancer-preventing effects, and extension of life span.

In contrast, some probiotic strains ameliorate cognitive impairment, CNS behavior, and depressive disorder. In many studies, probiotics have shown preventive and therapeutic potential in the case of AD. This review article aims to give a complete analysis of the role of probiotics in AD symptoms.

Keywords: Alzheimer's disease, Amyloid precursor protein, Brain-derived neurotrophic factors, Central nervous system, Neurofibrillary tangles, Short-chain fatty acids.

Asian Pac. J. Health Sci., (2021); DOI: 10.21276/apjhs.2021.8.4S.8

Introduction

Alzheimer's Disease (AD) is recognized as a progressive disorder that slowly destroys memory and other brain functions, and it is the most common cause of dementia. It is a neurodegenerative disorder which generally appears in elderly patients.[1] and thus, it is characterized by a progressive and irreversible decline in memory, cognition, and motor functions, which further causes the death of those diagnosed with it within 4–10 years.[2] However, in AD cases, aging is thus characterized as one of the major risk factor. In the past few years, many researches have been done on AD, but no treatment is available due to its unclear pathophysiology. It is thus believed that Neurofibrillary tangle (NFT), amyloid plaques and genetic factors are the major cause of pathogenesis in the events of AD. Therefore, more studies should be done in order to combat with the disease. Lately, many new studies have suggested the role of gut microbiota in AD, so it acts via regulating the gut-brain axis and further, its deregulation can lead to progression of AD.[3] In contrast, it is suggested that the use of probiotics can modulate the gut microbiota and thus possibly ameliorate the symptoms of AD. This review article focus on the link between gut-microbiota and AD and the role of probiotics in AD.

Relation Between AD and Gut Flora

Role of Gut Flora: The Gut-Brain Connection

In our body there is a bidirectional link in between the digestive system and the brain and such link or communication is termed as Gut-brain axis.[4] Gut-brain axis has a complex network which is composed of the gastrointestinal tract (GIT), Central nervous system (CNS), autonomic nervous system (ANS), immune system and enteric nervous system. Various environmental factors the CNS and HPA axis. By the autonomic and bidirectional pathway, CNS communicates to the ENS intestinal mucosa and gut muscle and thus modulates the permeability, mucus secretion, motility, and immunity.[5] The information received by the Central nervous system can thus modify gut functions, and the information received by the gut to the CNS can modify certain specific symptoms.[6] The alteration of the bidirectional communication can lead to pathogenesis of brain-related disorders and neuroinflammation. Gut plays an important role in the prionic proteins transmission and further shows prion like behavior similar to the major CNS diseases like AD and Parkinson's disease.[7] Recently, it is revealed that gut flora plays an important role in regulating the gut-brain axis.[8] Gut flora act as a catalyst in various conditions like neurological disease, immune system and metabolic homeostasis.[9] It is a wide collection of microorganisms, bacteria, fungi, and viruses found in the GIT and plays a pivotal role in physiological, immunological, and anatomical host functions.[10,11] The gut-microbiota has two different bacterial phyla namely, firmicutes and bacteriocides and other bacterias like proteobacteria, actinobacteria are in less number. Many researchers believe that the changes in the composition of gut flora can lead to the imbalance and homeostasis of the gut and can further cause harmful effects on the CNS.[12]

This Figure 1 illustrates that dysbiosis and the alteration of gut microbiome composition lead to many diseases such as Inflammatory bowel disease (IBD), metabolic syndrome, obesity, allergies, AD, type 2 diabetes, colorectal cancer.[13] Recent studies have shown that gut dysbiosis plays a role in various

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How to cite this article: Thakur SS, Khurana N, Sharma N, Sharma N. The Role of Probiotics in Alzheimer's Disease. Asian Pac. J. Health Sci., 2021; 8(4S):45-48

Source of support: Nil

Conflict of interest: None

Received: 17/06/2021 **Revised:** 28/09/2021 **Accepted:** 25/11/2021

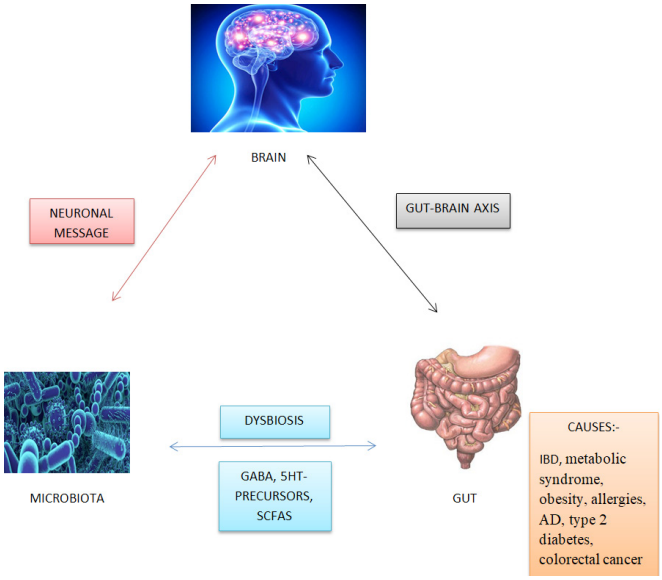

Figure 1: Alteration of gut bacteria causes various diseases.

neurological disorders like AD, so flora's proper and healthy composition should be maintained.

Role of Gut Microbiota in Alteration of AD

We have different molecules and pathways in our body by which gut flora can affect the brain's functioning. There are many neuro-active molecules present in our gut flora like serotonin, histamine, melatonin, catecholamines. They all have a role in regulating homeostasis in the brain and can further affect our brain functions.[14] It releases neuroactive molecules such as serotonin, which further transmit the information to the brain by activating the vagus nerve and producing a wide range of cytokines.[15] The gut bacteria also produce GABA, and it plays its role in calming nerve activity. It is a calming amino acid that is required for deep sleep. The gut microbiota also produces a neurotransmitter, glutamate, which plays a major role in learning, memory, and cognition, and it further helps maintain its level in an optimal state. However, in various conditions like depression, anxiety, and neurodegenerative disease like AD, both GABA and glutamate levels are very low or below normal.

There is various evidence of gut microbiota that its alteration can influence neurological disease such as AD. Various studies revealed that gut flora composition in AD patients shows a decrease in diversity of microbes and changes in the bacterial diversity such as decreased level of Firmicutes and Bifidobacterium and increased level of bacteriodetes compared to with control.[16] There was a study that involved 83 old patients, including (40 amyloid positive cognitive impaired patients, 33 amyloid negative cognitive impaired patients, and 10 amyloid negative cognitive healthy control patients) have shown a rise in the diversity of Escherichia, Shigella, *Enterococcus rectale,* and a low level of the anti-inflammatory taxon. All these are co-related with peripheral inflammatory state among cognitively impaired amyloid patients, and the result shows that the role of bacterial and amyloid aggregation leads to the pathogenesis of cognitive damage.[17] Another study involving APP-induced mice model shows that the pathology of AD has changed the composition of gut microbiota in case of inflammation linked with bacterial profile and proposed that these type of changes can cause progression of the disease.[18] All these studies associated with gut microbiota alteration, inflammatory responses, cognitive impairment and amyloid formation in the AD suggested that the alteration of gut microbiota with the help of probiotics can improve AD symptoms.

Probiotics

Probiotics are live bacteria or microorganisms intended to have health benefits when administered, especially in the digestive system. It has also shown influence in the brain activity related to happiness, motivation, emotions, mood and depression. The most commonly used probiotics in commercial products are Lactobacillus and Bifidobacterium. The Lactobacillus strains include *Lactobacillus acidophilus, Lacticaseibacillus casei,* and *Bifidobacterium longum*, *Bifidobacterium bifidum*.[19]
Probiotics are available in various forms as:[20]

- Probiotic drinks are juices that contain probiotic strain inside them, which helps maintain the gut healthy and improves an individual's health. They can be orally administered. Some of the examples of probiotics drinks are Yakult, Kevita sparkling probiotic drink, Karma probiotic water.
- Yoghurt is the most popular probiotic food and it gets is live-cultured from the milk of cows, sheep or goat and Streptococcus further ferments it further fermented with thermophiles or *Lactobacillus delbrueckii*. Examples of yoghurt are Soy yoghurt, Almond yoghurt, Goat yoghurt, and Greek yoghurt.
- *Capsules* – It is the most popular form of supplement administered orally and used to treat bowel problems such as diarrhea, IBS. Some examples of the probiotic capsules are VSL#3, Florajen, Florastor, MegaFood and MegaFlora.
- *Chewables* – These are primarily administered to the children. It contains various forms of organisms in chewable form and is easy to administer by children. They contain less sugar and have artificial ingredients. Examples of the chewable form of probiotic are Culturelle Kids Chewables Daily Probiotic, up4 Kids Cube Probiotic Supplement, OLLY Kids Multivitamin and Probiotic Gummy Supplement, Lil Critters Kids Probiotic Gummies, Nordic Naturals Probiotic Gummies, Renew Life Kids Probiotic.
- *Natto* – It is a Japanese dish that contains fermented soyabeans. A *Bacillus subtilis* bacteria do the fermentation. It is rich in fiber, vitamin K2, probiotic, and natto kinase and it is effective in many diseases.

Animal Studies

Various animal studies have been conducted to check the effect of Probiotics In AD. The Table 1 has shown various studies.

Human Studies

Till now there is only one clinical study of probiotics in AD patients. Randomized, double-blind and controlled trial which involves 60 elderly patients. These patients were randomly divided into two groups, the probiotic group in which 200 mL/day of probiotic milk containing *L. acidophilus, B. bifidum, L. casei,* and *Limosilactobacillus fermentum* ($2x10^9$ CFU/g) for 12 weeks was given and the control group was given plain milk

Table 1: Various animal studies to check the effect of probiotics in AD.

S. No.	*Study*	*Treatment*	*Duration*	*Result*	*Conclusion*	*Reference*
1.	Effect of probiotics for 6weeks on β amyloid induced AD rat model	500 mg Probiotic given daily by lavage + β amyloid administration by injection.	4 weeks + 2 weeks	Probiotic administration improved the learning but not the memory impairment, increase level of PPF ratio.	There was a positive impact observed in learning capacity in the β amyloid induced rat model.	[21]
2.	Effect of a probiotic formulation (*Lactobacillus. helveticus* R0052 and *Bifidobacterium. longum* R0175) on a lipopolysaccharide rat model.	Divided into 4 groups (control, LPS, Probiotics + LPS, Probiotics). Administered probiotics (10^9 CFU/ml/rat). Later saline or LPS (1mg/kg i.p single dose) was injected. Memory retention ability was assessed 4 hours after the injection.	14 days + 20 hours	It modified the effect of LPS on memory through BDNF.	The treatment with probiotic has shown positive effect in the symptoms of AD.	[22]
3.	Effect of Probiotic formulation SLAB51 in AD induced mice model.	Given SLAB51 (consist of Lactic acid bacteria and Bifidobacteria) by lavage.	4 months	It has shown improvement in the case of cognitive impairment and further reduces the progression of early stage of AD.	The probiotic formulation can show a positive result in the prevention of the progression of AD.	[23]

at the same amount. Each patient underwent the MMSE (mini-mental status exam), which is a test for mental function and is used to evaluate memory and learning. The MMSE includes activities like naming object, asking current date, backward counting from 100 etc. After the 12 weeks intervention, the probiotic treated patients improved the MMSE score (from 8.7–10.6 out of a maximum 30), whereas the control group (from 8.5 to 8.0). The treatment with probiotics in AD patients also showed low levels of serum triglycerides, very low-density lipoproteins (VLDL), changes in biomarker of oxidative stress that is Plasma malondialdehyde. Thus, probiotic supplementation has shown improvement in cognitive function and metabolic states in AD patients. Furthermore studies are required to test the beneficial effects of probiotics in AD.[24]

Effects of Probiotics Involved in AD-Modification of Immune Reactions

It is one of the mechanisms which is involved in the prevention of AD. Recent studies have shown that probiotics have improved the age-related modifications of immunological features. The probiotic administration can ameliorate the immune reaction by modulating cytokine production, improving the distribution and function of natural killer cells, macrophages, and T-cells granulocytes, and further enhancing systemic antibody responses.[25,26]

Modulation in Brain Activity by Bacteria Derived Metabolites

Many recent studies have shown that probiotics can modulate the gut microbiota an d can further lead to amelioration of the inflammatory status of AD through the production of SCFAs. It is believed that SCFAs produced by the gut microbiota can lead to the inhibition of the toxic soluble Aβ aggregates.[27] SCFAs can also modulate neurotransmitter synthesis and further has an effect on BDNF and nerve growth factor.[28,29] In the case of AD patients, there is a reduction in the BDNF signaling and such decline can be reversed with the help of probiotic treatment in the rodent model.[30,31] These studies suggested that probiotic modulation can enhance the production of microbiota-derived molecules like SCFAs and thus can improve the molecular event associated with cognitive impairment.

Conclusion

The present article has discussed the potential of probiotics in preventing the progression of AD. Probiotic therapy can ameliorate the cognitive impairment in AD and further improve the gut microbiota composition by modulating the gut dysbiosis in AD. But despite all the research done on humans and animals, more research is still required to determine the role of probiotics in preventing the progression and cognitive impairment in AD.

Acknowledgment

I want to thank Lovely Professional University, Panjab, India, for providing the Library services for the extensive literature survey.

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