A Comprehensive Review on Probiotics in Alzheimer’s Dementia: Modulating Microbial Imbalance for Neuroprotective

Lakshmi Devangam Ambe[1], Thota Praveen Roy[2], P.C. Jamuna[3,] Nagalarapu Niharika[4], B. Likitha[5], P.Vineetha Varma[6]

[1,2,3,4,5] *College of Pharmacy, Annamacharya University, Rajampeta, Y.S.R Kadapa dist, AP-516126.*

[6] *Associate Professor, College of Pharmacy, Annamacharya University, Rajampeta, Y.S.R Kadapa dist, AP-516126.*

***Abstract*—Alzheimer’s disease is a chronic and progressive neuro-degenerative disorder mainly affecting the older people then it leads to cause of dementia, around 60-80% of all cases. Around worldwide dementia cases are raised due to aging populations, understanding Alzheimer’s disease underlying mechanisms is increasingly critically. Emerging evidence highlights the bi-sectional communication between gut and brain known as gut-brain axis- it is a contributing factor in neurodegenerative diseases including Alzheimer’s disease. Gut microbiota plays an important role in regulating immune function, neuroinflammation, and blood-brain barrier (BBB) integrity. Dysbiosis or microbial imbalance, often linked to aging, diet, and environmental factors, may increase Alzheimer’s disease progression due to pr inflammation and disrupting the gut-brain axis. Altered gut microbiota composition in Alzheimer’s disease is associated with reduced beneficial bacteria and increased pro-inflammation species then influence the neurotransmitter production, neurotrophic factors like BDNF, and metabolic signaling pathways. Probiotics, particularly strains of lactobacillus, bifidobacterium, and saccharaomycesboulardii, have shown in restoring microbial balance and enhancing gut barrier function, modulating immune response, and reducing neuroinflammation., Furthermore, they increase the production of short-chain fatty acids(SCFAs), which support cognitive function and metabolic health.**

***Index Terms*—Alzheimer’s disease, gut dysbiosis, gut-brain axis, neuroinflammation, gut microbiota alterations, probiotics, neuro-protection.**

I. INTRODUCTION

Alzheimer's disease (AD) is a chronic-progressive neurodegenerative disorder and primarily affecting older adults which is characterized by the memory loss and cognitive dysfunction[.1], which leading to cause of dementia , and its prevalence is expected as to increase substantially due to an aging population[2] which is characterized by a gradually decreased in cognitive function includes memory loss,then it leads to behavioral problems. Among different types of dementia, Alzheimer’s disease is most common and it contributes to 60-80% of dementia cases[3]. Around 50 million people suffering with dementia. Every year approximately 10 million additional cases were reported worldwide.[4]

Emerging Role of the Gut-Brain Axis: Bidirectional gut–brain (GB) interactions regulate key physiological and homeostatic functions, including food intake, immune regulation, and sleep[5] .Bidirectional biochemical communication between the brain and the gut contribute to a variety of neurodegenerative and psychiatric diseases[6]Recently, a role for the gut microbiome in motor dysfunction in Parkinson’s disease has been highlighted[7]Cholesterol metabolism in the liver is thought to play a key role in AD[8]. Bile acid’s role in cholesterol clearance, BAs are major regulators for maintaining energy homeostasis through binding to nuclear receptors, including FXR and LXR among others. Bile acids can also be modulating the gut microbiome and it is indicators of gut dysbiosis.[9-10]The signal from the brain controls the secretory and sensory function of the gut.The communication between the brain and gut microbes is mediated by the physiological chanelsgut microbiome, which plays a key role in regulating the CNS function (such as brain circuitry, neurophysiology, and behavior)[11].

1. Gut Dysbiosis: Definition and Relevance

What is Gut Dysbiosis:The assemblage of bacteria, archaea and eukaryacolonising the GI region is nominated as the 'gut microbiota'[12]. The eventually for the mechanisms similar as adjusting the intestinal epithelium [13] harvesting energy[14], guarding against pathogens[15]and controlling host immunity[16] to be disrupted as a result of an altered microbial composition, known as dysbiosis[17].

Causes and Consequences of Microbiota Imbalance: dysbiosis is caused by the host- unique agencies like as heritable background, health status (infections, inflammation), and life habits or more importantly environmental agents like as diet (more sugar, less fibre), xenobiotics (antibiotics, drugs, food complements), and hygiene. These fluctuations own meaningful physiological effects as, for visual, diets heavy in plain sugars break up the intestinal barricade, sensor intestinal inflammation, and negatively affect host metabolism[18].

Gut Dysbiosis in aging and Neurodegeneration (alzheimer's disease): The link between gut microbiota and AD have led to the so-called theory of "age-related dysbiosis",which hypothesizes that AD may arise during the process of aging of the immune system. In fact, it has been observed that during the aging, there are changes in the composition of the gut microbiota, the increase of proteobacteria, and a reduction of probiotics, such as bifidobacteria, and neuroprotective molecules[19].Gut microbial dysbiosis, or altered gut microbial communities, in Alzheimer's Disease suggests a pathogenic role for gut inflammation and also associated with an increased risk of Alzheimer's Disease, diabetes and obesity[2].

2. The Gut-Brain Axis and Neuro-inflammation

Bidirectional Communication Between Gut and Brain:Bidirectional biochemical communication between the brain and the gut contribute to a variety of neurodegenerative and psychiatric diseases[21]

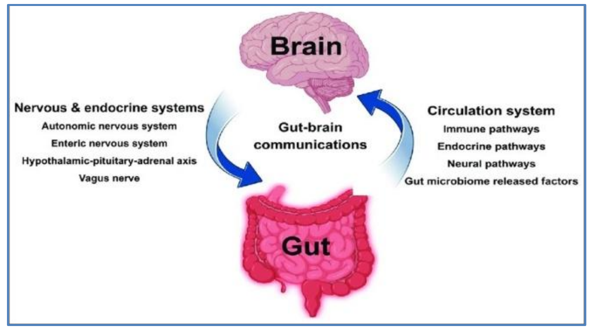

Fig. 1: Bidirectional Communication Between Gut and Brain

The communication between the gut microbiota and the brain includes neuronal, immunemediated, and metabolite-mediated pathways. Pro-inflammatory cytokines induce disruption of the blood–brain barrier permeability. probiotics have the potential to normalize the gut microbiota in microbiota–gut–brain processes.[22]

Role of Microbiota in Modulating Neuroinflammation:

The gut microbiota seems to play a vital role in regulation of and neurodegeneration in Alzheimer's disease[23].The gut microbiota plays an important role in the function and behavior of the neuroinflammatory system. The peripheral immune cells and exposure of glial cells in systemic inflammation is influenced by the gut flora microoraganisms, then its stimualtes and also regulates the modulation of production and metabolism of neurotransmitters.[24].The gut microbiome modulates the equilibrium of the gut–brain axis by interacting with the CNS, including the vagus nerve, immune system, and endocrine system[25]

Impact of Dysbiosis on Blood-Brain Barrier Integrity: The gut microbiotadysbiosis are also known to induce the generation of toxic metabolites and pro-inflammatory cytokines, resulting in disruption of BBB integrity[26]. Dysregulation of the gut microbiota triggers the release of inflammatory cytokines that can activate endothelial cells and actively traverse the brain endothelial cell layer, causing damage to BBB integrity[27].The impact of gut microbes and their metabolites have on blood-brain barrier integrity and brain function. The gut microbiota metabolites such as short-chain fatty acids, trimethylamines, amino acid derivatives, and vitamins have signaling functions which can modulate BBB integrity and brain function[28]

3. Gut Microbiota Alterations in Alzheimer's Disease

Microbiome Signatures in AD Patients:Alzheimer signature in intestinal microbiome that can be used to discriminate amyloid-positive AD patients from healthy controls. So many Scientists have discovered the changes in the gut flora composition (namely, dysbiosis) can contribute to Alzheimer's disease development and progression[29]

Correlation Between Microbial Changes and Cognitive Decline: The correlation between the changes in the gut microbiome, cognitive decline and behavioral problems then it leads to conditions like Alzheimer's disease and other forms of dementia[30]

4 Probiotics: Definition and Mechanisms of Action

What Are Probiotics: Probiotics are refered as living microorganisms but, when administered in adequate amounts, confer a health benefit on the host. probiotics are commonly used include bacteria from the genera Lactobacillus and Bifidobacterium, as well as yeast Saccharomyces boulardii.[31]. Probiotics are live nonpathogenic microorganisms administered to improve microbial balance, particularly in the gastrointestinal tract. They consist of Saccharomyces boulardii yeast or lactic acid bacteria, such as Lactobacillus and Bifidobacterium species[32.]

Mechanism of action: According to search of research articles of medline (pubmed), for the mechanisms of probiotics. The following mechanisms have been reviewed by above research articles :(a) colonization and normalization of perturbed intestinal microbial communities in children and adults;(b) competitive exclusion of pathogens and bacteriocin production; (c)enzymatic activity and production of volatile fatty acids;*(d)*cell adhesion, cell antagonism, and mucin production;*(e)* modulation of the immune system; and *(f)* interaction with the braingut axis.[33]. Above all mechanisms for probiotics but, one of the major mechanisms of action for probiotics is the regulation of host immune response[34]

Role in Modulating Gut Microbiota Composition: Probiotics plays a versatile role in restoring the composition of the gut microbiota, helping to improve host immunity and prevent intestinal disease phenotypes.[35.] probiotics play a critical role in altering the composition of the gut microbiota and helping inhibit the colonization of pathogenic bacteria in the gut, thereby assisting the host in building healthy intestinal mucosa.[36]

5. Potential Mechanisms Linking Probiotics to Neuroprotection

Regulation of Neurotransmitters and Brain-Derived Neurotrophic Factor (BDNF): Brain derived neurotrophic factor (BDNF) plays an important role in neuronal survival and growth, serves as a neurotransmitter modulator, and participates in neuronal plasticity, which is essential for learning and memory. Brain-derived neurotrophic factor regulates glucose and energy metabolism and prevents exhaustion of β cells[.37]. Decreased levels of BDNF are associated with neurodegenerative diseases with neuronal loss such as Alzheime's disease, Parkinson's disease (PD)[38], multiple sclerosis (MS)[39] and Huntington's disease[40]. After Several studies indicate a

direct involvement of neurotransmitters such as glutamate, GABA, acetylcholine, serotonin, and dopamine in the transcriptional regulation of the BDNF gene[41].

Improvement in Gut Barrier Function and Metabolite Production (e.g., SCFAs):

Resistant dietary carbohydrates are fermented to short-chain fatty acids (SCFAs) by the gut bacteria. Fiber and omega-3 rich diets increase SCFAs production and abundance of SCFA-producing bacteria. Likewise, SCFAs can improve gut barrier integrity, glucose, and lipid metabolism, regulate the immune system, the inflammatory response, and blood pressure. Therefore, targeting the gut microbiota with dietary strategies leading to increased SCFA production may benefit cardiometabolic health[42].The beneficial effects of probiotics in enhancing host immunity and modulating the gut microbiota and SCFA production[43].

6. Modulation of both systemic and central inflammation:

Modulation of systemic inflammation:

Immune System Modulation: Probiotics can enhance innate immunity and modulate pathogen-induced inflammation by interacting with toll-like receptors (TLRs) and other signaling pathways[44].

Regulation of Cytokines: They can suppress pro-inflammatory cytokines (like IL-1, IL-6 and TNF-α) while stimulating anti-inflammatory cytokines (like IL-4, IL-10, IL-11, and IL-13).[45]

Gut barrier function: Probiotics promotes the beneficial for the intestinal epithelium, increase barrier function and inhibit the pathogenic bacterial effects.[46]

Antioxidant capacity: By enhancing antioxidant capacity in patients which results in reducing systemic inflammation.[47]

Modulating the central inflammation:

Neuro-inflammation: probiotics induced neuro-inflammation by decreasing LPS-induced TLR4/MyD88/NF-κB signaling and prevention of microglia activation.

Neuroprotection mechanism: It includes probiotics inhibits the apoptosis and oxidative stress by up-regulation of SIRT1 signaling.[48]

Neurotransmitters: probiotics modulate the behaviour, affect cognitive brain function, and influence the memory processes.[49]

II. CONCLUSION

The most common type of dementia called Alzheimer's disease, is a world- wide global health in the aged population. Although the main cause is still unknown,but new research has talks about how important the gut-brain axis is in regulating neuro-inflammation, cognitive function, and the Alzheimer's disease progression. By causing systemic and neuroinflammation, impairing the integrity of the blood-brain barrier and changing the neurotransmitter signaling. Dysbiosis is an imbalance in gut microbiome, which results in increasing of Alzheimer's disease progression. with regard to improve the immunological function, restore microbial balance, and generate neuroprotective metabolites like short-chain fatty acids(SCFAs). Probiotics are become a favorable intervention, then it provides a potential possible secondary approach or choice for the treatment or prevention of Alzheimer's disease by influencing the composition of gut microbiome and providing intestinal and neuronal health.

Disclosure statement
The authors declare no potential conflicts of interest.

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