Impact of Gut Microbiome Lactobacillus spp. in Brain Function and its Medicament towards Alzheimer’s Disease Pathogenesis

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Abstract

Alzheimer’s disease is neurodegenerative dementia which has significant health complications in the old age group. An imbalance in gut microbiota can influence to cause several diseases like chronic disorders, depression, type II diabetics, and neurological disorders like AD. Aging is one of the major causes of the development of neurodegenerative disease due to the decreasing levels of neurotransmitters, oxidative stress, chronic inflammation, and apoptosis. These harmful effects of aging can be prevented by probiotics usage. The gut-microbiota is capable to control the brain function through the gut-brain axis. Lactobacillus strains are considered as beneficial microorganism because of its importance of the maintenance in healthy intestinal microflora, immunomodulation, and intestinal pathogenic intervention. They have diverse applications in the medical field with properties like antioxidant, anticancer, anti-inflammatory, anti-proliferative, anti-obesity, and anti-diabetic activities. Probiotic supplementation with Lactobacillus strains shows an optimistic trend to use it as a significant therapy for cognitive symptoms. This review article put forwards the significance of the gut-brain axis and the contribution of Lactobacillus strains as a probiotic supplement and its therapeutic innovations for future aspects and the limitation to treat AD-related pathogenesis are briefly elucidated.

Keywords: Alzheimer’s disease, neurodegenerative disease, Lactobacillus strains, dementia, gastrointestinal tract, gut-microbiota, gut-brain axis

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INTRODUCTION

Alzheimer’s disease (AD) is a highly prevalent neurodegenerative disease in the aged group of people and nearly 44 million of the world population have AD associated dementia and estimated to be raised as 4 million in India and 5.3 million in the United States respectively. It is a progressive, neurodegenerative ailment, a beginning of neurological decline, and stands to be an extreme and inevitably a life-threatening disease unless the death is intervened by another cause. AD mostly affects the parts of the brain related with higher mental capacities, explicitly the neocortex and hippocampus.

The etiology of AD is not completely perceived due to the multifactorial mechanisms underlying the disease. There are many factors which have been linked to the development and progression of AD which includes aging, cholinergic deficit, extracellular deposition of amyloid-β protein, formed from amyloid precursor protein (APP), intracellular deposition of hyperphosphorylated tau as neurofibrillary tangles, oxidative stress, loss of neuronal synapses and pyramidal neurons. Among these factors, the cholinergic deficit, extracellular deposition of amyloid-β protein, intracellular deposition of tau as neurofibrillary tangles, and oxidative stress are considered to play a significant part in AD pathogenesis.

In cholinergic deficit, the damage of cholinergic neurons happens due to the decrease of neurotransmitter like acetylcholine, an important neurotransmitter involved in critical physiological processing of the brain will get hydrolysed by the acetylcholinesterase in the synaptic cleft, an essential reaction to allow the cholinergic neurons into its resting state. The level of acetylcholine can be maintained by using an acetylcholinesterase inhibitor is used as the treatment for AD.

The extracellular accumulation of amyloid-β protein is formed by the β pathway due to the hydrolysis of amyloid precursor protein (APP) by β-secretase (BACE1) and then by γ-secretase but causes serious side effects like blindness and large catalytic pocket.

The tau is a microtubule-binding protein that helps in stabilizing and providing flexibility to the microtubules. In pathological condition, the tau will get disintegrated from the microtubules and forms tau aggregations causing intracellular deposition of neurofibrillary tangles causes impairment in neuronal axons and therefore causes neurodegeneration. Due to the incomplete understanding of AD, the tau-targeted treatment stays challenging. Oxidative stress is another significant factor of AD pathogenesis brought about by the imbalance between Reactive Oxygen species (ROS) production and antioxidants levels making harm to the cells by excessive production of ROS.

Based on different strategies, different drugs are used for the treatment of AD. which includes Aβ plagues inhibitors (Tramiprosate and ALZ-801), anti-tau (EpoD), anti-inflammatory (NSAID) and cholinergic enhancement drug (Donepezil, Galantamine, Rivastigmine, and Tacrine) which inhibits the acetylcholinesterase (AChE) but these drugs can cause serious side effects like nausea, vomiting, muscle cramps, increased bowel movement frequencies, loss of appetite, dizziness, confusion, constipation.

Various studies showed that the loss of biodiversity in the gastrointestinal tract of humans can lead to AD. The gut microbiota can maintain the homeostasis of the brain by producing neurotransmitters, nerve signals, and metabolites transmitted along the gut-brain axis. Human lifestyle changes contributed a depletion in gut microbiota which could lead to a high risk of AD pathogenesis. So, an alteration in gut microbiota through a probiotic supplementation with beneficial microorganisms could reduce the risk of AD pathogenesis and also side effects associated with the AD drugs.

The Gut microbiota and the Gut-Brain Axis

The gut microbiota consists of numerous bacterial species dwelling inside the gastrointestinal tract (GIT) existing as symbionts with the human host and is believed to play an essential role in physiology. A 51% of gut microbiota are belonging to the Firmicutes phyla comprising the groups of Clostridium coccoides and Clostridium leptum and the most acknowledged Lactobacillus.
genera and 48% consists of the Bacteroidetes phyla comprising well-recognized genera of Prevotella and Bacteroides\textsuperscript{19,20}. The remaining 1% of microbiota is the less-known phyla, comprising Proteobacteria, Actinobacteria, Bifidobacteria, Fusobacteria, Spirochaetes, Verrucomicrobia, and Lentisphaerae\textsuperscript{19,21}.

The gut microbiota got recognition due to its connectedness to the body parts remarkably the brain. The GIT is connected with the central nervous system (CNS) through a signaling pathway of networks including the autonomic, immune systems, neuroendocrine, bacterial metabolites, and neuromodulatory molecules are collectively called as the “gut-brain axis”\textsuperscript{19,22,23}. The regulatory factors are mainly common in between enteric nervous system (ENS) and CNS\textsuperscript{19,24}.

The microbiota and intestinal enterochromaffin (EC) cells secreted hormones and metabolites cross with several biochemical pathways influencing the CNS processing creating a way to communicate between the external environment in link with the gut microbiota and brain\textsuperscript{19}. The enteric nervous system formed by millions of nerves end in the GIT mucosa, helps to control the functions of intestine and communicates with the brain through the nerve vagus and is responsible for the transmission of signals from the brain to GIT through the autonomic nervous system\textsuperscript{23}. Studies suggest that an imbalance in the gut microbiota can influence the progression of neurological disorder and can initiate disease onset and also collapses the permeability of the intestine which leads to inflammatory conditions in both gut and brain, because of the proinflammatory cytokines which can enter into the bloodstream and reach the brain\textsuperscript{19,25,26}. Evidence suggests that the importance of inflammation should not be underrated, since it plays a critical role in various chronic disorders, like type II diabetes\textsuperscript{27}, AD\textsuperscript{28}, and depression\textsuperscript{23,29}.

**The genus Lactobacillus**

The lactobacilli are Gram-positive, rods or coccobacilli non-spore formers, strict fermentative, aero-tolerant, or anaerobic with complex nutritional requirements like carbohydrates, amino acids, peptides, fatty acid esters, salts, nucleic acid derivatives, and vitamins\textsuperscript{30}. Lactobacilli are either homofermentative (yielding lactic acid more than 85%) or heterofermentative (yielding lactic acid, carbon dioxide, and ethanol/acetic acid) depends upon a carbon source as glucose\textsuperscript{30}. The strains of Lactobacillus are referred to as safe consumption bacteria because of their efficiency in gut defense mechanisms\textsuperscript{31}. Lactobacillus is a genuine member of lactic acid bacteria (LAB) and other genera includes Streptococcus, Pediococcus, Lactococcus, Leuconostoc, Bifidobacterium, Carnobacterium, Enterococcus and Sporolactobacillus\textsuperscript{32}.

A probiotic is a supplementary diet consist of beneficial living microorganisms which is found as normal flora with little or no pathogenicity\textsuperscript{33,34}. These probiotics are believed to have an effect on preventing or treating diseases like gastrointestinal sickness, diarrhoea, irritable bowel syndrome, and inflammatory bowel disease (IBD)\textsuperscript{35}, and also possess antiancer, antioxidant, anti-obesity, antidiabetic, and antihyperlipidemic activities\textsuperscript{1}. Using of Lactobacilli as a probiotic strain have a long history of safe use because of its normal inhabit in human and animal GIT\textsuperscript{36} and also considered as a beneficial microorganism because of its roles in immunomodulation, enteric pathogenic intervention, and healthy intestinal microflora maintenance\textsuperscript{37}. Due to the attractiveness of “all-natural” products to treat diseases, Lactobacillus sp. (Table 1) supplemented products received popularity\textsuperscript{38}.

**Lactobacillus sp. studies in Alzheimer’s disease**

The gut microbiota’s contribution to AD pathogenesis is well studied in human and animal models. Most of the studies on probiotics were associated with its effects on oral bacteriotherapy in numerous neurological diseases and function, and only a few examines have been done to find the relationship between probiotic treatment and the mechanisms connected with AD\textsuperscript{48}. The scientists have shown the benefits of probiotics to improve cognitive impairment in humans. The probiotics are hypothesized to be a cognition booster because of its two-way communication between gut microbiota, the GIT, and the brain through the immune system, nervous system, and hormones\textsuperscript{49}. The contribution of Lactobacillus strains to the AD pathogenesis is well depicted in AD models (Table 2).

**DISCUSSION**

The relationship between the brain and the gut is a rapidly emerging field of study due to
<table>
<thead>
<tr>
<th>Table 1. Description of <em>Lactobacillus</em> sp. used as probiotics</th>
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<tr>
<td><strong>Species name</strong></td>
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<tr>
<td><em>Lactobacillus acidophilus</em></td>
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<td><em>Lactobacillus crispatus</em></td>
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<td><em>Lactobacillus amylovorus</em></td>
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<td><em>Lactobacillus gasseri</em></td>
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<td><em>Lactobacillus galinarum</em></td>
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<td><em>Lactobacillus johnsonii</em></td>
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<td><em>Lactobacillus helveticus</em></td>
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<tr>
<td><em>Lactobacillus delbrueckii</em> subsp. <em>bulgaricus</em></td>
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<tr>
<td><em>Lactobacillus salivarius</em> subsp. <em>salivarius</em></td>
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<tr>
<td>Species name</td>
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<tr>
<td><em>Lactobacillus casei</em></td>
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<tr>
<td><em>Lactobacillus paracasei</em> subsp. <em>paracasei</em></td>
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<tr>
<td><em>Lactobacillus paracasei</em> subsp. <em>tolerans</em></td>
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<td><em>Lactobacillus plantarum</em></td>
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<td><em>Lactobacillus rhamnosus</em></td>
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<td><em>Lactobacillus fermentum</em></td>
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<td><em>Lactobacillus reuteri</em></td>
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<tr>
<td>Lactobacillus sp. used</td>
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<tr>
<td>L. helveticus R0052</td>
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<tr>
<td>L. helveticus</td>
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<tr>
<td>L. casei W56, L. lactis W19, L. acidophilius W22, L. paracasei W20, L. plantarum W62, and L. salivarius W24 Human Patients with International Classification of Disease (ICD)-10 criteria of AD (f 00.1).</td>
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<td>L. Plantarum MTCC1325 Wistar Rats</td>
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<tr>
<td>L. paracasei BD87E6 In vitro studies</td>
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### Table 2. Cont...

<table>
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<tr>
<th>Lactobacillus sp. used</th>
<th>Type of study</th>
<th>Treatment</th>
<th>Major findings</th>
<th>Future aspect or limitation of the study</th>
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<tr>
<td>Lactobacillus sp. and other microbial community</td>
<td>UAS-ArcAβ42 flies and e-lav-GAL4c155 Drosophila models were set up by expressing Aβ in the CNS for the investigation of molecular mechanisms of AD.</td>
<td>The proportion of Lactobacillus and Acetobacter and the production of acetate were remarkably got decreased. A dysregulation in the microbiota can lead to AD by regulating SCFA</td>
<td>The molecular pathology understanding of AD model can be further used to develop an alternative therapeutic method in the future.</td>
<td>53</td>
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<td>L. fermentum, L. Casei, L. acidophilus</td>
<td>AD patients</td>
<td>Treating of AD patients with a probiotic formulation containing L. acidophilus, L. casei, L. fermentum, and Bifidobacterium bifidum</td>
<td>Cognitive signs improved slightly, some antioxidant factors raised and normalization of some lipid profiles.</td>
<td>The group of AD patients were under the severe stage of disease (83.5 vs. 67%) and less were under moderate stage (16.5 vs. 33%)</td>
<td>54</td>
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<tr>
<td>L. plantarum MTCC 1325</td>
<td>Albino rats</td>
<td>D-galactose induced AD</td>
<td>Ability to produce the neurotransmitter acetylcholine, healthy neurons with hyperchromatic nuclear chromatin were observed, showed a significant decrease in acetylcholinesterase (AChE) level compared to the AD-model group. Improved learning impairment, improved cognitive function, Probiotic and selenium co-supplementation on AD patients had a favourable effect on MMSE score, hs-CRP, TAC, GSH, insulin metabolism markers, triglycerides, VLDL, LDL, total-/HDL-cholesterol. Also, an improvement in gene expression of TNF-α, PPAR-γ, and LDLR.</td>
<td>Compared to the control group, the strain alone could not make any effect on AChE activity. Further investigation on the underlying mechanism of the relationship between L. plantarum MTCC 1325 and AD should be done. Probiotic Supplementation did not show an impact on spatial memory</td>
<td>55,56</td>
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<td>L. acidophilus CU60, L. acidophilus CUL21</td>
<td>Middle-aged rats</td>
<td>Aβ (1-4) induced spatial learning impairment by the pre-treatment with L. acidophilus, B. bifidum, and B. longum NINDS-ADRDA criteria and revised criteria from the National Institute of Aging-Alzheimer’s association diagnosed AD patients.</td>
<td>No effect on inflammation biomarkers, oxidative stress, FPG, other lipid profile, and gene expression of IL-8 and TGF-β. Faecal bacterial loads and plasma selenium level quantification by the intake of probiotic and selenium were not accessed and also their co-supplementation on gene expression related to oxidative stress was not examined.</td>
<td>58</td>
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<td><em>Lactobacillus C29</em></td>
<td>Male C57Bl/6J mice</td>
<td>Memory impairment with D-galactose induced aging</td>
<td>D-galactose excessive intake caused chronic inflammation due to the generation of ROS. Treatment with C29 increased the suppressed expression of DCX, BDNF, and CREB in the hippocampus region of the mouse. The findings of the study suggest that C29 can be used to inhibit inflammaging.</td>
<td>Suppressed M2 markers arginase 1 and CD206 59 suggesting that inflammation can be induced by D-galactose by activating M1 macrophages. The expression of autophagy proteins was influenced by neither C29 nor D-galactose.</td>
<td>59</td>
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<tr>
<td><em>L. fermentum, L. rhamnosus, L. plantarum, L. brevis, L. casei, L. helveticus, L. salivarius, L. sakei, L. reuteri, L. mucosa, L. crispatus, L. buchneri, L. gasseri</em></td>
<td>In vitro</td>
<td>Synthesis of GABA from Lactobacillus and Bifidobacterium strains</td>
<td>Food derived Lactobacillus strains produced a high amount of GABA (involved in neurotransmission and brain metabolism) (<em>L. buchneri WP2001, L. brevis NCL912, L. brevis K203, and L. plantarum strains</em>). GABA impaired function is involved in AD neuropathy.</td>
<td>The genes gadB and gadC are required for the synthesis and export of GABA from bacteria. The gadB gene is active in the acidic medium and the gut pH is almost close to neutral.</td>
<td>60</td>
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<td><em>L. plantarum</em></td>
<td>Adult male specific-pathogen-free (SPF) Sprague-Dawley rats</td>
<td>Chronic restraint stress in rat</td>
<td>Chronic treatment with the probiotic can lead to an anxiolytic and antidepressant effects, boost cognition, decrease the levels of plasma CORT and ACTH, modulate the balance of anti-inflammation and pro-inflammation, restore the content of 5-HT, NE, BDNF in the hippocampus region. The modification of gut microbiota can affect several pathways and as a result, delays the progression of AD.</td>
<td>The probiotic supplementation can be used as an efficient treatment for chronic-stress-induced depression.</td>
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<td><em>Lacidophilus, L. plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus,</em></td>
<td>3xTg-AD mice</td>
<td>AD mice model (reliable model of human AD patients) was treated with nine live strains of bacteria (<em>Lactobacilli, Bifidobacteria, and Streptococcus</em>)</td>
<td>The diminution of Aβ load and cognitive function improvement supports the idea of gut microbiota modulation for the prevention and treatment of AD.</td>
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<td>62</td>
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<td>L. brevis, L. acidophilus, L. casei, L. fermentum, and Bifidobacterium bifidum</td>
<td>Consumption of probiotics had favourable effects on MDA, hs-CRP, insulin metabolism markers, serum levels of triglyceride, and VLDL. The probiotic supplements can have clinical significance on the impact of probiotic supplementation reduced the amplicin-induced spatial memory deterioration and improved its chronic restraint stress.</td>
<td>Patients cognition was assessed based only on MMSE test. NMDA receptor and MR levels in hippocampus not been measured.</td>
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<td>L. plantarum MTCC 1325</td>
<td>L. paracasei BD87E6 was reported to produce (S)-rivastigmine, an anticholinesterase inhibitor that serves the cholinergic hypothesis. A dysregulation in the gut microbiota can lead to AD by regulating short-chain fatty acid (SCFA). Lactobacillus strains can be used as a preventive measure to treat AD, cognitive enhancer, memory enhancer, and safe treatment for chronic-stress-induced depression.</td>
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| L. paracasei BD87E6 | | A study from the University of Geneva, Switzerland confirms the correlation between an imbalance of gut microbiota linked to the Aβ plaques development in the brain. Studies on the links between metabolic and AD demonstrate an increment in Type 3 diabetes due to the unhealthy nutrigenomic diets down-regulated brain and hepatic Sirt1 (Sirtuin 1) related with insulin resistance, aggregation of α-synuclein and, Aβ dyshomeostasis in AD and PD. Increased exposure to Gram-negative bacterial derived LPS can cause dysbiosis in gut microbiota which may initiate metabolic and liver diseases and promote systemic chronic low-grade inflammation. In vitro studies on investigating the Lactobacillus and Bifidobacterium probiotics on colonic LPS the importance of a healthy gut specifically for immune systemic functions as well as for mental health. Once the most ignored area (the gut) has now become the most appreciated area because of its effects on most chronic diseases including neurodegenerative diseases. Lactobacillus strains as a probiotic supplement got a long history of safe uses because of their normal inhabit in the gastrointestinal tract of human beings. The studies on probiotic supplementation with Lactobacillus strains showed a decrease in the neuroinflammation responses stimulated by lipopolysaccharides (LPS) which produce proinflammatory cytokines. L. plantarum MTCC 1325 was reported to produce acetylcholine (Ach) neurotransmitter which has properties against D-galactose induced AD impairment. L. paracasei BD87E6 was reported to produce (S)-rivastigmine, an anticholinesterase inhibitor that serves the cholinergic hypothesis. A dysregulation in the gut microbiota can lead to AD by regulating short-chain fatty acid (SCFA). Lactobacillus strains can be used as a preventive measure to treat AD, cognitive enhancer, memory enhancer, and safe treatment for chronic-stress-induced depression. Studies on AD mice models treated with Lactobacillus strains proved that the modification on the gut microbiota can affect the various pathways which can result in the delaying of AD progression. The treatment with probiotic supplements showed a reduction in Aβ load and an improvement in cognitive function which supports the idea of modulation of gut microbiota for the treatment and prevention of AD.

A study from the University of Geneva, Switzerland confirms the correlation between an imbalance of gut microbiota linked to the Aβ plaques development in the brain. Studies on the links between metabolic and AD demonstrate an increment in Type 3 diabetes due to the unhealthy nutrigenomic diets down-regulated brain and hepatic Sirt1 (Sirtuin 1) related with insulin resistance, aggregation of α-synuclein and, Aβ dyshomeostasis in AD and PD. Increased exposure to Gram-negative bacterial derived LPS can cause dysbiosis in gut microbiota which may initiate metabolic and liver diseases and promote systemic chronic low-grade inflammation. In vitro studies on investigating the Lactobacillus and Bifidobacterium probiotics on colonic LPS...
and inflammatory cytokine concentrations using human colonic microbiota models uncovered that the particular probiotic strains can diminish the concentrations of colonic LPS, which may further reduce the secretion of inflammatory cytokines in macrophage cells\(^6\). LPS alters the cell phospholipid dynamics associated with the recruitment of the Aβ peptide with the advancement of toxic Aβ oligomers. With the induction of a neuroinflammatory response, LPS can act on Blood-Brain Barrier (BBB) with BBB disruption or through receptors\(^6\). Through the inflammatory process, the bacterial LPS corrupts astrocyte which thus delays Aβ clearance in the brain with an increased amyloid plaque formation in different networks related to excessive feeding and abnormal liver metabolism\(^6\). Researchers have been now recognized that the gene Sirt 1 to be defective and has been linked to genetic disease, non-alcoholic fatty liver disease (NAFLD), diabetics, and neurodegenerative diseases and the bacterial LPS may act as a competitive inhibitor to Sirt 1 with glucose and cholesterol toxicity to different cells and tissues\(^7\). To reactivate Sirt 1 and to improve drug-induced toxicity nutritional diets are required. For early identification of AD, researchers are working to identify the specific bacterial strains that produce inflammatory LPS and short-chain fatty acids (SCFAs). Understanding these underlying factors may give a new point of view on novel therapeutic strategies for AD and pathologies.

**CONCLUSION**

Biotherapy with Lactobacillus strains shows an enormous ability to treat against AD-related pathogenesis. Thus, Modulation of the gut with a personalized diet can become a treatment for various disorders including AD with decreased or no side effects. Further research to confirm the gut-microbiota and related linkages to the gut-brain axis are required to completely understand the scope of probiotics to treat these impaired diseases with a good safety profile. Researchers have been identified the inflammatory molecules LPS, from bacteria been linked to AD and chronic gut inflammation, and SCFAs. The increased degrees of LPS are identified with chronic diseases such as NAFLD, diabetics, obesity, and neurodegenerative disease. The interest in probiotics treatments for AD is quite compelling with importance to its interaction with LPS. LPS is associated with the aggregation of Aβ with impacts on nuclear and cell receptors prompts to neurotoxicity and Aβ plaque formation. In future researchers can contribute to the perspective of probiotic therapy with Lactobacillus strains and interaction with LPS to prevent Aβ aggregation and neurodegeneration as a safe and effective therapy.

**ACKNOWLEDGMENTS**

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**CONFLICT OF INTEREST**

The author declares that their is no conflict of interest.

**AUTHORS’ CONTRIBUTION**

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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**DATA AVAILABILITY**

All datasets generated or analysed during this study are included in the manuscript.

**ETHICS STATEMENT**

This article does not contain any studies with human participants or animals performed by any of the authors.

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