John et al. | J Pure Appl Microbiol | 15(3):1029-1041 | September 2021
Article 6694 | https://doi.org/10.22207/JPAM.15.3.02

Print ISSN: 0973-7510; E-ISSN: 2581-690X

REVIEW ARTICLE OPEN ACCESS

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

Shani Kunjamma John, Vani Chandrapragasam* and Pinaki Dey

Department of Biotechnology, Karunya Institute of Technology and Sciences, Karunya Nagar, Coimbatore - 641 114, Tamil Nadu, India.

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

***Correspondence:** vani@karunya.edu; +91 9842215562

(Received: October 03, 2020; accepted: June 09, 2021)

Citation: John SK, Chandrapragasam V, Dey P. Impact of Gut Microbiome Lactobacillus spp. in Brain Function and its Medicament towards Alzheimer's Disease Pathogenesis. *J Pure Appl Microbiol.* 2021; 15(3):1029-1041. doi: 10.22207/JPAM.15.3.02

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[1]. 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[2]. AD mostly affects the parts of the brain related with higher mental capacities, explicitly the neocortex and hippocampus[3].

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[4], oxidative stress, loss of neuronal synapses and pyramidal neurons[5,6]. 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[7].

In cholinergic deficit, the damage of cholinergic neurons happens due to the decrease of neurotransmitter like acetylcholine[8], 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[7].

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 results in the development of insoluble Aβ plagues[7]. Aβ plagues are the potential target for AD due to its pathological feature of severe neuronal loss. The treatment strategy to reduce the Aβ production is by targeting on β- and γ-secretase but causes serious side effects like blindness and large catalytic pocket[7,9].

The tau is a microtubule-binding protein that helps in stabilizing and providing flexibility to the microtubules[10]. 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[7]. Due to the incomplete understanding of AD, the tau-targeted treatment stays challenging[7]. 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[11].

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)[12,13] but these drugs can cause serious side effects like nausea, vomiting, muscle cramps, increased bowel movement frequencies, loss of appetite, dizziness, confusion, constipation[14].

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[15]. Human lifestyle changes contributed a depletion in gut microbiota which could lead to a high risk of AD pathogenesis[15]. 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[16] and is believed to play an essential role in physiology[17,18]. 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[19,20]. The remaining 1% of microbiota is the less-known phyla, comprising *Proteobacteria, Actinobacteria, Bifidobacteria, Fusobacteria, Spirochaetes, Verrucomicrobia,* and *Lentispaerae*[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"[19,22,23]. The regulatory factors are mainly common in between enteric nervous system (ENS) and CNS[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[19]. The enteric nervous system formed by millions of nerves end in the GIT mucosa, helps to control the functions of the 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[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[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[27], AD[28], and depression[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[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[30]. The strains of Lactobacillus are referred to as safe consumption bacteria because of their efficiency in gut defense mechanisms[31]. *Lactobacillus* is a genuine member of lactic acid bacteria (LAB) and other genera includes *Streptococcus, Pediococcus, Lactococcus, Leuconostoc, Bifidobacterium, Carnobacterium, Enterococcus* and *Sporolactobacillus*[32].

A probiotic is a supplementary diet consist of beneficial living microorganisms which is found as normal flora with little or no pathogenicity[33,34]. These probiotics are believed to have an effect on preventing or treating diseases like gastrointestinal sickness, diarrhoea, irritatable bowel syndrome, and inflammatory bowel disease (IBD)[35], and also possess anticancer, antioxidant, anti-obesity, antidiabetic, and antihyperlipidemic activities[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[36] and also considered as a beneficial microorganism because of its roles in immunomodulation, enteric pathogenic intervention, and healthy intestinal microflora maintenance[37]. Due to the attractiveness of "all-natural" products to treat diseases, *Lactobacillus* sp. (Table 1) supplemented products received popularity[35].

***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[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[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 1. Description of *Lactobacillus* sp. used as probiotics

Species name	Morphological characteristics	Growth requirements	Strains isolated from	Ref.
Lactobacillus acidophilus	Acid-loving bacteria. rods cells with rounded ends, 0.6-0.9 by 1.5-6 µm, seen as single, in pairs, and in short chains	Obligatory homofermentative Requires riboflavin, pantothenic acid (vitamin B5), folic acid, and niacin for growth	Isolated from the human and animal intestinal tract, human mouth and vagina	38,39
Lactobacillus crispatus	Straight to slightly curled rod cells, 0.8-1.6 by 2.3-11 µm, occur in single or in short chains	Obligatory homofermentative A few strains can grow at 48-53°C	Isolated from human faeces,vagina, and buccal cavities	38
Lactobacillus amylovarus	Rod-shaped cells, 1.0 by 3.0-5.0 µm, existing as single and in short chains	Obligatory homofermentative Requires pantothenic acid, folic acid, nicotinic acid, and riboflavin for growth	Pig intestinal epithelial cells	37
Lactobacillus gallinarum	Shorter to long rod-shaped cells, 0.5-1.5 by 1.5-10 µm, existing as single, in pairs, or in short chains.	Obligatory homofermentative Tolerant to 4% NaCl	Chicken intestine	38,40
Lactobacillus gasseri	Rods with rounded end cells, 0.6-.08 by 3.0-5.0 µm, existing in single or in chains (mini- cells and snake formation)	Obligatory homofermentative Growth is exceptionally expanded by anaerobiosis and 5% CO_2	Mouth, intestine, faeces, and vagina	38,41
Lactobacillus johnsonii	Shorter to long rod-shaped cells, 0.5-1.5 by 1.5-10 µm, existing in single, pairs, or in short chains	Obligatory homofermentative Tolerant to 4% NaCl	Chicken faeces, mice, calves, and pigs	38
Lactobacillus helveticus	Rod cells, 0.7-0.9 by 2.0-6.0 µm, existing in single, or in chains	Obligatory homofermentative Requires thiamine, folic acid, biotin, vitamin B12 for development, a few strains can likewise grow at 50-52 °C	Sour milk, cheese starter culture, and cheese (emmental and gruyere in particular)	38
Lactobacillus delbrueckii subsp. *bulgaricus*	Rods with rounded end cells, 0.5-.08 by 2.0-9.0 µm, existing as single, or in short chains	Obligatory homofermentative Requires pantothenic acid and niacin. Some strains need riboflavin, folic acid, vitamin BI2, and thymidine.	Yoghurt and cheese	38,42
Lactobacillus salivarius subsp. *salivarius*	Rods cells with rounded ends,0.6-0.9 by 1.5-5.0 µm, existing as single or in chains with varying length	Obligatory homofermentative Ferments salicin and esculin	The intestinal tract of human, hamster, and chicken	38,43

Table 1. Cont...

Species name	Morphological characteristics	Growth requirements	Strains isolated from	Ref.
Lactobacillus casei	Rod-shaped cells, 0.7-1.1 by 2.0-4.0 µm, existing as square ends and tends to form chains	Facultatively heterofermentative Requires riboflavin, folic acid, calcium pantothenate, and niacin for development, needs pyridoxal or pyridoamine as fundamental or stimulatory growth prerequisite	Milk, cheese, dairy products, dairy environment, sourdough, cow dung, silage, human intestinal tract, mouth, vagina, and sewage	38,44
Lactobacillus paracasei subsp. *paracasei*	Rod-shaped square-ended cells, 0.8-1.0 by 2.0-4.0 µm, existing as single or in chains	Facultatively heterofermentative Develop at 10 and 40°C a few strains can develop at 5 and 45°C	Dairy products, sewage, silage, human and clinical sources	38,45
Lactobacillus paracasei subsp. *tolerans*	Rod cells with square ends,0.8-1.0 by 2.0-4.0 µm, existing as single or in chains	Facultatively heterofermentative Withstand at 72°C for 40 sec	Dairy products	38,42
Lactobacillus plantarum	Straight rod cells with rounded ends, 0.9-1.2 by 3.0-8.0 µm, existing as single, in pairs, or in short chains	Facultatively heterofermentative Require calcium pantothenate and niacin for growth	Dairy products environments, silage, sauerkraut, pickled vegetables, sourdough, cowdung, the human mouth, intestinal tract, faeces, and from sewage	38,46
Lactobacillus rhamnosus	Rod-shaped cells with square ends, 0.8-1.0 by 2.0-4.0 µm, existing as single or in chains	Facultatively heterofermentative Some of the strains grow at 48°C	dairy products, sewage, humans, and clinical sources	38,42
Lactobacillus fermentum	Rod cells, 0.5-0.9 µm, mostly existing in single or in pairs, the length is highly variable	Obligately heterofermentative Require calcium pantothenate, niacin, and thiamine for growth	Yeast, milk products, sourdough, fermenting plant material, manure, sewage, and human mouth and faeces	38
Lactobacillus reuteri	Slightly irregular cells with bend rods meat products and rounded ends, 0.7-1.0 by 2.0-5.0 µm, existing as single, pairs or in small clusturs	Obligately heterofermentative	Human and animal faeces, and sourdough	38,47

Table 2. *Lactobacillus* sp. study on Alzheimer's disease

Lactobacillus sp. used	Type of study animal/human	Treatment	Major findings	Future aspect or limitation of the study	Ref.
L. helveticus R0052	Male Wistar rats	Peripheral neuroinflammation induced by Lipopolysaccharides (LPS).	Probiotic treatment showed a decrease in both systemic and neuroinflammation responses stimulated by LPS. Proinflammatory cytokines (TNF-α and IL1-β) levels are significantly decreased in the hippocampus and serum of the model.	The effects are not observed in the behavioural test, further research is needed to confirm the conclusion	48
L. helveticus	ddY mice	Scopolamine induced memory impairment	Calpis sour milk whey powder (prepared by using *L. helveticus* and *S. cerevisiae*) treated mice indicated an improvement in scopolamine-induced memory deterioration and memory of object recognition.	Can be used as a preventive measure from AD and as a learning and memory enhancer in humans. Further analysis with *L. helveticus* fermented milk to be done to clarify its potential in the enhancement of cognition in humans.	50,51
L. casei W56, L. lactis W19, L. acidophilus 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).	Probiotic supplementation results in an increase of kynurenine levels in serum. Stimulation of anergic immune cells may capable to initiate mechanisms that are helpful to eliminate the amyloid aggregates and damaged cells.	Increased activating events may exert a negative impact on gut barrier function and may stimulate the neurodegenerative process further. The study was not placebo-controlled	52
L. Plantarum MTCC1325	Wistar Rats	D-galactose induced AD	Activities of membrane transport ATPases were improved significantly. The bacterium stabilized the structural and functional condition of the membranes by controlling the ionic gradient through its antioxidant activity.	Studies on higher mammalian models like a rabbit, owl monkeys, vervet monkeys, squirrel monkeys should be done to understand better on Lactobacillus strains and its protection against neurodegenerative disease.	1
L. paracasei BD87E6	*In vitro* studies	L. paracasei BD87E6 used as a biocatalyst.	(S)-rivastigmine drug synthesized in a mild, cheap, and nature-friendly process using this strain as biocatalyst	Can be used as an attractive strain for biocatalytic preparation of other carbinols	20

Table 2. Cont...

Lactobacillus sp. used	Type of study animal/human	Treatment	Major findings	Future aspect or limitation of the study	Ref.
Lactobacillus sp. and other microbial community	UAS-ArcAβ42 flies and elav-GAL4c155 Drosophila	*Drosophila* models were set up by expressing Aβ in the CNS for the investigation of molecular mechanisms of AD.	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	The molecular pathology understanding of AD model can be further used to develop an alternative therapeutic method in the future.	53
L. fermentum, L. Casei, L. acidophilus	AD patients	Treating of AD patients with a probiotic formulation containing *L. acidophilus, L. casei, L. fermentum,* and Bifidobacterium bifidum	Cognitive signs improved slightly, some antioxidant factors raised and normalization of some lipid profiles.	The group of AD patients were under the severe stageof disease (83.5 vs. 67%) and less were under moderate stage (16.5 vs.33%)	54
L. plantarum MTCC 1325	Albino rats	D-galactose induced AD	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.	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.	55,56
L. acidophilus CUL60, *L. acidophilus* CUL21	Middle-aged rats	Aβ (1-4) induced spatial learning impairment by the pre-treatment with *L. acidophilus, B. bifidum,* and *B. longum*	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	Probiotic Supplementation did not show an impact on spatial memory	57,58
L. *acidophilus*	AD patients	NINDS-ADRDA criteria and revised criteria from the National Institute of Aging-Alzheimer's association diagnosed AD patients.	markers, triglycerides,VLDL, LDL, total-/HDL-cholesterol. Also, an improvement in gene expression of TNF-α, PPAR-γ, and LDLR.	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.	58

Table 2. Cont...

Lactobacillus sp. used	Type of study animal/human	Treatment	Major findings	Future aspect or limitation of the study	Ref.
Lactobacillus C29	Male C57BL/6J mice	Memory impairment with D-galactose induced aging	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.	Suppressed M2 markers arginase 1 and CD206 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.	59
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	*In vitro*	Synthesis of GABA from Lactobacillus and Bifidobacterium strains	Food derived Lactobacillus strains produced a high amount of GABA (involved in neuro-transmission and brain metabolism) (*L. buchner* WP2001, L. brevis NCL912, L. brevis K203, and *L. plantarum* strains). GABA impaired function is involved in AD neuropathy.	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.	60
L. helveticus NS8	Adult male specific-pathogen-free (SPF) Sprague-Dawley rats	Chronic restraint stress in rat	Chronic treatment with the probiotic can leads 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 probiotic supplementation can be used as an efficient safetreatment for chronic-stress-induced depression.	61
L.acidophilus, L plantarum, L. paracasei, L. delbrueckii subsp. bulgaricus,	3xTg-ADmice	AD mice model (reliable model of human AD patients) was treated with nine live strains of bacteria (*Lactobacilli,* Bifidobacteria, and *Streptococcus*	The modification of gut microbiota can affect several pathways and as a result, delays the progression of AD.	The diminution of Aβ load and cognitive function improvement supports the idea of gut microbiota modulation for the prevention and treatment of AD.	62

Table 2. Cont...

Lactobacillus sp. used	Type of study animal/human	Treatment	Major findings	Future aspect or limitation of the study	Ref.
L. brevis *L. acidophilus, L. casei, L. fermentum*	AD patients	*thermophilus*). Patients are treated with probiotic milk containing L. *acidophilus, L. casei, L. fermentum,* and *Biffobacterium bifidum.*	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 cognitive symptoms.	Patients cognition was assessed based only on MMSE test.	63
L. fermentum strain NS9	Male Sprague-Dawley rats	Ampicillin induced physiological and psychological irregularity in rats.	Probiotic supplementation reduced the ampicillin-induced spatial memory deterioration and improved its chronic restraint stress.	NMDA receptor and MR levels in hippocampus not been measured.	64

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[48]. *L. plantarum* MTCC 1325 was reported to produce acetylcholine (Ach) neurotransmitter which has properties against D-galactose induced AD impairment[1]. *L. paracasei* BD87E6 was reported to produce (S)-rivastigmine, an anticholinesterase inhibitor that serves the cholinergic hypothesis[20]. A dysregulation in the gut microbiota can lead to AD by regulating short-chain fatty acid (SCFA)[53]. *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[62].

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[65]. 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[66]. 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[67]. 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[68]. Through the inflammatory process, the bacterial LPS corrupts asterocyte 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[69]. 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[70]. 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

We would like to thank the Department of Biotechnology, Karunya Institute of Technology and Sciences.

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.

FUNDING

This research was supported by UGC-Maulana Azad Fellowship, grant number F1-17.1/2016-17/MANF-2015-17-KER-70961.

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.

REFERENCES

1. Mallikarjuna N, Praveen K, Yellamma K. Role of *Lactobacillus plantarum* MTCC1325 in membrane-bound transport ATPases system in Alzheimer's disease-induced rat brain. *Bioimpacts.* 2016;6(4):203-209. doi:10.15171/bi.2016.27
2. Barber RC. The Genetics of Alzheimer's Disease. *Scientifica.* 2012;2012:246210. doi: 10.6064/2012/246210
3. Francis PT, Palmer AM, Snape M, Wilcock GK. The cholinergic hypothesis of Alzheimer's disease: a review of progress. *J Neurol Neurosurg Psychiatry.* 1999;66(2):137-147. doi:10.1136/jnnp.66.2.137
4. Liu PP, Xie Y, Meng XY, Kang JS. History and progress of

hypotheses and clinical trials for Alzheimer's disease. *Signal Transduct Target Ther*. 2019;4(1):29. doi: 10.1038/s41392-019-0063-8

5. Olasehinde TA, Olaniran AO, Okoh AI. Macroalgae as a Valuable Source of Naturally Occurring Bioactive Compounds for the Treatment of Alzheimer's Disease. *Mar Drugs.* 2019;17(11):609. doi: 10.3390/md17110609
6. Subash S, Essa MM, Al-Asmi A, Al-Adawi S, Vaishnav R. Chronic Dietary Supplementation of 4% Figs on the Modification of Oxidative Stress in Alzheimer's Disease Transgenic Mouse Model. *BioMed Research Int.* 2014;2014:546357. doi: 10.1155/2014/546357
7. Du X, Wang X, Geng M. Alzheimer's disease hypothesis and related therapies. *Translational Neurodegeneration.* 2018;7(1):2. doi:10.1186/s40035-018-0107-y
8. Teles AP, Takahashi JA. Paecilomide, a new acetylcholinesterase inhibitor from Paecilomyces lilacinus. *Microbiol Res.* 2013;168(4):204-210. doi: 10.1016/j.micres.2012.11.007
9. Klaver DW, Wilce MCJ, Cui H, et al. Is BACE1 a suitable therapeutic target for the treatment of Alzheimer's disease? Current strategies and future directions. *Biological Chemistry.* 2010;391(8):849-859. doi:10.1515/bc.2010.089
10. What is Tau Protein? Accessed September 16, 2020. https://healthfully.com/466916-what-is-tau-protein.html
11. Gandhi S, Abramov AY. Mechanism of Oxidative Stress in Neurodegeneration. *Oxid Med Cell Longev.* 2012;2012:428010. doi: 10.1155/2012/428010
12. Pan H, Zhang J, Wang Y, et al. Linarin improves the dyskinesia recovery in Alzheimer's disease zebrafish by inhibiting the acetylcholinesterase activity. *Life Sciences.* 2019;222:112-116. doi:10.1016/j.lfs.2019.02.046
13. Benek O, Korabecny J, Soukup O. A Perspective on Multi-target Drugs for Alzheimer's Disease. *Trends Pharmacol Sci.* 2020;41(7):434-445. doi: 10.1016/j.tips.2020.04.008
14. FDA-approved-treatments-alzheimers-ts.pdf. Accessed September 16, 2020. https://alz.org/media/Documents/fda-approved-treatments-alzheimers-ts.pdf
15. Fox M, Knorr DA, Haptonstall KM. Alzheimer's disease and symbiotic microbiota: an evolutionary medicine perspective. *Ann NY Acad Sci.* 2019;1449(1):3-24. doi:10.1111/nyas.14129
16. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;464(7285):59-65. doi:10.1038/nature08821
17. Gill SR, Pop M, Deboy RT, et al. Metagenomic analysis of the human distal gut microbiome. *Science.* 2006;312(5778):1355-1359. doi:10.1126/science.1124234
18. Kim N, Yun M, Oh YJ, Choi H-J. Mind-altering with the gut: Modulation of the gut-brain axis with probiotics. *J Microbiol.* 2018;56(3):172-182. doi:10.1007/s12275-018-8032-4
19. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. *Cell Mol Life Sci.* 2017;74(20):3769-3787. doi:10.1007/s00018-017-2550-9
20. Oksuz S, Sahin E, Dertli E. Synthesis of Enantiomerically Enriched Drug Precursors by *Lactobacillus paracasei* BD87E6 as a Biocatalyst. *Chemistry & Biodiversity.* 2018;15(6):e1800028. doi:10.1002/cbdv.201800028
21. Stojanović MR, Smidt H, Vos WMD. Diversity of the human gastrointestinal tract microbiota revisited. *Environmental Microbiology.* 2007;9(9):2125-2136. doi:10.1111/j.1462-2920.2007.01369.x
22. Quigley EMM. Microbiota-Brain-Gut Axis and Neurodegenerative Diseases. *Curr Neurol Neurosci Rep.* 2017;17(12):94. doi:10.1007/s11910-017-0802-6
23. Luca M, Di Mauro M, Di Mauro M, Luca A. Gut Microbiota in Alzheimer's Disease, Depression, and Type 2 Diabetes Mellitus: The Role of Oxidative Stress. *Oxid Med Cell Longev.* 2019;2019:4730539. doi:10.1155/2019/4730539
24. Burns AJ. Migration of neural crest-derived enteric nervous system precursor cells to and within the gastrointestinal tract. *Int J Dev Biol.* 2005;49(2-3):143-150. doi:10.1387/ijdb.041935ab
25. Catanzaro R, Anzalone M, Calabrese F, et al. The gut microbiota and its correlations with the central nervous system disorders. *Panminerva Med.* 2014;57(3):127-143.
26. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking Down the Barriers: The Gut Microbiome, Intestinal Permeability and Stress-related Psychiatric Disorders. *Front Cell Neurosci.* 2015;9:392. Accessed September 16, 2020. doi: 10.3389/fncel.2015.00392
27. Xu Y, Zhou H, Zhu Q. The Impact of Microbiota-Gut-Brain Axis on Diabetic Cognition Impairment. *Front Aging Neurosci.* 2017;9:106. doi:10.3389/fnagi.2017.00106
28. Luca M, Luca A, Calandra C. The Role of Oxidative Damage in the Pathogenesis and Progression of Alzheimer's Disease and Vascular Dementia. *Oxid Med Cell Longev.*2015;2015:504678. doi: 10.1155/2015/504678
29. Kim JM, Stewart R, Kim JW, et al. Changes in pro-inflammatory cytokine levels and late-life depression: A two year population based longitudinal study. *Psychoneuroendocrinology.* 2018;90:85-91. doi:10.1016/j.psyneuen.2018.02.006
30. Hammes WP, Vogel RF. The genus Lactobacillus. In: Wood BJB, Holzapfel WH, eds. The Genera of Lactic Acid Bacteria. *The Lactic Acid Bacteria. Springer US.* 1995:19-54. doi:10.1007/978-1-4615-5817-0_3
31. Arasu MV, Al-Dhabi NA, Ilavenil S, Choi KC, Srigopalram S. *In vitro* importance of probiotic Lactobacillus plantarum related to medical field. *Saudi J Biol Sci.* 2016;23(1, Suppl):S6-S10. doi:10.1016/j.sjbs.2015.09.022
32. Wood BJB. The Lactic Acid Bacteria: Volume 1: The Lactic Acid Bacteria in Health and Disease. Springer Science & Business Media; 2012.
33. Alvarez-Olmos MI, Oberhelman RA. Probiotic Agents and Infectious Diseases: A Modern Perspective on a

Traditional Therapy. *Clin Infect Dis.* 2001;32(11):1567-1576. doi:10.1086/320518

34. Salminen S, Arvilommi H. Probiotics Demonstrating Efficacy in Clinical Settings. *Clin Infect Dis*. 2001;32(11):1577-1578. doi:10.1086/320529
35. Slover CM, Danziger L. Lactobacillus: a Review. *Clin Microbiol Newsl.* 2008;30(4):23-27. doi:10.1016/j.clinmicnews.2008.01.006
36. Floch MH, Walker WA, Guandalini S, et al. Recommendations for probiotic use--2008. *J Clin Gastroenterol.* 2008;42(Suppl 2):S104-108. doi:10.1097/MCG.0b013e31816b903f
37. Kant R, Paulin L, Alatalo E, de Vos WM, Palva A. Genome Sequence of *Lactobacillus amylovorus* GRL1118, Isolated from Pig Ileum. *J Bacteriol.* 2011;193(12):3147-3148. doi:10.1128/JB.00423-11
38. Wood BJB, Holzapfel WHN. The Genera of Lactic Acid Bacteria. Springer Science & Business Media. 1995;2.
39. Altermann E, Russell WM, Azcarate-Peril MA, et al. Complete genome sequence of the probiotic lactic acid bacterium *Lactobacillus acidophilus* NCFM. *Proc Natl Acad Sci* . 2005;102(11):3906-3912. doi:10.1073/pnas.0409188102
40. Sun Z, Harris HMB, McCann A, et al. Expanding the biotechnology potential of *lactobacilli* through comparative genomics of 213 strains and associated genera. *Nat Commun.* 2015;6(1):8322. doi:10.1038/ncomms9322
41. Marcotte H, Brandsborg E, Hammarstrom L. *Lactobacillus gasseri* DSM 14869. Accessed September 16, 2020. https://www.uniprot.org/proteomes/UP000217220
42. Pot B, Felis GE, Bruyne KD, et al. The genus Lactobacillus. In: Lactic Acid Bacteria. *John Wiley & Sons, Ltd;* 2014:249-353. doi:10.1002/9781118655252.ch19
43. Goodfellow M, Whitman WB, Bergey DH, et al. Eds. Bergey's Manual of Systematic Bacteriology. Vol. 5: The Actinobacteria 2. Ed. Springer; 2012.
44. Makarova K, Slesarev A, Wolf Y, et al. Comparative genomics of the lactic acid bacteria. *Proc Natl Acad Sci* . 2006;103(42):15611-15616. doi:10.1073/pnas.0607117103
45. Collins MD, Phillips BA, Zanoni P. Deoxyribonucleic Acid Homology Studies of Lactobacillus casei, Lactobacillus paracasei sp. nov., subsp. paracasei and subsp. tolerans, and *Lactobacillus rhamnosus* sp. nov., comb. nov. *Int J Syst Evol Microbiol*. 1989;39(2):105-108. doi:10.1099/00207713-39-2-105
46. van Kranenburg R, Golic N, Bongers R, et al. Functional Analysis of Three Plasmids from *Lactobacillus plantarum*. *AEM.* 2005;71(3):1223-1230. doi:10.1128/AEM.71.3.1223-1230.2005
47. Vos P, Garrity G, Jones D, et al. Bergey's Manual of Systematic Bacteriology: Volume 3: The Firmicutes (Bergey's Manual of Systematic Bacteriology (Springer-Verlag)). Accessed September 16, 2020. https://b-ok.asia/book/1273128/4c6e79?redirect=29896517&regionChanged=&signAll=1
48. Mohammadi G, Dargahi L, Peymani A, et al. The Effects of Probiotic Formulation Pretreatment (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) on a Lipopolysaccharide Rat Model. *J Am Coll Nutr*. 2019;38(3):209-217. doi:10.1080/07315724.2018.1487346
49. Probiotics improve cognition in Alzheimer's patients. Science & research news. Frontiers. 2016. Accessed September 16, 2020. https://blog.frontiersin.org/2016/11/10/probiotics-improve-cognition-in-alzheimers-patients/
50. Kim B, Hong VM, Yang J, et al. A Review of Fermented Foods with Beneficial Effects on Brain and Cognitive Function. *Prev Nutr Food Sci.* 2016;21(4):297-309. doi:10.3746/pnf.2016.21.4.297
51. Ohsawa K, Uchida N, Ohki K, Nakamura Y, Yokogoshi H. *Lactobacillus helveticus*-fermented milk improves learning and memory in mice. *Nutr Neurosci.* 2015;18(5):232-240. doi:10.1179/1476830514Y.0000000122
52. Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. *Current Alzheimer Research.* 2018;15(12):1106-1113. doi:10.2174/1389200219666180813144834
53. Kong Y, Jiang B, Luo X. Gut microbiota influences Alzheimer's disease pathogenesis by regulating acetate in Drosophila model. *Future Microbiology.* 2018;13(10):1117-1128. doi:10.2217/fmb-2018-0185
54. Agahi A, Hamidi GA, Daneshvar R, et al. Does Severity of Alzheimer's Disease Contribute to Its Responsiveness to Modifying Gut Microbiota? A Double Blind Clinical Trial. *Front Neurol.* 2018;9:662. doi:10.3389/fneur.2018.00662
55. Stephenson M, Rowatt E. The production of acetylcholine by a strain of *Lactobacillus plantarum*. *J Gen Microbiol.* 1947;1(3):279-298. doi:10.1099/00221287-1-3-279
56. Nimgampalle M, Kuna Y. Anti-Alzheimer Properties of Probiotic, *Lactobacillus plantarum* MTCC 1325 in Alzheimer's Disease induced Albino Rats. *J Clin Diagn Res.* 2017;11(8):KC01-KC05. doi:10.7860/JCDR/2017/26106.10428
57. Rezaeiasl Z, Salami M, Sepehri G. The Effects of Probiotic *Lactobacillus* and *Bifidobacterium* Strains on Memory and Learning Behavior, Long-Term Potentiation (LTP), and Some Biochemical Parameters in β-Amyloid-Induced Rat's Model of Alzheimer's Disease. *Prev Nutr Food Sci.* 2019;24(3):265-273. doi:10.3746/pnf.2019.24.3.265
58. Tamtaji OR, Heidari-soureshjani R, Mirhosseini N, et al. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: A randomized, double-blind, controlled trial. *Clinical Nutrition.* 2019;38(6):2569-2575. doi:10.1016/j.clnu.2018.11.034
59. Woo JY, Gu W, Kim KA, Jang SE, Han MJ, Kim DH. *Lactobacillus pentosus* var. *plantarum* C29 ameliorates memory impairment and inflammaging in a d-galactose-induced accelerated aging mouse model. *Anaerobe.* 2014;27:22-26. doi:10.1016/j.anaerobe.2014.03.003
60. Yunes RA, Poluektova EU, Dyachkova MS, et al. GABA production and structure of gadB/gadC genes in *Lactobacillus* and *Bifidobacterium* strains from

human microbiota. *Anaerobe*. 2016;42:197-204. doi:10.1016/j.anaerobe.2016.10.011

61. Liang S, Wang T, Hu X, et al. Administration of *Lactobacillus helveticus* NS8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. *Neuroscience.* 2015;310:561-577. doi:10.1016/j.neuroscience.2015.09.033
62. Bonfili L, Cecarini V, Berardi S, et al. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. *Scientific Reports.* 2017;7(1):2426. doi:10.1038/s41598-017-02587-2
63. Akbari E, Asemi Z, Daneshvar Kakhaki R, et al. Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial. *Front Aging Neurosci.* 2016;8:256. doi:10.3389/fnagi.2016.00256
64. Wang T, Hu X, Liang S, et al. *Lactobacillus fermentum* NS9 restores the antibiotic induced physiological and psychological abnormalities in rats. *Beneficial Microbes.* 2015;6(5):707-717. doi:10.3920/BM2014.0177
65. Marizzoni M, Cattaneo A, Mirabelli P, et al. Short-Chain Fatty Acids and Lipopolysaccharide as Mediators between Gut Dysbiosis and Amyloid Pathology in Alzheimer's Disease. *J Alzheimer's Dis.* 2020;78(2):683-697. doi:10.3233/JAD-200306
66. Martins IJ. Diabetes and cholesterol dyshomeostasis involve abnormal α-synuclein and amyloid beta transport in neurodegenerative diseases. *Austin Alzheimer's Journal of Parkinson's Disease*. 2015;2(1):1020. https://austinpublishinggroup.com/aapd/fulltext/aapd-v2-id1020.php
67. Rodes L, Khan A, Paul A, et al. Effect of probiotics Lactobacillus and Bifidobacterium on gut-derived lipopolysaccharides and inflammatory cytokines: an *in vitro* study using a human colonic microbiota model. *J Microbiol Biotechnol.* 2013;23(4):518-526. doi:10.4014/jmb.1205.05018
68. Martins IJ. Bacterial lipopolysaccharides change membrane fluidity with relevance to phospholipid and amyloid beta dynamics in Alzheimer's disease. *Journal of Microbial & Biochemical Technology*. 2016;8(4):322-324. doi:10.4172/1948-5948.1000304
69. Martins IJ. Unhealthy Diets Determine Benign or Toxic Amyloid Beta States and Promote Brain Amyloid Beta Aggregation. *Austin Journal of Clinical Neurology.* 2015;2(7):1060.
70. James MI. The Future of Genomic Medicine Involves the Maintenance of Sirtuin 1 in Global Populations. *IJMBOA.* 2017;2(2):42-45. doi:10.15406/ijmboa.2017.02.00013