JMRI
Dr. Varshil Mehta
www.jmri.org.in
Quick Access
Review Article

Probiotics: An Adjuvant therapy for D-Galactose induced Alzheimer's disease

Varshil Mehta*[1], Kavya Bhatt[2], Nimit Desai[1], Mansi Naik[3]

Abstract

Alzheimer's disease (AD) is a slowly progreessing and chronic neurodegenerative disorder which has now become a major health concern worldwide. The previous literature has shown that oxidative stress is one of the most important risk factors behind the etiopathogenesis of AD. Oxidative stress subsequently leads to the production of Reactive Oxygen Species (ROS).

D-Galactose, a reducing sugar, reacts with amines of amino acids non-enzymatically in the proteins and peptides to form Advanced Glycation End products which further activates its receptors coupled to biochemical pathways that stimulate ROS production and induces mitochondrial dysfunction which damages the neuron intracellularly. High dosage of D-Galactose also suppresses the production of nerve growth factors and its associated proteins which results in the degeneration of nerve cells and reduction of acetylcholine levels in brain regions. This article put forwards the advantages of using Lactic Acid Bacteria (Probiotics) possessing anti-oxidant properties and which produces Acetyl Choline against D-Galactose induced Alzheimer's disease.

Keywords: D-Galactose, Alzheimer's disease, Adjuvant therapy, Probiotics.

Introduction

Alzheimer's disease (AD) is one of the most chronic and slowly progressing neurodegenerative disorder known till date. Approximately, 44 million patients have been already affected by Alzheimer's related dementia and the researchers believe that more than 4 million and 5.3 million individuals have Alzheimer's disease in India and the United States, respectively [1,2].

It is predicted that, by 2050, more than 13.5 million individuals will be having AD [3]. AD is often associated with cognition and memory deficits which arises due to accumulation of the amyloid plaques and neurofibrillary tangles along with disruption of cholinergic neurons in the basal forebrain of aged people [4].

The cognitive decline is associated with the AD pathogenesis which is due to decrease in Acetyl Choline (A.Ch) [5], which also proposes that deficit of Acetylcholine is life-threatening in the creation of the symptoms of AD [6]. Therefore, a major milestone in the treatment of AD should involve an attempt to prevent the degeneration of cholinergic neurons and increase the Acetylcholine levels in central nervous system. In addition, several reserachers suggested that Reactive Oxygen species (ROS) is associated with etiopathogenesis of AD and it leads to a cumulative damage of cellular macromolecules and impairment of mitochondria function which further leads to a decrease in cellular energy production [7].

Prolonged supplementation of D-Galactose induces oxidative stress followed by mitochondrial dysfunction and intracellular damage of neurons, accelerating aging, and influencing age-related cognitive decline in experimental animals [8].

D-Galactose Induced Alzheimer's Disease

D-Galactose induces aging-inducible oxidative stress in vivo, which resembles the natural aging process in mice [9, 10]. D-Galactose is metabolized to galactose-1-phosphate at a normal concentration by D-galactokinase or galactose-1-phosphate uridyl-transferase, but not at high levels. Instead, at increased concentration, D-galactose is converted to galactitol, which accumulates in cells and then induces osmotic stress and generates reactive oxygen species (ROS) which induces mitochondrial dysfunction and is the major cause of intracellular damage [11]. D-Galactose also reacts with the free amines of amino acids in peptides and proteins forming advanced glycation end-products (AGE) [12]. High dosage of D-Galactose also suppresses the expression of nerve growth factors and its associate protein resulting in the degeneration of nerve cells and reduction of acetylcholine levels in brain regions (Figure 1).

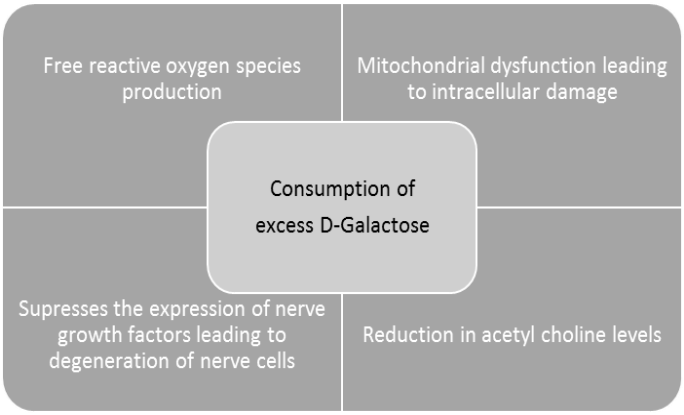

Figure 1. D-Galactose induced Alzheimer's Disease

ROS activate inflammatory signaling molecules, such as the phosphatidylinositol 3-kinase (PI3K), nuclear factor-kappa B

(NF-kB), Janus kinase (JAK) and mitogen-activated protein kinases (MAPK). It also induces the expression of tumor necrosis factor-alpha, interleukin-1b (IL-1b) and IL-6 [13]. D-Galactose increases replicative senescence markers p16 expression and telomere shortening but reduces doublecortin (DCX) expression [14]. Therefore, D-galactose continuously stimulates low-grade inflammation, which is associated with the acceleration of aging.

Lactic Acid Bacteria (Probiotics) and D-Galactose Induced Alzheimer's Disease

Lactic acid bacteria (LAB) are gram-positive, acid-tolerant and generally non-sporulating bacteria. The LAB is found in various food stuff like cheese, yogurt, and among the vagina and gastrointestinal microbiota. LAB are considered as safe food products [15], which are the best studied amongst the beneficial probiotics useful for the prevention of diarrhea, lactose intolerance, treating ulcer, infectious disease prevention, restore the composition of the gut microbiome and introduce beneficial functions to host through immune, neuro modulation [16].

Lactobacillus is a gram-positive facultative anaerobic or microaerophilic rod-shaped bacteria. They also possesss various properties like anticancer, antioxidant, antidiabetic, antiobesity, and antihyperlipidemic effects [17].

Recent studies have found that the L. plantarum versus pentosus showed a protective effect against memory deficit in AD-induced mice by D-Galactose and scopolamine [12,18]. Further, another study reported that L. Plantarum NDC75017 improves the learning and memory ability in aging rats [19]. Previous reports proved that strong antioxidants increases the Na+, K+-ATPases activities by decreasing AChE (Acetyl cholinesterase) levels and improves the cognition by enhancing cholinergic transmission [20].

Lactobacillus plantarum MTCC1325 strain has the ability to produce Acetylcholine Neurotransmitter via both externally and internally pathway [21] and this strain also possess potential antioxidant activity.

Chronic injection of D-Galactose induces memory impairment, neurodegeneration and oxidative damage in mice [22]. L. plantarum MTCC 1325 has the ability to produce the neurotransmitter viz. Acetylcholine [23] and also possesses potential antioxidant activity.

Biochemically, it was well established that AD has been related to a significant decrease in the brain neurotransmitter ACh [24] and oxidative stress, eventually leading to imbalance production and detoxification of ROS, which is considered to be the important factor in the development of AD. AD-model rats showed a significant decline in total body weight, organ index, hair loss and skin elasticity[25]. Chronic administration of D-Galactose caused significant decline in spatial memory and reduced gross behaviorall activity which suggests impairment of memory [8].

From the comparative studies conducted for 60 days in rats, it was evident that chronic administration of L. plantarum MTCC1325 for 60 days showed significant improvement and recovery from AD. There was significant improvement in the activities of the membrane transport ATPases system in the selected brain regions of AD-induced group as well. Further, it was revealed that L. Plantarum MTCC1325 protects the neurons by stabilizing the structural and functional integrity of the biological membranes through the regulation of ionic concentration gradient by its antioxidant properties [26].

Similarly, the results on the cholinergic system indicated that chronic administration of D-Galactose caused a significant reduction in ACh level in brain due to dysfunction of cholinergic neurons and reduced activity of Choline acetyltransferase [27] while elevation in AChE activity was responsible for cognitive deficit, this condition was significantly ameliorated in both the regions of brain such as hippocampus and cerebral cortex by oral supplementation of L. plantarum MTCC1325.

This may be associated with its potential antioxidant nature, Acetylcholine producing activities of L. plantarum MTCC1325 and also bidirectional communication between the Gut-Bain Axis (Enteric Nervous System) [28]. The recent reviews on Gut-Bain Axis communication describe the bacteria (micro biome) present in the gastro-intestinal tract may communicate with the brain and nervous system by different ways.

Microbes have the ability to produce neurochemicals or neurotransmitters that are exact analoges in structure to those produced by the host nervous system and act as vehicles for neurotransmitters and influence the mood and behavior [29]. Microbes have also shown immunomodulatory effect by the release of host immune factors such as cytokines and inflammatory mediators that have known neuronal targets within both the CNS & ENS [30]. Most of the lactic acid bacteria and Probiotics may also activate the vagal nerves, which interacts with all neurons involved in the alleviation of behavioural changes like anxiety, learning and memory, Depression etc. [28]. It has been demonstrated that a probiotic bacterium (L. rhamnosus JB-1) influences the emotional behaviour in mice mediated via GABA receptor [31].

Hence by above studies, it is observed that probiotics especially LAB could be useful in preventing/treating D-Galactose Induced Alzheimer's Disease. However, further research is required, so on to better understand the possible role of Lactobacillus strains in the protection against neurodegenerative diseases.

Conclusion

Antioxidant and ACh producing L. plantarum MTCC 1325 has Anti-Alzheimer properties against D-Galactose induced Alzheimer's disease since it resulted in body weight gain and

organ index, improved the behavioral activity and learning skills through an elevation in the cholinergic neurotransmitter in the hippocampus and cerebral cortex regions of the brain and restored histopathological abnormalities back to the normal conditions.All these preliminary findings suggested that, the L. plantarum MTCC 1325 might have exerted ameliorative effect against Alzheimer's disease induced by D-Galactose.

References

1. Alzheimer's and Dementia in India. Available from: http://www.alz.org/in/dementia-alzheimers-en.asp. Accessed on 3rd March, 2017.
2. Changing the Trajectory of Alzheimer's Disease. Available from: http://www.alz.org/alzheimers_disease_trajectory.asp. Accessed on 3rd March, 2017.
3. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, Park DC. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia. 2011 May 31;7(3):280-92.
4. Kumar A, Singh A. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological Reports. 2015 Apr 30;67(2):195-203.
5. Mesulam M. The cholinergic lesion of Alzheimer's disease: pivotal factor or side show?. Learning & Memory. 2004 Jan 1;11(1):43-9.
6. Terry, A.V, Jr. Buccafusco, J.J. The cholinergypothic thesis of age and Alzheimer's disease-released cognitivedeficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Therapy. 2003; 306:821-827
7. Zhu X, Perry G, Moreira PI, Aliev G, Cash AD, Hirai K, Smith MA. Mitochondrial abnormalities and oxidative imbalance in Alzheimer disease. Journal of Alzheimer's Disease. 2006 Jan 1;9(2):147-53.
8. Lei M, Su Y, Hua X, Ding J, Han Q, Hu G, et al. Chronic systemic injection of D-galactose impairs the septohippocampal cholinergic system in rats. Neuroreport. 2008; 19: 1611-1615.
9. Ho S, Liu J, Wu R. Establishment of the mimetic aging effect in mice caused by D-galactose. Biogerontology 2003;4:15e8.
10. Lei M, Hua X, Xiao M, Ding J, Han Q, Hu G. Impairments of astrocytes are involved in the d-galactose-induced brain aging. Biochem Biophys Res Commun 2008;369:1082e7.
11. Zhang Z, Fan S, Zheng Y, Lu J, Wu D, Shan Q, et al. Purple sweet potato color attenuates oxidative stress and inflammatory response induced by d-galactose in mouse liver. Food Chem Toxicol 2009;47:496e501.
12. 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 Jun 30;27:22-6.
13. Gill R, Tsung A, Billiar T. Linking oxidative stress to inflammation: toll-like receptors. Free Radic Biol Med 2010;48:1121e32.
14. Yoo DY, Kim W, Lee CH, Shin BN, Nam SM, Choi JH, et al. Melatonin improves D-galactose-induced aging effects on behavior, neurogenesis, and lipid peroxidation in the mouse dentate gyrus via increasing pCREB expression. J Pineal Res 2012;52:21e8.
15. Bernardeau M, Vernoux JP, Henri-Dubernet S, Guéguen M. Safety assessment of dairy microorganisms: The Lactobacillus genus. Int J Food Microbiol 2008;126(3):278-85.
16. Masood MI, Qadir MI, Shirazi JH, Khan IU. Beneficial effects of lactic acid bacteria on human beings. Critical reviews in microbiology. 2011 Feb 1;37(1):91-8.
17. Islam MS, Choi H. Antidiabetic effect of Korean traditional Baechu (Chinese cabbage) kimchi in a type 2 diabetes model of rats. J Med Food 2009;12:292-7.
18. Jung IH, Jung MA, Kim EJ, Hem MJ, Kim DH. Lactobacillus pentosus var. plantarum C29 protects scopolamine induced memory deficit in mice. J Appl Microbiol 2012;113:1498-506.
19. Peng X, Meng J, Chi T, Liu P, Man C, Liu S, et al. Lactobacillus plantarum NDC 75017 alleviates the learning and memory ability in aging rats by reducing mitochindraildysfunction. Exp Ther Med 2014; 8: 1841-6. doi:10.3892/etm.2014.2000.
20. Hanish Singh JC, Alagarsamy V, Diwan PV, Sathesh Kumar S, Nisha JC, Narsimha Reddy Y. Neuroprotective effect of Alpiniagalanga (L.) fractions on Abeta(25-35) induced amnesia in mice. J Ethnopharmacol 2011;138(1):85-91.
21. Girvin GT, Stevenson JW. Cell free" choline acetylase" from Lactobacillus plantarum. Canadian journal of biochemistry and physiology. 1954 Mar 1;32(2):131-46.
22. Cui X, Zuo P, Zhang Q, Li X, Hu Y, Long J, Packer L, Liu J. Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: Protective effects of R-α-lipoic acid. Journal of neuroscience research. 2006 Jun 1;83(8):1584-90.

23. Stephenson M, Rowatt E, Harrison K. The production of acetylcholine by a strain of Lactobacillus plantarum. Microbiology. 1947 Sep 1;1(3):279-98.
24. Lane RM, Potkin SG, Enz A. Targeting acetylcholinesterase and butyrylcholinesterase in dementia. International Journal of Neuropsychopharmacology. 2006 Feb 1;9(1):101-24.
25. Yi ZJ, Fu YR, Li M, Gao KS, Zhang XG. Effect of LTA isolated from bifidobacteria on d-galactose-induced aging. Experimental gerontology. 2009 Dec 31;44(12):760-5.
26. 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.
27. Zhang WW, Sun QX, Liu YH, Gao W, Li YH, Lu K, Wang Z. Chronic administration of Liu Wei Dihuang protects rat's brain against D-galactose-induced impairment of cholinergic system. Sheng li xue bao:[Acta physiologica Sinica]. 2011 Jun;63(3):245-55.
28. Liu X, Cao S, Zhang X. Modulation of gut microbiota–brain axis by probioticsprebiotics, and diet. Journal of agricultural and food chemistry. 2015 Sep 1;63(36):7885-95.
29. Lyte M. Microbial endocrinology and nutrition: a perspective on new mechanisms by which diet can influence gut-to-brain communication. PharmaNutrition. 2013 Jan 31;1(1):35-9.
30. Wood JD. Entericneuroimmunophysiology and pathophysiology. Gastroenterol. 2004;127:635-657.
31. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proceedings of the National Academy of Sciences. 2011 Sep 20;108(38):16050-5.

Author's Profile

Dr. Varshil Mehta

Dr. Kavya Bhatt

Dr. Nimit Desai

Dr. Mansi Naik

Article Details

Author Details
1. MGM Medical College, Navi Mumbai, India.
2. Santosh Medical College, Ghaziabad, India.
3. Government Medical College, Bhavnagar, India.

***Corresponding Author Details**
Varshil Mehta,
103, Sky high Tower, Orlem, Tank Road, Malad West, Mumbai 400064, India.
Email I'D: varshil91@gmail.com

Date of Submission: 30/01/2017 | **Date of Peer review**: 13/02/2017 | **Date of Acceptance**: 26/02/2017 | **Date of Publishing**: 04/03/2017

Financial or Other Competing Interests: None

How to cite this article
Mehta, V., Bhatt, K., Desai, N,. & Naik, M. (2017). Probiotics: An Adjuvant therapy for D-Galactose induced Alzheimer's disease. *Journal Of Medical Research And Innovation*, 1(1), 30-33.