IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 6, May 2025
Impact Factor: 7.67

Potential Lipid Lowering Effect Ofprobiotic Inchronic Stress Induced Alzheimer's Disease in Animal Model

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Abstract: *Stress is major problem among people now a days. Prolonged stress may have an impact on the body's physiological processes.The purpose of this work was to assess the antihyperlipidemic potential of probiotic instressed animal model. Probiotics are live microbial food supplements with certain benefits for consumers and are thought to maintain or improve the intestinal microbial balance. In this study animals were divided in to five groups. Stress was induced in rats by restraining rat for 6 hrs daily for 21 days. Stress in animal was determined by using open field and hole board method. The effect ofprobiotics ($1x10^9$ CFU) daily p.o. for 21 days on blood lipid profile was assessed. The rats showed a notable change in the lipid profile of the negative control group.The results demonstrated that administering probiotics restored abnormal lipid profiles.The present finding indicates that the probiotics exhibits antihyperlipidemic potential at ($1x10^9$ CFU) daily*

Keywords: Probiotcs, Hyperlipidemia, antihyperlipidemic activity, lipid lowering

I. INTRODUCTION

Stress and stress-related disorders are a significant cause of disease in modern times, contributing to perhaps 75% of all illnesses. Stress has been postulated to be involved in the etiopathogenesis of a diverse variety of diseases ranging from psychiatric disorder such as anxiety and depression, immunosuppression, endocrine disorders including diabetes mellitus, male sexual dysfunction, cognitive dysfunctions, peptic ulcer, hypertension and ulcerative colitis [Swati Singh et al., 2014]. This could damage certain brain areas which are normally involved in performing the key functions such as inhibition of memory formation and consolidation process by damaging the hippocampus [Maroun M et al., 2003].

As per WHO (2019) Alzheimer disease (AD) is the most common form of dementia and may contribute to 60–70% of cases. Dementia is a syndrome usually of a chronic or progressive nature in which there is deterioration in cognitive function (i.e. Theability to process thought) beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not affected.

Worldwide, around 50 million people have dementia every year; there are nearly 10 million new cases. The total number of people with dementia is projected to reach 82 million in 2030 and 152 in 2050(Dementia, WHO,2019). The cognitive decline is associated with the AD pathogenesis which is due to decrease in acetylcholine, which also proposes that deficit of acetylcholine is life-threatening in the creation of the symptoms of AD. In addition, several researcher 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(Nagpal R et.al., 2019). Alterations in bidirectional brain-gut interactions are believed to be involved in the pathogenesis of well-known brain-gut disorders such as irritable bowel syndrome (IBS) and related functional gastrointestinal (GI) disorders and have more recently been implicated as a possible mechanism in the pathophysiology of several brain disorders including autism spectrum disorders, parkinson's disease, disorders of mood and affect, and chronic pain (E A Mayer, et.al., 2015). Moreover, it has been shown that the absence and/or modification of the gut microflora in mice affects the hypothalamic–pituitary–adrenal (HPA) axis(Javier A. Bravo et.al. 2011).

DOI: 10.48175/IJARSCT-26777

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Probiotics are live microbial food supplements with certain benefits for consumers and are thought to maintain or improve the intestinal microbial balance. Probiotics have been displayed to improve brain-gut-microbiota axis and regulate nervous system through neuroendocrine, neurometabolic and neuroimmunologic mechanisms. They can also reduce some oxidative stress biomarkers and inflammatory cytokines (Zahra Rezaei Asl et.al., 2019). Probiotics are beneficial to humans and animals when adequately administered. Probiotic bacteria make proficient interaction with the gut microbiota and provide health benefits. In recent years, attempts are devoted to find a link between the gutmicrobiome with neurological disease(Shima Mehrabadi, et.al.2020, Samaneh Bagheri,2019). Probiotics exhibit health promoting properties by improving the immune system, supplying antioxidants and improving mental health (Yodai Kobayashi, et.al.2017). Probiotics exhibit health promoting properties by improving the immune system, supplying antioxidants and improving mental health (B S Sivamaruthi et.al., 2019)

In this way, the present study aims to investigate the use of probiotics in hyperlipidemia in chronic stressed induced A;zheimers disease in rats.

II. METHODS

ANIMALS

8 weeks old healthy female Sprague-dawley rats (weighing 150-250 gm) were used for this study. Animals were housed in polypropylene cages with wire mesh top and husk bedding and maintain under control condition of light (12h-light, 12h-dark), temperature(25±2ºC), and humidity (60±5%) and fed with a standard pellet diet and water ad libitum, were used for the entire animal study. The experiments were performed during day (8.00- 16hrs). The rats were housed and treated according to the rules and regulations of CPCSEA and IAEC. The protocol for all the animal study was approved by Institutional Animal Ethics Committee (IAEC). For this study animals were divided in to following groups

1. Control Group: Animals were treated with vehicle alone
2. Negative control Group: Alzheimer's Disease in rats was produced by using Restraint stress for 21 days.
3. BL Group: Alzheimer's Disease in rats was produced by using Restraint stress and treated with Bifidobacterium longum probiotic (1x109 CFU) daily p.o. for21 days.
4. STD Group: Alzheimer's Disease in rats was produced by using Restraint stress and treated with Donepezil (5 mg/kg) orally for 28 days.

Induction of Stress in animals

All groups were subjected for 21 days for restraint stress except normal control group which was placed in normal condition in animal house.

A saline bottle was used to cause memory impairment in female Sprague Dawley rats. Whenrats were firmly packed in a saline container for 6 hours every day for 28 days (Madhyastha S et al., 2008). Animalmodels of depression are subjected to constant stressors such as food deprivation, waterdeprivation,and being tightly packed in a saline bottle. Chronic stress may inhibit the immune system and increase the synthesis of interleukin 1β under such circumstance. In rats, persistent psychological stress promoted neuroinflammation and neurodegeneration.

Dosing of Probiotics and Donepezil

Daily dose of Probiotic Bifidobacterium longum (1x109 CFU)p.o.was given to animals for the duration of 21 days. Donepezil (5mg/kg) was used as standard drug. All solutions were prepared freshly on test days and administered according to their standard routes.

Determination of stress in rats

Open-field test

A large plywood box (75×75×29 cm) painted grey with a black grid (15×15 cm squares) on the floor was used for investigational testing. The rat was placed into a corner of the box and allowed to explore freely for 10 min. The box was thoroughly cleaned between subjects with a disinfectant solution. All test sessions were videotaped and the following measures were later recorded: number of rears (animal on hind limbs), number of grid boxes entered (front 2

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paws over a line), time in center 9 squares, and latency to leave the corner box initially [Angela M. Gouirand and Leslie Matuszewich, 2005].

Hole-board test

The apparatus was composed of a gray wooden box (50 cm×50 cm× 50 cm) with four equidistant holes 3 cm in diameter in the floor. The centre of each hole was 10 cm from the nearest wall of the box. The floor of the box was positioned 15 cm above the ground and divided into squares of 10 cm×10 cm with a water resistant marker. An animal was placed in the center of the hole-board and allowed to freely explore the apparatus for 5 min. The total locomotor activity (numbers of squares crossed), and the number and duration of head-dippings were recorded. A head dip was scored if both eyes disappeared into the hole [Armario A, 1991].

Biochemical Estimation

Determination of Cholesterol

Cholesterol level in serum was measured by using Ambica diagnostic kit. The kit utilize the colorimetric procedure in which Cholesterol & its ester are release from lipoproteins by detergents. Cholesterol esterase hydrolyzed the esters. In the subsequent enzymatic oxidation by cholesterol oxidase, H2O2 is formed. This is converted into a coloured quinonine in a reaction with 4- aminoantipyrine and phenol catalysed by peroxidation. Absorbance was measured at 505 nm. (Trinder P. etal 1969 and Kerner W. etal 2014)

Determination of Triglyceride

Triglyceride level in serum was measured by using Ambica diagnostic kit. The kit utilize the colorimetric procedure in which enzymatic splitting with lipoprotein lipase. Indicator is quinoneimine, which is generated from 4-aminoantipyrine and 4- chlorophenol by hydrogen peroxide under the catalytic action of peroxidase. Absorbance was measured at 546 nm. (Trinder P. etal 1969 and Kerner W. etal 2014)

Determination of HDL

HDL level in serum was measured by using Ambica diagnostic kit. The kit utilize the colorimetric procedure in which Chylomicrons, VLDL & LDL are precipitated by adding phosphotungstic acid and magnesium ions to the sample. Centrifugation leaves only the HDL in the supernatant. Their cholesterol content is determined enzymatically using Ecoline S and Cholesterol. Absorbance was measured at 505 nm.

Determination of LDL (Maruyama, C., et.al 2003 and Masashi, K.,et.al 2004)

LDL were calculated by using following formula

$$\text{VLDL} = \frac{\text{TG}}{5}$$

LDL = TC – (HDL-VLDL)

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RESULTS

Table 1. Effect of probiotics alone on stressed rats using Open field test apparatus

Sr. No.	Groups	No. Of box entered		No. Of rears		Latency to inside portion of the field (sec.)		Duration of time in the inside portion of the field (sec.)	
		0 Days	21 days	0 Days	21 days	0 Days	21 days	0 Days	21 days
1.	Normal Control	188.19±2.35	190.19±5.85	40.22±2.45	40.1±3.49	113.90±4.71	113.90±4.71	44.45±2.70	44.20±2.56
2.	Negative Control	189.12±3.45	123.96±6.53**	39.24±1.75	58.31±5.99**	112.24±4.71	92.34±3.79**	43.80±2.56	15.80±2.61**
3.	BL Group	190.25±2.51	199.13±3.80@@	41.15±1.45	44.96±2.01@@	112.80±4.71	105.37±2.28@@	43.50±2.56	32.92±3.26@@
5.	Donepezil	188.25±2.72	122.56±9.87	40.22±2.28	59.56±3.63	111.25±4.71	97.64±3.32	44.45±2.77	17.86±5.16

Values are expressed in Mean±SD, (n=6)

** P<0.01, compared to Group I; @@P<0.01, compared to Group II

Table 2: Effect of probiotics on stressed rats using Hole board test

Sr. No.	Groups	Number of box crossing		Number of nose poking	
		0 Days	21 days	0 Days	21 days
1.	Normal Control	36.33 ± 1.86	36.33 ± 1.86	42 ± 1.58	43 ± 1.78
2.	Negative Control	36.33 ± 1.86	6.33 ± 1.36**	43 ± 1.57	5 ± 2.36**
3.	BL Group	36.33 ± 1.86	25.33 ± 1.36@@	43 ± 1.45	31.66 ± 2.25@@
5.	Donepezil	36.33 ± 1.86	7.33 ± 1.36	43 ± 1.35	6 ± 0.89

Results are expressed as mean ± SD, (n=6)

@p<0.01 Compared with corresponding normal control group, **p<0.01 Compared with negative control group, *p<0.05 compared with negative control group

Table 3. Effect of probiotics on transfer latency (TL) of rats in EPM apparatus

Sr. No.	Groups	Transfer latency in seconds on Day 0	Transfer latency in seconds on Day 28
1.	Normal Control	21.61 ± 2.22	21.35± 2.26
2.	Negative Control	23.36± 2.89ns	36.1± 2.37@
3.	BL Group	23.1± 1.79ns	20.67± 1.37**
4.	Donepezil (5 mg/kg)	22.67 ± 1.87ns	12.67± 1.87**

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Results are expressed as mean ± SD, (n=6)

@p<0.01 Compared with corresponding normal control group, **p<0.01 Compared with negative control group, *p<0.05 compared with negative control group

Table 4 :Effect of probioticson Escape latency of rats in EPM apparatus

Sr. No.	Groups	Escape latency in seconds on Day 0	Escape latency in seconds on Day 28
1.	Normal Control	31.31± 2.60	30.31± 3.62
2.	Negative Control	31.64± 0.52ns	69.67± 2.39@
3.	BL Group	31.13± 2.70ns	35.98± 1.79**
4.	Donepezil (5 mg/kg)	31.21±2.29ns	30.64± 2.26**

Results are expressed as mean ± SD, (n=6)

@p<0.01 Compared with corresponding normal control group, **p<0.01 Compared with negative control group, *p<0.05 compared with negative control group

Table 5: Effect of Probiotic on Retention time (RT) of rats in MWM apparatus

Sr. No.	Groups	Retention time in seconds on Day 0	Retention time in seconds on Day 28
1.	Normal Control	39.31± 0.53	42.62± 2.43
2.	Negative Control	37.80± 1.79^{ns}	30.64± 0.98$^{@}$
3.	BL Group	40.18±1.23^{ns}	38.31± 1.31**
4.	Donepezil (5 mg/kg)	38.00± 0.90^{ns}	44.43± 1.87**

Results areexpressed as mean ± SD, (n=6)

@p<0.01 Compared with corresponding normal control group, **p<0.01 Compared with negative control group, *p<0.05 compared with negative control group

Table 6. Effect of probiotics on serum Cholesterol level in Stressed Rats

SrNo.	Groups	Cholesterol (mg/dl)	
		0day	21day
1.	Normal Control	48.08 + 1.92	47.31 +1.76
2.	Negative Control	48.13+ 1.99	62.64+ 1.37@
3.	BL Group	48.27+ 1.53	47.64 + 1.52 **
5.	Donepezil	48.43+ 2.16	47.48 +1.96 **

All values are Mean ± SD @ p<0.01 compared with control group,**p<0.01 compared with negative control group.

Table 7. Effect of probiotics on serum Triglyceride level in Stressed Rats

SrNo.	Groups	Triglyceride (mg/dl)	
		0day	21day
1.	Normal Control	67.25±2.66	67.14 ± 2.52
2.	Negative Control	67.15±2.46	83.64 ± 2.97@
3.	BL Group	66.91±2.70	69.67± 2.85**
5.	Donepezil	67.37±2.70	67.48 ±2.65**

All values are Mean ± SD @ p<0.01 compared with control group,**p<0.01 compared with negative control group.

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Table 8. Effect of probiotics on serum HDL level in Stressed Rats

SrNo.	Groups	HDL (mg/dl)	
		0day	21day
1.	Normal Control	36.81 ± 0.76	38.14 ± 0.76
2.	Negative Control	36.90± 0.79 ns	31.24 ± 0.52@
3.	BL Group	36.40± 0.63 ns	35.93± 0.63**
5.	Donepezil	36.70± 0.71 ns	37.94 ± 0.76**

All values are Mean ± SD @ p<0.01 compared with control group,**p<0.01 compared with negative control group.

Table 9. Effect of probiotics on serum LDL level in Stressed Rats

SrNo.	Groups	LDL (mg/dl)	
		0day	21day
1.	Normal Control	25.21±0.64	23.40±0.78
2.	Negative Control	24.92±0.73 ns	42.04±0.98@
3.	BL Group	24.82±0.68 ns	29.12±0.75**
5.	Donepezil	25.02±0.61 ns	25.81± 0.65**

All values are Mean ± SD @ p<0.01 compared with control group,**p<0.01 compared with negative control group.

Table 1 shows the effect of probiotic on stressed rats using Open field test. In negative control there was significant decrease (p<0.01) in the number of box entered or latency to inside portion and significant increase (p<0.01) in the number of rears as compared to control, but probiotic (1x109 CFU) daily p.o.treated group shows significant increase (p<0.01) in the number of box entered or latency to inside portion and significant decrease (p<0.01) in the number of rears as compared to negative control.

Table 2 show the effect of probiotic on stressed rats using Hole board test. Negative control shows significant decrease (p<0.01) in the number of box crossing and nose poking behavior as compared to control, but probiotic (1x109 CFU) daily p.o. treated group shows significant (p<0.01) increase in the number of box crossing and nose poking behavior as compared to negative control.

Table 3 shows the effect of probiotic on transfer latency of rats on EPM apparatus in stressed rats. There was significant increase (p<0.01) in transfer latency in negative control group compared to normal control group on 21th day. Probiotic treated shows significant (p<0.05) decrease in the transfer latency at(1x109 CFU) daily p.o. compared to negative control group on 21th day.

Table 4 shows the effect of probioticon Escape latency of rats on Morris Water maze apparatus in stressed rats. There was significant increase (p<0.01) in Escape latency in negative control group compared to normal control group on 21th day. Probiotic shows significant (p<0.05) decrease in the Escape latency at (1x109 CFU) daily p.o. compared to negative control group on 21th day. Table 5 shows the effect of probiotic on Retention time of rats on Morris Water maze apparatus in stressed rats. There was significant decrease (p<0.01) in Retention time in negative control group compared to normal control group on 21th day. Probiotic treated shows significant (p<0.05) increase in the Escape latency at(1x109 CFU) daily p.o.compared to negative control group on 21th day.

Table 6 shows the effect of Probiotic on Cholesterol level. There was significant increase (p<0.01) in the Cholesterol level in negative control group compared to normal control group on 21th day. After treatment with Probiotic, significant (p<0.01) reduction was observed in the Cholesterol level compared to negative control group at (1x109

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CFU) daily p.o. on 21th day.

Table 7 shows the effect of Probioticon Triglyceride level. There was significant increase ($p<0.01$) in the Triglyceride level in negative control group compared to normal control group on 21th day. After treatment with Probiotic, significant ($p<0.01$) reduction was observed in the Triglyceride level compared to negative control group at (1x109 CFU) daily p.o.on 21thday.

Table 8 shows the effect of Probioticon HDL level. There was significant decrease ($p<0.01$) in the HDL level in negative control group compared to normal control group on 21th day. After treatment with Probiotic, significant ($p<0.01$) reduction was observed in the HDL level compared to negative control group at (1x109 CFU) daily p.o. on 21th day.

Table 9 shows the effect of Probioticon LDL level. There was significant increase ($p<0.01$) in the LDL level in negative control group compared to normal control group on 21th day. After treatment with Probiotic, significant ($p<0.01$) reduction was observed in the LDL level compared to negative control group at (1x109 CFU) daily p.o. on 21th day.

III. DISCUSSION

Numerous studies have demonstrated a connection between immunological network changes, stress exposure, and the advancement of disease, especially in neurodegenerative conditions like Alzheimer's disease (AD). However, nothing is known about how this interaction works. B-amyloid buildup, which results in plaques strewn throughout the brain, is the primary characteristic of AD neuropathology. It begins in the neocortical regions of the brain, moves progressively to the midbrain as the disease worsens, and eventually spreads to the cerebellum and brain stem. Like major depressive disorder (MDD), chronic stress frequently leads to cognitive impairment, which is similar to the pathology seen in AD.

Glutamate, a stress marker, has been discovered to be elevated in AD patients and those experiencing chronic stress, which may indicate that stress speeds up the onset of neurodegenerative diseases. (Feng Yilin and others, 2023) The primary cause of dementia, which is typified by a loss of thinking and independence in one's own everyday activities, is Alzheimer's disease (AD), a condition that results in the degradation of brain cells. The cholinergic and amyloid hypotheses are the two main theories put up as the causes of AD, which is thought to be a complex disease.

Scopolamine, streptozotocin, alcohol, and the dysregulation of heavy metals like aluminum (Al), copper (Cu), zinc (Zn), lead (Pb), and reducing sugar (D-galactose) are some of the typical substances used to imitate AD. (Mahdi Onesimus et al., 2019) Restraint stress, a modified version of immobilization stress, is one of the often used models.

Probiotics are living microorganisms that provide health benefits to the host when administered in adequate amounts. The health benefits of probiotics are living microorganisms that have a positive effect on human health when taken in sufficient amounts. Lactic acid bacteria, bifidobacteria, and yeast are commonly used as probiotics. Probiotic can easily get accommodated in human gut. So, in this study Bifidobacterium longum probiotics are studied and used to cure the disease. (Nicoleta Maricia Maftei et al., 2024) In elevated plus maze apparatus, there was significant increase in the transfer latency in negative control group as compared to the normal control group. Whereas probiotic (27 × 1010 CFU/gm) and Donepezil (5 mg/kg) treated group showed significant decrease in transfer latency as compared to negative control group after 21 days. In morris water maze apparatus, there was significant increase in the escape latency in negative control group as compared to the normal control group. Whereas probiotic (27 × 1010 CFU/gm) and Donepezil (5 mg/kg) treated group showed significant decrease in escape latency as compared to negative control group after 21 days.

In morris water maze apparatus, there was significant decrease in the retention time in negative control group as compared to the normal control group. Whereas probiotic (27 × 1010 CFU/gm) and Donepezil (5 mg/kg) group showed significant increase in retention time as compared to negative control group after 21 days.

In this study a variety of biochemical markers, including cholesterol, triglycerides, HDL and LDL were examined. Our finding shown that, there was significant increase in cholesterol, triglycerides, LDL and significant decrease in the HDL level in negative control group as compared to the normal control group. Whereas Probiotic and Donepezil (5 mg/kg) treated group showed significant decrease in cholesterol, triglycerides, LDL and significant increase in the HDL level as compared to negative control groupafter21 days.

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IV. CONCLUSION

The present finding indicates that the probiotics (27 × 1010 CFU/gm) exhibits significant antihyperlipidemic potential in rats.

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IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 6, May 2025
Impact Factor: 7.67

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International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 6, May 2025
Impact Factor: 7.67

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