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ANTIALZHEIMER ACTIVITY OF METHANOLIC EXTRACT OF *BUCHNANIA LANZAN* LEAVES BY USING BEHAVIOUR MODELS ON ALBINO WISTAR RAT

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ABSTRACT: Objective: The key objective of the study is to evaluate the Anti-Alzheimer activity of methanolic extracts of *buchnania Lanzan* leaves by Aluminum Chloride induced Alzheimer's. *Buchanania lanzan* Spreng a well-known forest plant of the family Anacardiaceae. It is reported to have numerous uses in the indigenous system of medicine in India. **Material and Methods:** Albino Wistar rats were administered with $AlCl_3$ at a dose of 4.2 mg/kg/day i.p. for 4 weeks. Experimental rats were given *Buchnania Lanzan* Leaf extract in two different doses of 200 mg and 400 mg/kg/day orally 1hr before the $AlCl_3$ administration for 4 weeks. Learning and memory parameters were evaluated using elevated plus maze (EPM), Radial Arm Maze, and T Maze paradigms. **Results:** The preliminary phytochemical investigation of *Buchnania Lanzan* Extract showed the presence of carbohydrates, alkaloids, flavonoids, phenols, tannins, saponins. In this study, *Buchnania lanzan* leaves extract was an administration for 28 days showed significant neuroprotective activity in aluminum chloride-induced rats of cognitive impairment and oxidative stress analyzed by using various behavioral Studies. **Conclusion:** In this study leaf part of *Buchnania lanzan* was found to be more effective in attenuating memory deficits as compared to other parts, and the mechanism by which *Buchnania lanzan* leaf produced memory retention appears to be similar as compared to standard drugs.

INTRODUCTION: Neurodegenerative diseases, such as Alzheimer's disease (AD) are major causes of death worldwide and are characterized by a progressive loss of specific neuronal cell populations due to the accumulation of aggregated proteins within neurons. Alzheimer's disease represents a degenerative brain disease that is characterized by a decline in cognitive function, memory, and understanding.

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There were various structural and functional damages in specific regions of the brain that occur in AD, leading to a decline in neural connectivity within those regions [1].

Of the changes that occur in the brain that is associated with AD, the two main changes are β-amyloid plaques, which are protein fragments that accumulate outside neurons and contribute to cell death interfering with neuron-to-neuron communication at synapses, and tau tangles, clusters of abnormal tau proteins inside neurons that block the transport of nutrients and other essential molecules inside neurons [2]. Because dementia occurs mostly in people older than 60 years, the growing expansion of lifespan, leading to a rapidly increasing number of patients with

dementia [3] & mainly AD, has led to an intensive growth in research mainly focused on the treatment of the disease. However, despite all arduous research efforts, at the moment, there are no effective treatment options for the disease [4, 5]. The Pathophysiology and neuropathology of AD that drives the current research to suggest that the primary histopathology lesions of AD are the extracellular amyloid plaques and the intracellular Tau neurofibrillary tangles (NFTs) [5]. The amyloid or senile plaques (SPs) are constituted chiefly of highly insoluble and proteolysis-resistant peptide fibrils produced by β-amyloid (Aβ) cleavage. The Aβ peptides with Aβ38, Aβ40, and Aβ42 as the most common variants are produced after the sequential cleavage of the large precursor protein amyloid precursor protein (APP) by the 2 enzymes, β-secretase (BACE1) and γ-secretase. Nevertheless, Aβ is not formed if the APP is first acted on and then cleaved by the enzyme α-secretase instead of β-secretase [6].

According to the "amyloid hypothesis" An Aβ production in the brain initiates a cascade of events leading to the clinical syndrome of AD. It is a formation of amyloid oligomers to which cause neurotoxicity is mainly attributed and initiates the amyloid cascade. The elements of the cascade include local inflammation, oxidation, excite-toxicity (excessive glutamate), and tau hyper-phosphorylation [5]. Tau protein is a microtubule-associated protein that binds microtubules in cells to facilitate the neuronal transport system [7].

Microtubules also stabilize by growing axons necessary for neuronal development and function. Abnormally hyperphosphorylated tau forms insoluble fibrils and folds into intraneuronal tangles. Consequently, It is uncoupled from microtubules, inhibits transport, and results in microtubule disassembly [6]. Although in the amyloid hypothesis, tau hyperphosphorylation was thought to be a downstream event of Aβ deposition, and it is equally probable that tau and Aβ act in parallel pathways, causing AD and enhancing each other's toxic effects [3].

Progressive neuronal destruction leads to shortage and imbalance between various neurotransmitters such as (*e.g.,* acetylcholine, dopamine, serotonin) and to the cognitive deficiencies seen in AD [5].

MATERIALS AND METHODS:

Sample Collection: *Buchnania Lanzan* leaf was collected from the locality of Shyamla Hills, Bhopal, and authenticated from the Department of Botany, Safia Science College, and Bhopal (M.P.). The voucher specimen number was Ref: 298/Bot./ Safia/18

Animals: Albino Wistar rat 150-200 g were used. The animals were obtained from the animal house, pinnacle biomedical research institution Bhopal. Animals were randomized and allocated to different treatment groups. Animals were housed separately in polypropylene cages and fed a standard pellet diet kept under hygienic conditions. Rats were kept on a 12 h light and dark cycle with free access to water *ad libitum* and were kept under standard conditions at 23-25 ºC, 35 to 60% relative humidity. The rat was acclimatized to the laboratory conditions a week before the experiment. The experimental protocol was duly approved by the institutional animal ethics committee (IAEC), and care of the animals was carried out as per the guidelines of the committee for the purpose of control and supervision of experiments on animals. (CPCSEA) (PBRI/ IAEC/PN-19012).

Acute Toxicological Studies: Acute oral toxicity was performed by as per OECD 423 guidelines. The administered dose was assigned as toxic if mortality was observed in two or three animals. The same dose was repeated if mortality was observed in one animal to confirm the toxic dose. The animals were observed for toxic symptoms of behavioral changes, locomotion, convulsion, and mortality. The Herbal extract was found to be non – Toxic at 2000 mg/kg, and the LD50 of 2000 ng/kg and above is said to be unclassified according to OECD 423. $1/10^{th}$ (200 mg/kg) and $1/5^{th}$ (400 mg/kg) of this dose were selected for *in-vivo* pharmacological activity [8].

Induction of Neurotoxicity and Grouping: Neurotoxicity is induced by intraperitoneal injection of $AlCl_3$ (4.2 mg/kg) for 28 days. Animals were randomly divided into five groups of each six rat. The Group I is vehicle control received normal saline (0.9% NaCl, p.o.) once daily for 28 days, Group II: negative control received only with i.p. injection of $Alcl_3$ daily 28 days, Group III and IV

animals were injected with intraperitoneal injection $Alcl_3$ and treated with 200 and 400 mg/kg (p.o) low & high dose extract, for 28 days, Group V: standard group received i. p. injection of $Alcl_3$ and treated with Piracetam 100 mg/ kg p.o.). All drugs solution prepared freshly and given once daily. The body weights were measured before and after treatment with extracts and drug control. The bodyweight of all experimental animals was measured using a digital weighing scale.

Behavioral Studies: Before starting the behavioral studies 1 week of training was conducted. Only food and water were administered during this period.

1. Elevated Plus Maze (EPM) Test: Elevated Plus Maze The elevated plus maze consisted of two open arms (50 cm × 10 cm × 40 cm) and two closed arms (50 cm × 10 cm × 40 cm), with an open roof, arranged so that the two arms open one in front of the another The maze was raised to a height of 50 cm from the ground to measure the anxiety index in rats [19-21]. It is a simple test of recognition of two tests to measure the memory of spatial recognition, it does not require the learning of a rule and, therefore, it is useful for the study of memory in rodents [9].

2. Radial Arm Maze (RAM) Test: An apparatus is a wooden elevated eight-arm radial maze with the arms extending from a central platform 26 cm in diameter. Each arm of apparatus is 56 cm long and 5 cm wide with 2 cm high rails along the length of the arm. A maze is well illuminated, and numerous cues are present. Food pellets (reward) are placed at the end of the arms. During this test, rats are fed once a day, and their body weight is maintained at 85% of their free-feeding weight to motivate the rat to run the maze. Animals are trained daily in the maze to collect food pellets. The session is terminated after 8 choices, and the rat has to obtain the maximum number of rewards with a minimum number of errors [10, 11].

3. T Maze: The T Maze consisted of a start box 15 × 12 cm, a stem 35 × 12 cm, a choice area 15 × 12 cm, and two arms 35 × 12 cm each, at the end of which was the goal areas 15 × 12 cm each, containing the food pellets. The side walls were 40 cm in height. A sliding door separated the stem from the start box. 'T -maze was kept in a sound-attenuated room.

Rats were starved for two days before the test in order to motivate them for a food reward. Subsequently, food was restricted so that the bodyweight was maintained at 85% of the pretest weight. Rats were placed in the T-maze for 30 min every day, for 2 days, to orient them to the T -maze environment.

During these sessions, 15 pellets of food (10 mg each) were kept in each goal area. In the following 4 days, six trials were given daily. In every trial, the rat was placed in the start box, and the door opened, thus allowing it to enter into the stem and arms of the T -maze. After the rat ate the pellet in the goal area, it was replaced in the start box. In every trial, the arm chosen by the rat and the number of alternations made were noted. The inter-trial interval was one minute. The rat was deemed to have entered into a particular arm when it entered that arm with all its four limbs [12].

RESULTS:

1. Elevated Plus MAZE:

TABLE 1: NUMBER OF ENTRIES OF RAT IN OPEN ARM BY USING ELEVATED PLUS MAZE

Treatment group	Mean ± SD (number of entries in open Arm)	Mean ± SD (number of entries in close Arm)
Vehicle	4.5 ±0.100	1.5 ±0.577
Aluminum Chloride	2.25 ±0.957**	5.5 ±0.100***
Extract 200 mg/kg	3.75 ±0.500*	4.0 ±0.816 **
Extract 400 mg/kg	4.25 ±0.500*	3.25 ±0.500*
Piracetam (100 mg/kg)	5.25 ±0.500*	1.75 ±0.957*

Values are expressed as MEAN ± SD at n = 4, One way Anova followed by Tukey-Kramer Multiple Comparisons Test , Vehicle *vs.* $Alcl_3$ 2.250 6.162 ** P<0.01, Vehicle *vs.* extract 200 mg/kg 0.7500 2.054 ns P>0.05, vehicle *vs.* extract 400 mg/kg 0.2500 0.6847 ns P>0.05, vehicle *vs.* piracetam 100 mg/kg -0.7500 2.054 ns P>0.05 as compared to the Vehicle group in open Arm Values are expressed as MEAN ± SD at n=4, One way Anova followed by Tukey-Kramer Multiple Comparisons Test , Vehicle *vs.* $Alcl_3$ -4.000 10.052 *** P<0.001, vehicle *vs.* extract 200 mg/kg -2.500 6.283 ** P<0.01, Vehicle *vs.* extract 400 mg/kg $^{-1}$.750 4.398 *P<0.05, vehicle vs. piracetam 100 mg -0.2500 0.6283 ns P>0.05 as compared to the Vehicle group in close arm.

TABLE 2: TIME SPENT OF RAT IN ARMS BY USING ELEVATED PLUS MAZE

Treatment group	Mean ± SD (Time spent in open Arm)	Mean ± SD (Time Spent in close Arm)
Vehicle	140.0±7.483	91.0±5.774
Aluminum Chloride	91.7±4.573***	129.7±7.848***
Extract 200 mg/kg	113.0±8.246***	108.5±8.813 *
Extract 400 mg/kg	118.0±5.354**	103.5±8.180 *
Piracetam (100 mg/kg)	146.5±8.021*	86.7±9.287*

Values are expressed as MEAN±SD at n=4, One-way Anova followed by Tukey-Kramer Multiple Comparisons Test, Vehicle vs. Alcl3 48.250, 13.989 P<0.001, Vehicle vs. extract200mg/kg 27.000, 7.828 *** P<0.001, vehicle *vs.* extract 400 mg/kg 22.000 6.379** P<0.01, Vehicle *vs.* piracetam 100 mg -6.500 1.885 ns P>0.05, as compared to the Vehicle group in open arm. Values are expressed as MEAN ± SD at n=4, One-way Anova followed by Tukey-Kramer Multiple Comparisons Test , Vehicle *vs.* $Alcl_3$ -38.750 9.602 *** P<0.001, vehicle *vs.* extract 200mg/kg -17.500 4.336 ns P>0.05, vehicle vs. extract 400 mg/kg -12.250 3.035 ns P>0.05, Vehicle vs. Piracetam 100mg /kg 4.250 1.053 ns P>0.05, as compared to the Vehicle group in the close arm.

2. Radial Arm Maze:

TABLE 3: EFFECT OF *BUCHNANIA LANZAN* LEAF EXTRACT ON NUMBER OF ERROR

Treatment Group	Mean ± SD
Vehicle	1.00 ±0.000
$Alcl_3$	13.25±1.500***
Extract 200 mg/kg	7.75±0.957***
Extract 400 mg/ kg	4.00±0.000***
Piracetam (100 mg/kg)	1.25±0.500*

Values are expressed as MEAN±SD at n=4, One way Anova followed by Tukey-Kramer Multiple Comparisons Test Vehicle *vs.* $Alcl_3$ -12.250 29.638 *** P<0.001, Vehicle *vs.* extract 200 mg/kg -6.750 16.331 *** P<0.001, Vehicle *vs.* extract 400 mg/kg -3.000 7.258 *** P < 0.001, Vehicle *vs.* piracetam 100 mg /kg -0.2500 0.6049ns = P>0.05 as compared to the vehicle group.

TABLE 4: TIME SPENT OF RAT IN ARMS BY USING RADIAL ARM MAZE

Treatment Group	Mean ± SD
Normal saline	100.45±2.532
$AlCl_3$	286.00±8.165***
Extract (200 mg/kg)+Alcl3	174.25±7.588***
Extract (400 mg/kg)+Alcl3	133.25±8.139***
Piracetam	96.50±4.435*

Values are expressed as MEAN±SD at n=4, One way Anova followed by Tukey-Kramer Multiple Comparisons Test, Vehicle *vs.* $Alcl_3$ -185.55 56.386 *** P<0.001, Vehicle *vs.* extract 200 mg/kg -73.800 22.427 *** P<0.001, Vehicle *vs.* extract 400 mg/kg -32.800 9.967 *** P<0.001, Vehicle *vs.* piracetam 100 mg / kg 3.950 1.200 ns P>0.05 as compared to the vehicle group

3. T Maze:

TABLE 5: EFFECT OF *BUCHNANIA LANZAN* LEAF EXTRACT ON SPONTANEOUS ALTERNATION BY USING T MAZE

Treatment Group	Mean ± SD
Vehicle	42.50 ±9.574
Aluminum Chloride	25.00±5.774*
Extract 200 mg/kg	40.00 ± 8.165*
Extract 400 mg/kg	52.50±9.574 *
Piracetam 100 mg/kg	65.00± 10.000*

Values are expressed as MEAN±SD at n=4, One-way ANOVA followed by Tukey-Kramer Multiple Comparisons Test compared to the vehicle group, Vehicle *vs.* $Alcl_3$ 17.500, 3.997 ns P>0.05, vehicle vs. extract 200 mg/kg 2.500 0.5710 ns P>0.05, Vehicle *vs.* extract 400 mg/kg -10.000 2.284 ns P>0.05, vehicle *vs.* piracetam 100 mg -22.500 5.139 * P<0.05, as compared to the Vehicle group.

DISCUSSION: Scientific studies have described the use of various medicinal plants and their bioactive constituents for the treatment of Alzheimer's disease (AD). The major hurdle in understanding Alzheimer's disease (AD) is a lack of knowledge about the etiology and pathogenesis of selective neuron death. In recent years, considerable data have been accrued, indicating that the brain in AD is under increased oxidative stress, and this may have a role in the pathogenesis of neuron degeneration and death due to this disorder. The Ayurvedic system of medicine "Medhya drugs" -a group of herbal medicines are known for their actions on the nervous system.

The "Medhya drugs" which are mentioned in Ayurvedic texts are said to improve mental abilities. Some of these herbal drugs reported to act on the nervous system include-Clitoria ternatea (Sivaranjan and Balachandran 1994) (Warrier., 1994), *Acorus calamus*, *Centella Asiatica* (Dash et al.,1996), *Withania somnifera*, *Celastrus paniculatus*, *Guduchi*, *and* Areca. "Medhya Rasayana" a rejuvenating Technique containing *Buchnania lanzan* is considered wholesome for intellect (Sharma and Dash., 1998). Based on the Ethnobotanical survey, we selected *Buchnania Lanzan* leaves Extract for Management of Alzheimer's disease in animal models. An acute oral toxicity study of *Buchnania lanzan* was carried out as per OECD guideline 423. From the limit test results, it was observed that the *Buchnania lanzan* leaves extract was safe up to a dose level of 2000 mg/kg. after that, there was no mortality, and the experimental animals did not show any toxic effect throughout the observation period of 14 days. In this study, *Buchnania lanzan* leaves extract was an administration for 28 days showed significant neuroprotective activity in aluminum chloride-

induced rats of cognitive impairment and oxidative stress analyzed by using various behavioral and biochemical studies. In this study aluminum chloride, Piracetam, and *Buchnania lanzan* leaf extract were used to treat in different groups, and the groups were classified into 5groups (Group 1 to 5). Significant changes were observed in all the groups after treated with reference drug and test extract (200 and 400 mg/kg b/w). In this study, we used Aluminum Chloride for neurotoxicity induction. It was used because the Neurotoxic Behavior of Aluminum is known to occur up to entry into circulatory Systems, Where it can Migrate to the brain and Inhibit Some function of crucial Function of the Blood-Brain Barrier.

In-vivo, a pharmacological behavioral study was performed by using the validated method used for the study of cognition improving the activity of *Buchnania lanzan* leaf extract in rats are elevated plus maze, T maze, and radial arm maze. Elevated plus-maze was used to determine the number of entries and time spent of Treatment groups of Animals in open and Close Arm. In this the rats were given vehicle, 200 mg/kg and 400 mg/kg extract p.o., 4.2 mg/kg $Alcl_3$ and 100 mg/kg Piracetam (p.o.) The maze was then thoroughly cleaned with 70% alcohol before the next test session to minimize the effect of residual odors from the previous test.

The Radial arm maze method was used to study the working memory in a wooden eight-arm maze; in this, rats are trained on experimental days; rats were administered 200 mg/kg and 400 mg/kg extract, the vehicle was given p.o. 4.2 mg/kg $Alcl_3$ inducer, 100 mg/kg Piracetam (p.o.). The time was taken by the rat to eat the food in all four arms was recorded and determine the number of errors done was recorded. The maze was then thoroughly cleaned with 70% alcohol before the next test session to minimize the effect of residual odors from the previous test. The T maze was used to determine the spontaneous alteration in Memory More number of alternations and less % bias was considered as an index of improved learning ability. The maze was then thoroughly cleaned with 70% alcohol before the next test session to minimize the effect of residual odors from the previous test. In this study, *Buchnania lanzan* leaves extract was an administration for 28 days showed significant neuroprotective activity in aluminum chloride-induced rats of cognitive impairment and oxidative stress analyzed by using various behavioral and biochemical studies. The results of the present study revealed that *Buchnania Lanzan* Leaf extract had memory-enhancing properties that had no or little effect on the general motor activity and other behaviors in rats.

CONCLUSION: The present study suggests that the leaf of *Buchnania lanzan* extract possesses potent antioxidant activity. Therefore *Buchnania lanzan* could be a potential source of natural antioxidants that could have great importance as a therapeutic agent in preventing or slowing down the process of aging and age-associated oxidative stress-related neurodegenerative and neurological disorders.

To conclude, the leaf part of *Buchnania lanzan* was found to be more effective in attenuating memory deficits as compared to other parts, and the mechanism by which *Buchnania lanzan* leaf produced memory retention appears to be similar as compared to standard drugs. From the present study it was demonstrated that methanolic leaf extract of *Buchnania lanzan* has significant neuroprotective activity and showed marked constructive effects for improving learning and memory. Therefore, this leaf extract can be used to treat various cognitive dysfunctions connected with neurodegenerative disorders, predominantly Alzheimer's disease. Regardless of these findings, further investigations will be necessary to illustrate the active nootropic compound.

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