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To Evaluate Manilkara Zapota Fruit Peel Extract for Neuroprotective Activity in Chronic Stress Induced Alzheimer Disease in Rats

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Abstract: *Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with memory loss and cognitive impairment. Chronic stress contributes to the development of AD through euronal damage. The present study aims to evaluate the Neuroprotective activity of Manilkara zapota fruit peel extract in chronic stress-induced Alzheimer's disease in rats. Chronic restraint stress was used to induce cognitive dysfunction, and behavioural assessments were carried out using open field test, holeboard test, elevated plus maze, and Morris water maze. The study is expected to demonstrate that Manilkara zapota fruit peel extract improves memory and learning due to its antioxidant and anti-inflammatory properties. The findings may support its potential as a natural therapeutic agent for the management of Alzheimer's disease...*

Keywords: Alzheimer's disease, Chronic stress, Neuroprotection, Manilkara zapota, Memory impairment, Herbal medicine, Cognitive dysfunction.

I. INTRODUCTION

Stress is a major public health problem in modern society and is often referred to as the "health epidemic of the 21st century." It affects physical, mental, and emotional well-being and is associated with several chronic disorders. Prolonged stress can disturb the body's homeostasis and activate neuroendocrine responses that negatively affect the nervous, endocrine, and immune systems. Chronic stress is known to impair memory, learning, concentration, and cognitive function neuroinflammation, and neuronal damage.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia among elderly individuals. It is characterized by memory loss, cognitive decline, behavioral disturbances, and impaired daily functioning. The major pathological features of AD include accumulation of amyloid-β plaques, neurofibrillary tangles formed by hyperphosphorylated tau protein, cholinergic dysfunction, and neuronal degeneration. Chronic stress has been identified as an important risk factor for the development and progression of Alzheimer's disease by increasing cortisol levels, damage, and inflammatory responses in the brain.

Although currently available drugs such as donepezil, rivastigmine, galantamine, and memantine provide symptomatic relief, they do not completely cure the disease and may produce adverse effects. Therefore, there is growing interest in medicinal plants and natural products as safer alternatives for the management of neurodegenerative disorders.

Manilkara zapota (Sapota/Chikoo), belonging to the family Sapotaceae, is a tropical medicinal plant rich in flavonoids, tannins, polyphenols, vitamins, and antioxidant compounds. Different parts of the plant have been reported to possess antioxidant, antiinflammatory, antimicrobial, antidiabetic, and neuroprotective activities. The fruit peel contains important phytochemicals such as phenolic compounds and flavonoids, which may help reduce oxidative stress and neuronal damage associated with Alzheimer's disease.

Therefore, the present study was undertaken to evaluate the neuroprotective activity of Manilkara zapota fruit peel extract in chronic stress-induced Alzheimer's disease in rats.

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Plant profile

Manilkara zapota

Manilkara zapota, commonly known as Sapota, Chikoo, or Sapodilla, is a tropical evergreen tree belonging to the family Sapotaceae. The plant is native to Mexico and Central America and is now widely cultivated in India and other tropical countries. It is well known for its nutritional and medicinal value. Different parts of the plant such as fruit, peel, leaves, bark, and seeds are traditionally used for the treatment of various diseases.

The plant contains several bioactive phytochemicals including flavonoids, tannins, polyphenols, alkaloids, saponins, triterpenoids, glycosides, vitamins, and minerals. These constituents contribute to its antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and neuroprotective activities.

Synonyms -Achras zapota L. Achras sapota L. Manilkara achras (Mill.) Fosberg Lucuma zapota (L.), Achras mammosa ,Sapodilla, Sapota, Chikoo / ChdikuNaseberry, Chicozapote

Common name: Sapota, Chikoo / Chiku, Sapodilla, Naseberry, Chicozapote, Sapodilla

Geographical Distribution –

Manilkara zapota is native to Mexico, Central America, and the Caribbean regions. It is widely cultivated in tropical and subtropical countries due to its nutritional and medicinal importance. In India, the plant is extensively grown in states such as Maharashtra, Gujarat, Karnataka, Tamil Nadu, Andhra Pradesh, and West Bengal. It grows well in warm, humid climates and is commonly cultivated in tropical regions of Asia, America, and parts of Africa.

Fig no:-1. Pulp and seeds of Manilkara zapota fruit

Fig no:-2. Leave of Manilkara zapota fruit

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Fig no:-3. Peels of the Manilkara zapota fruit

Kingdom	Plantae
Division	Magnoliopsida
Class	Sapotaceae
Order	Ericales
Family	Sapotaceae
Sub-Family	Sapotoideae
Genus	Manilkara
Species	Manilkara zapota

Table No:-1Taxonomical Classification

Plant	Manilkara zapota is a medium-sized evergreen tropical tree belonging to the family Sapotaceae. It grows up to 20–30 meters in height and contains milky latex in its bark and leaves.
Leave	Leaves are simple, shiny, thick, oval to elliptic in shape, dark green in color, and arranged alternately on branches.
Flowers	Flowers are small, cream to white colored, bell-shaped, bisexual, and usually grow singly or in clusters in the leaf axils.
Pulp	The pulp is soft, sweet, juicy, brownish-yellow in color, and rich in sugars, vitamins, minerals, and antioxidants.
Fruit	The fruit is round to oval-shaped with rough brown skin and sweet edible flesh containing black shiny seeds.
Peel	The peel is thin, rough, brown-colored, and rich in phenolic compounds, flavonoids, tannins, and antioxidant phytochemicals with medicinal importance

Table No:-2. Botanical description of Manilkara zapota

Phytoconstituent present in Manilkara zapota

Manilkara zapota contains a diverse range of bioactive phytochemicals and essential nutrients, including polyphenols, tannins, alkaloids, saponins, glycosides, triterpenoids, steroids, and other phenolic compounds. The fruit is also rich in anthocyanins, flavanols, catechins, epicatechin, quercetin, kaempferol, gallic acid, ellagic acid, chlorogenic acid, ferulic acid, and protocatechuic acid, which contribute significantly to its antioxidant and therapeutic properties. In addition,

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the presence of lycopene, vitamin C (ascorbic acid), and β-carotene enhances its nutritional and antioxidant potential. Furthermore, the fruit contains essential amino acids, carbohydrates, and important minerals such as calcium, potassium, iron, zinc, copper, and magnesium, which play crucial roles in various physiological and metabolic functions.

Pharmacological Activity of Manilkara zapota

- Antioxidant activity
- Anti-inflammatory activity
- Antibacterial activity
- Antifungal activity
- Antidiarrheal activity
- Anti-dysentery activity
- Antidiabetic activity
- Neuroprotective activity
- Anti-mutagenic activity
- Anti-carcinogenic activity
- Cardioprotective activity
- Anti-platelet activity
- Anti-allergic activity
- Activity against pulmonary diseases
- Analgesic activity (pain relief)
- Antispasmodic activity
- Cough relieving activity
- Photocatalytic treatment of pollutants
- Immunoprotective activity
- Memory-enhancing activity

Materials and methods

Material:

Animals:-8-weeks-old healthy Sprague dawley male or female rats (170-220 gm) will be used for this study. Rats were housed in polythene cages with wire mesh husk bedding was maintained under controlled condition of light, temperature and humidity and standard feed and water were provided ad libitum to the rats during study.

Chemical and Reagents

The chemicals and reagents used in the study included ethanol, concentrated H_2SO_4, concentrated HCl, ferric chloride, ninhydrin solution, lead acetate, and ammonia solution obtained from Thermosile Fine Chem Industries; donepezil procured from Alkem Laboratories Ltd.; Mayer's reagent obtained from Prayogina Laboratories India; and glacial acetic acid purchased from Samar Chemical India.

Instrument and company name

The instruments used in the study included a weighing balance, elevated plus maze apparatus, Morris water maze apparatus, open field apparatus, and hole board apparatus manufactured by K-roy, while the stirrer and china dish were obtained from Remi.

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Method:

1. Collection and authentication of plant material

The peel of the Manilkara zapota fruit belonging to the family of Sapotaceae was collected from the local area of Yavatmal district, Maharashtra India. The plant material was identified and authentication by Vasantrao naik college of agricultural biotechnology, yavatmal (reference no: vncabt/ytl/hort/1137. Date: 18/11/2025)

2. Preparation of Ethanolic extract of Manilkara zapota fruit peel .

The collected peels were dried under shade then coarsely powdered peel was subjected to Ethanolic extraction by maceration. In maceration procedure, powdered peel was macerated in solvent it occasionally stirred at regular intervals of time .it was filtered and concentrated. Then it was dried by evaporation with the help of water bath.

3. Phytochemicals screening

Manilkara zapota fruit was subjected to phytochemical screening and was found to contain various phytoconstituents such as alkaloids, tannins, saponins, anthraquinones, anthocyanins, flavonoids, phenolic compounds, carbohydrates, proteins, steroids, terpenoids, and cardiac glycosides, which were identified by standard qualitative chemical tests based on characteristic color changes, precipitate formation, and foam production.

Experimental design:-

Rats were divided in five groups 6 in each for study .

• Group 1 (vehicle control) :- rats were received only normal saline solution for 21 days .

• Group 2 (negative control):- memory & learning impairment were produced in rats by using chronic restraint stress for 21 days .

• Group 3 (low dose) :- memory & learning impaired rats were treated with low dose (200mg/kg) of Manilkara zapota fruit peel extract for 21 days .

• Group 4 (high dose) :- memory & learning impaired rats were treated with high dose (400mg/mg) Manilkara zapota fruit peel extract for 21 days.

• Group 5 (standard dose) :- memory & learning impaired rats were treated with standard drug. (Donepezil 5mg/kg) by oral route for 21 days.

• Induction of Chronic Restraint Stress

Chronic restraint stress was induced in experimental rats by restraining each animal individually inside a well-ventilated saline bottle for 6 hours daily upto to 21 days . The restraint procedure restricts the movement of the animals without causing physical injury. After each stress session, the rats were returned to their home cages and provided free access to food and water. Control animals were handled similarly but were not subjected to restraint stress

Confirmation of Stress

Stress induction following chronic restraint stress was confirmed by assessing changes in body weight and behavioral parameters using the Open Field Test and Hole Board Test. Animals were subjected to memory assessment only after confirmation of stress.

Assessment of Stress in rats • Open Field Test

The Open Field Test was used to evaluate locomotor, exploratory, and anxietyrelated behavior in rodents. Animals were allowed to explore the arena for 5 minutes, and head dipping behavior was recorded as the main parameter for assessing exploratory and anxiety-related responses. (Prut & Belzung, 2003)

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• Hole Board Test

The Hole Board Test was performed to assess exploratory and anxiety-related behavior. Animals were placed individually in the apparatus for 5 minutes, and the number of head dips was recorded as the primary parameter. (Casarrubea et al., 2023).

Memory Assessment

Memory impairment was evaluated using the Elevated Plus Maze (EPM) and Morris Water Maze (MWM).

• Elevated Plus Maze

The Elevated Plus Maze was used to assess anxiety-related behavior and memory by recording entries and time spent in open and closed arms over a 5-minute period. (Walf & Frye, 2007)

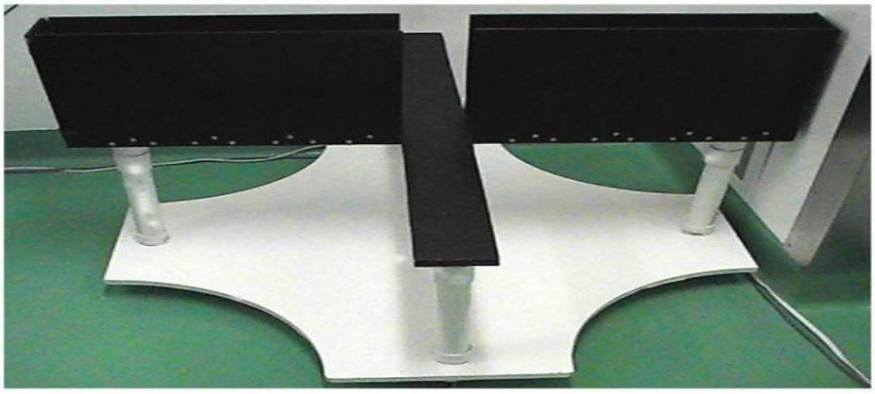

Fig no.4 levated plus maze apparatus (Alicia A. Walf, Et.al .(2007).

• Morris Water Maze

The Morris Water Maze was used to evaluate spatial learning and memory using a circular pool with a hidden platform submerged in opaque water. Animals were trained to locate the platform using spatial cues. (Venkataramaiah et al., 2018)

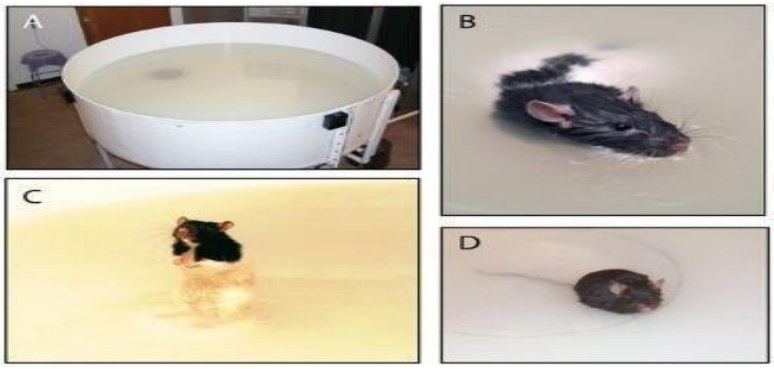

Fig no:5 Morris Water Maze Apparatus . (Richard G.M (2008)

Results

Phytochemical screening Analysis

The Phytochemical present in Ethanolic extract of Manilkara zapota fruit peel is shown in Following table:

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Table no:- 3

Sr no	Phytoconstituent	Test performaned	Extract result
1	Alkaloids	Mayers test	+
2	Carbohydrates	Mollis test	+
3	Cardiac glycoside	Killer killani test	-
4	Tannin	Brayers test	+
5	Protein and ammino acid	Ninhydrin test	+
6	Saponin	Foam test	+
7	Anthraquinones	Brontrager test	-
8	Terpenoid	Salkowski's test	+
9	Flavonoids	Ammonia test	+
10	Phenolic compound	Lead acetate test	+

Percentage Practical Yield of EEMZ fruit peel.

The Coarsely powdered bark of Manilkara zapota peels was used for extraction process Extraction by Maceration using Ethanolic solvent.

Filtration by filter paper

Solvent removal (Evaporation) by using water bath. Drying and storage.

Weighing the final extract to calculate the yield. Weight of extract = 740 gm.

Weight of empty jar = 43.24 gm.

Weight of petri dish containing Ethanolic extract of fruit peels of Manilkara zapota= 783.24gm

Actual weight of Ethanolic extract of peels of Manilkara zapota

= 250 – 43.24 = 206.76 % Practical yield of Ethanolic extract of fruit peel of Manilkara zapota

% Practical yield = 296 %w/w.

Sr.no	Groups	Day 0	Day14	Day21
1	Normal control	210±23	186±22	231 ±22
2	Negative control	183±24	148±22	151 ±21 @@
3	EEMZ 200mg/kg	208±14	191 ±30 **	198 ±15
4	EEMZ 400mg/kg	203±35	208 ±28 **	216 ±15
5	Donepezil 5mg/kg	191 ±20	172 ±20 *	227 ±9

Table No:- 4. Effect of Treatment on body weight of rats are shown in following table:

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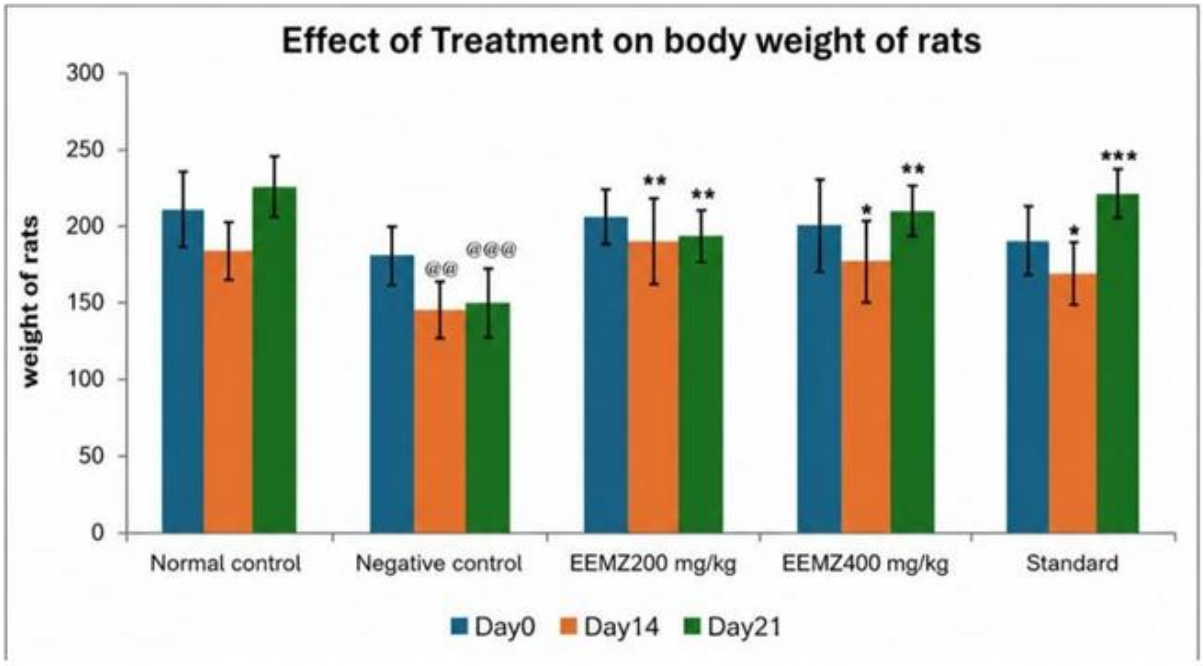

Fig no:- 7 weight of rats

Values are expressed as Mean ± SD (n = 6). Statistical analysis was performed using One-way ANOVA followed by Dunnett's multiple comparison test.

@@= the negative control is significantly decreased

@ = the negative control decrease when compared with normal control ($p < 0.05$)

*= The low dose group increase Significantly ($p < 0.05$)

** = The high dose group increase (Highly significant ($p < 0.01$))

*** = The standard group increase as compared to negative control (Very highly significant ($p < 0.001$))

Chronic Stress caused significant body weight loss in rats. EEMZ treatment improved body weight in a dose-dependent manner, with 400 mg/kg showing better recovery than 200 mg/kg. Donepezil showed the maximum improvement. Overall, EEMZ exhibited protective effects against stressinduced weight loss.

Evaluation of behaviour parameter Open field test Apparatus :

Number of Square Crossing,

Effect of EEMZ on Square Crossing of rats in Open field test

Table no:5

Sr no	Group	Day 0	Day14	Day21
1	Normal control	81.33±2.066	80±1.414	80.33±3.27
2	Negative control	81.66±1.862	70.5±3.507@	47.66±11.2@@@
3	EEMZ 200mg/kg	81.66±2.422	74.5±3.017**	58±6.4*
4	EEMZ 400mg/kg	81±5.797	78.166±1.47**	77.66±4.1**
5	Donepezil 5mg/kg	80.5±3.146	77.16±2.85*	78.83±3.7**

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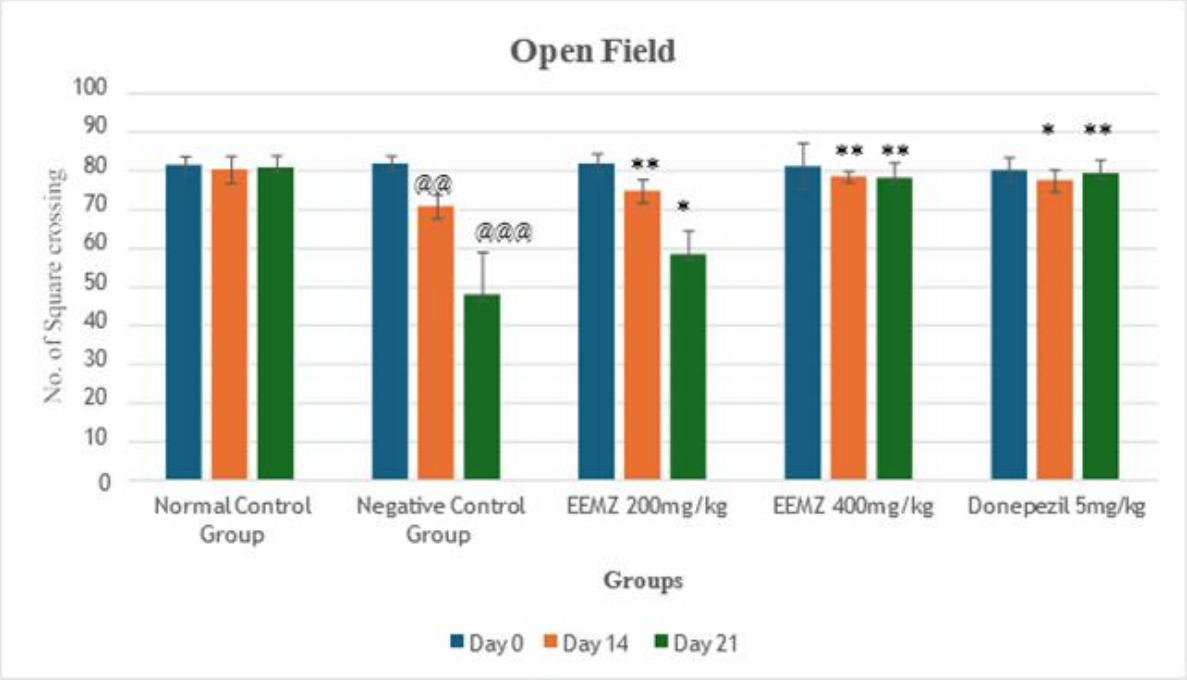

Fig no. 8 effect of EEMZ on Square crossing

Activity of rats in Open field The negative control group showed reduced square crossing activity, indicating impaired locomotor and exploratory behavior. EEMZ treatment at 200 mg/kg and 400 mg/kg significantly improved square crossing activity, with the 400 mg/kg dose showing better effect. Donepezil-treated animals showed values close to the normal control group.

Values are expressed as Mean ± SD (n = 6). Statistical analysis was performed using One-way ANOVA followed by Dunnett's multiple comparison test.

@ = the negative control group Significantly decrease weight of rats when compared with normal control ($p < 0.05$)

@@@ = the negative control decreased weight when compared with normal control (Very highly significant when compared with normal control ($p < 0.001$))

*= The low dose group increase Significanttly $p < 0.05$)

** = The high dose group Increased significantly (Highly significant ($p < 0.01$))

**= the standard group increase Significantly

Hole Board Test Number of Head Dips

Table No.6. Effects of EEMZ on number of head dipping on rats in Hole Board apparatus

Sr no.	Group	Day 0 o	Day 14	Day 21
1	Normal Control	30.5±2.42	33.166±2.13	30.833±2.787
2	Negative Control	30.33±3.5	24.33±2.73@@@	23±1.789@@
3	EEZM 200mg/kg	31.166±3	28.33±3.204**	27.5±1.871**
4	EEMZ400mg/kg	31±2.88	31.5±1.87**	25.5±4.44**
5	Donepezil 5mg/kg	30.33±3.83	31.5±2.739	29.66±1.507**

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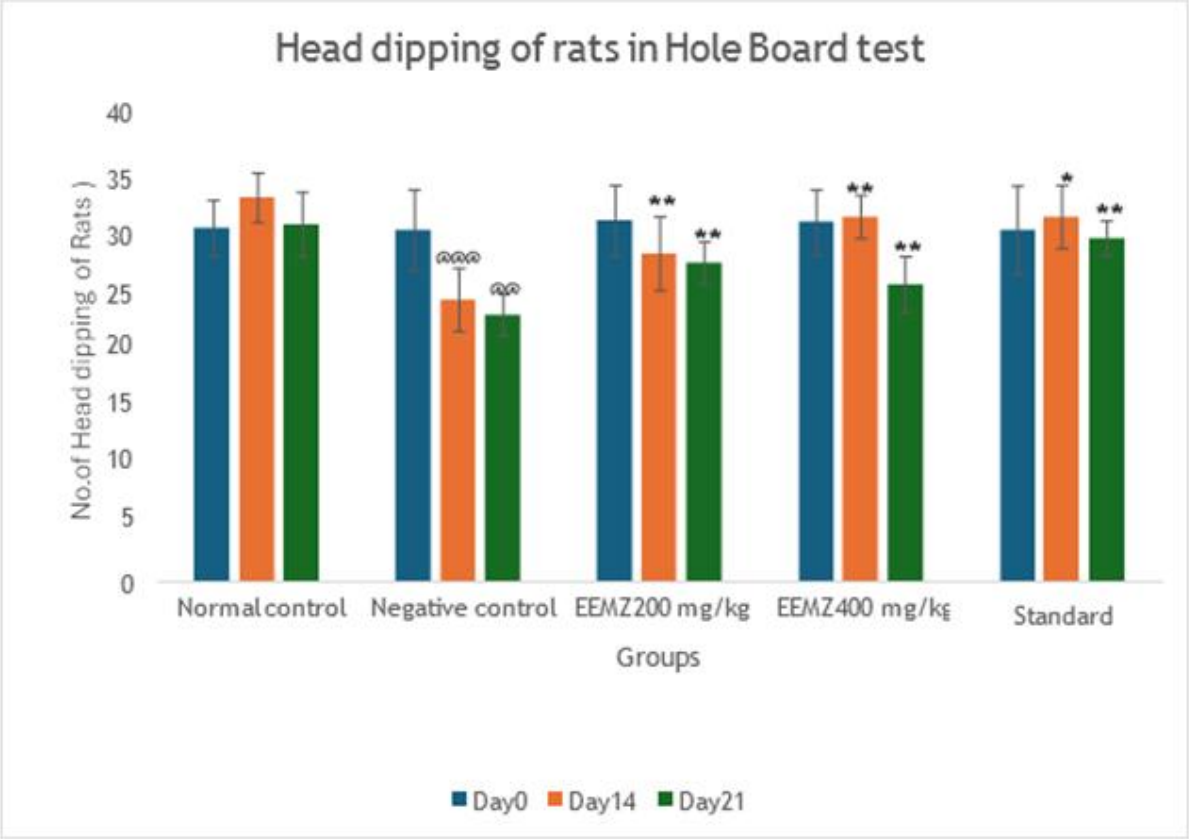

Fig no:-9. Head dipping of rats in Hole Board test

Values are expressed as Mean ± SD (n = 6). Statistical analysis was performed using One-way ANOVA followed by Dunnett's multiple comparison test.

@@ = the negative control group is decreased (Highly significant when compared with normal control ($p < 0.01$))

@@@ = negative control group Significantly decrease (Very highly significant when compared with normal control ($p < 0.001$))

*= The low dose is increased Significantly ($p < 0.05$)

** =The high dose group increase Significantly (Highly significant ($p < 0.01$))

**= The standard group increase Significantly as compared to negative control

Elevated plus maze apparatus . Transfer latency:

Effect of EEMZ on Transfer latency of rats in EPM apparatus

Table no:7

Sr.no.	Group	Day 0	Day14	Day 21
1	Normal control	42± 3.03	55.83+-4.07	41.16±4.58
2	Negative control	43± 4.47	59.33+6.35 @	59.66±5.007 @@
3	EEMZ 200mg/kg	45.33± 4.13	58.50+3.62 **	52.50 ±3.728**
4	EEMZ 400mg/kg	44.67 ±3.27	56± 7.07 **	45± 4.243**
5	Donepezil 5mg/kg	44.50 ±3.08	53.67 ±5.01 **	42.66 ±4.457**

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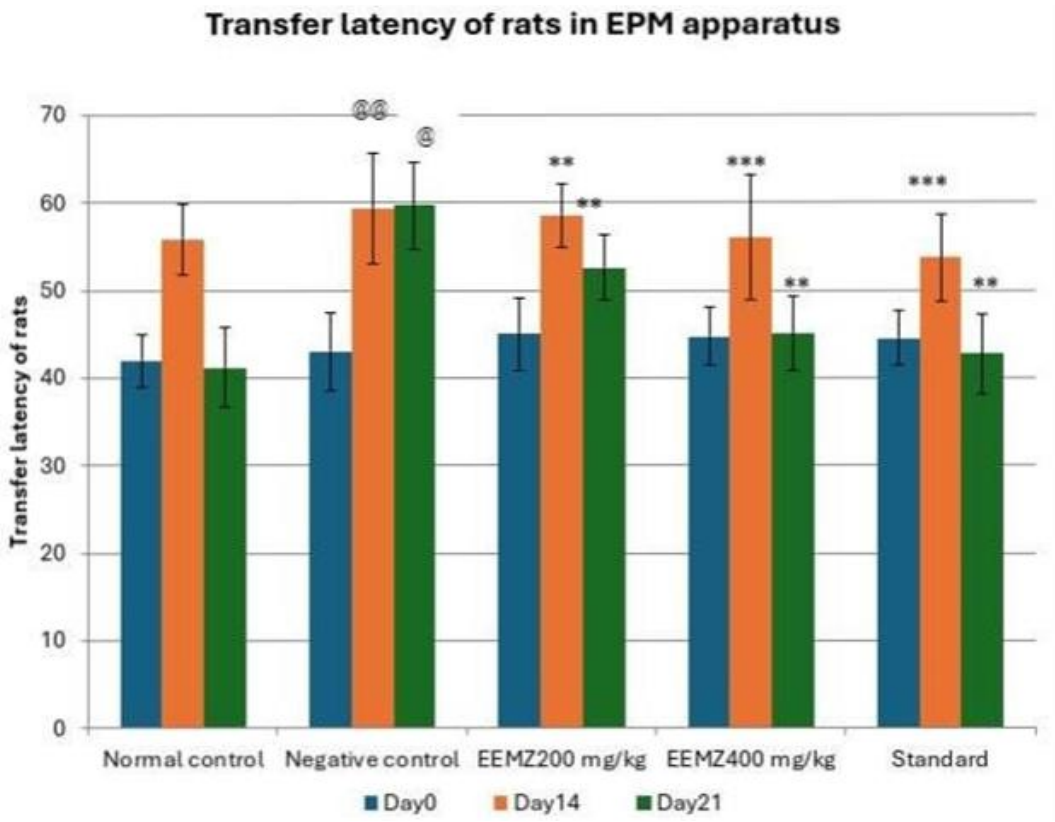

Fig no:-10. Transfer latency of rats in EPM apparatus

Values are expressed as Mean ± SD (n = 6). Statistical analysis was performed using One-way ANOVA followed by Dunnett's multiple comparison test.

@ = the negative control group decreased (Significant when compared with normal control ($p < 0.05$))

@@ =the negative control group decreased .(Highly significant when compared with normal control ($p < 0.01$))

*= The low dose group Increased Significantly ($p < 0.05$)

** =The high dose group increased (Highly significant ($p < 0.01$))

Negative control group showed significant increase in transfer latency compared to normal control group, indicating stress-induced memory impairment. Treatment groups showed reduction in transfer latency compared to negative control group, suggesting improvement in learning and memory."

Morris Water Maze Apparatus:

Escape latency.

Effect of EEMZ on Escape latency of rat in MWM

Table no:8

Sr.no	Group	Day0	Day14	Day 21
1	Normal control	25.83± 2.86	27± 2.376	25.17 ±3.882
2	Negative control	25.83± 4.07	59.33± 3.78@@	54.50 ±3.20@@
3	EEMZ200mg/kg	25.33 ±4.08	53± 4.38**	46.83 ±4.79**
4	EEMZ400 mg/kg	26.50± 2.66	48.83 ±2.48***	34.50± 5.68**
5	Donepezil 5 mg/kg	26.67± 2.94	48.17. ± 2.644***	32 ±6.78**

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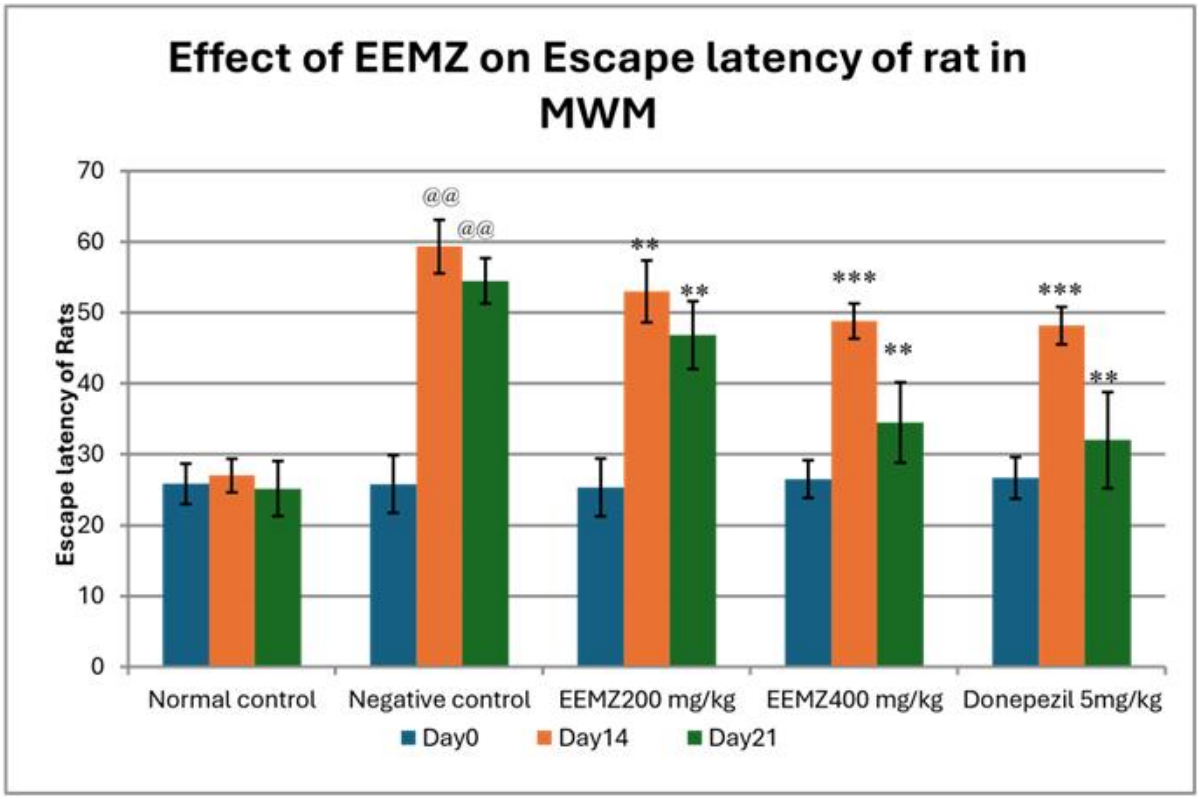

Fig no:-11. Escape latency of rats in MWM

Values are expressed as Mean ± SD (n = 6). Statistical analysis was performed using One-way ANOVA followed by Dunnett's multiple comparison test.

@@ = Highly significant when compared with normal control ($p < 0.01$)

*= Significant ($p < 0.05$)

** = Highly significant ($p < 0.01$)

*** = Very highly significant ($p < 0.001$)

The negative control group showed a significant increase in escape latency on Day 14 and Day 21 compared to the normal control group, indicating stress-induced impairment in learning and memory.

Low dose, high dose and standard treatment groups showed reduced escape latency compared to the negative control group, suggesting improvement in learning and memory. High dose and standard treated groups showed maximum improvement.

Retention time

Morris Water Maze Apparatus

Effect of EEMZ on Retention time of rats on MWM apparatus.

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Table no:9

Sr .no	Group	Day0	Day14	Day 21
1	Normal control	66.33 ±4.84	61±4.98	63.4.5+4.231**
2	Negative control	59.67±3.98	39.17±3.71@@@	38.833+3.4@@@
3	EEMZ 200 mg/kg	57.33±3.98	44.83±3.66**	45+5.394**
4	EEMZ 400mg/kg	58.50±2.88	51.67±4.27*	55.66+4.844*
5		62.83 ±3.49	55.17±5*	58.33+3.882**

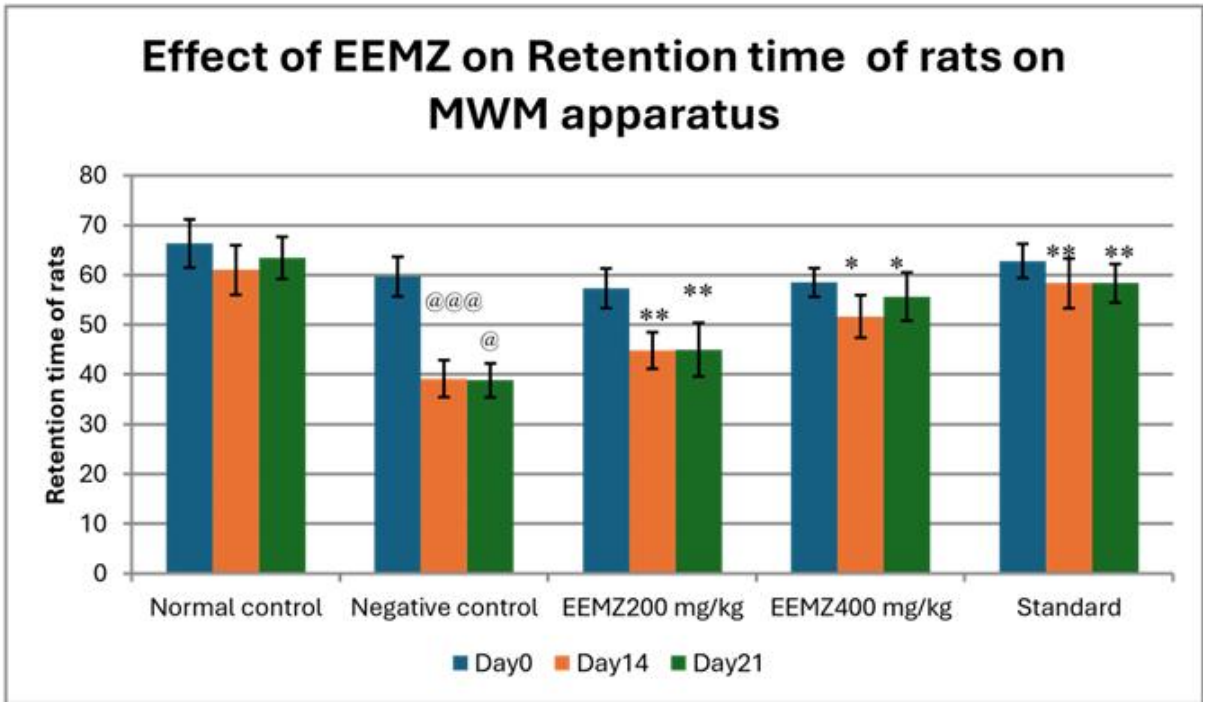

Fig.no:- 12. Retention time of rats on MWM

Values Are expressed as Mean ± SD (n = 6).

Statistical analysis was performed using One-way ANOVA followed by Dunnett's multiple comparison test.

@@@ = Very highly significant when compared with normal control ($p < 0.001$)

*= Significant ($p < 0.05$)

** = Highly significant ($p < 0.01$)

The negative control group showed a significant decrease in retention time on Day 14 and Day 21 compared to the normal control group, indicating stress-induced memory impairment.

Low dose, high dose and standard treatment groups showed improvement in retention time compared to the negative control group, suggesting enhancement of learning and memory.

Standard treated animals showed values closer to the normal control group.

Discussion

Chronic stress is one of the major factors responsible for impairment of learning, memory, and cognitive functions. Prolonged stress exposure increases oxidative stress, neuronal damage, and disturbances in neurotransmitter systems,

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leading to Alzheimer-like behavioral and cognitive changes in experimental animals. In the present study, chronic restraint stress was used to induce stress in rats because it is a reliable and widely accepted experimental model for producing anxiety, depression-like behaviour, and cognitive impairment similar to neurodegenerative conditions. Chronic restraint stress activates the hypothalamic–pituitary–adrenal (HPA) axis and elevates glucocorticoid levels, resulting in hippocampal neuronal damage and memory deficits (McEwen, 2007).

Several stress models are available for inducing chronic stress in animals, including chronic unpredictable mild stress, social isolation stress, forced swim stress, immobilization stress, cold stress, and restraint stress models. Among these, restraint stress was selected in the present study because it is simple, reproducible, economical, and capable of producing significant behavioural and biochemical alterations within a shorter duration (Kim et.al,2006).

Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory loss, cognitive impairment, and behavioral changes. Various experimental models are used to induce Alzheimer-like symptoms in laboratory animals for the evaluation of neuroprotective and memory-enhancing agents. Commonly used models include scopolamine-induced amnesia, aluminum chloride ($AlCl_3$)-induced neurotoxicity, streptozotocin (STZ)-induced dementia, amyloid beta (Aβ)-induced model, lipopolysaccharide (LPS)-induced neuroinflammation, transgenic animal models, aging-induced models, and chronic restraint stress-induced models. In the present study, the chronic restraint stress model was used because prolonged restraint produces stress-related cognitive and behavioral alterations similar to those observed in Alzheimer's disease. Chronic stress leads to impairment of learning, memory, exploratory behavior, and locomotor activity. This model is simple, reliable, reproducible, and widely used for evaluating the neuroprotective effects of test drugs and herbal extracts.(Futch et al., 2017; Caruso et al., 2019).

Different behavioural models were employed in this study to assess anxiety, locomotor activity, exploratory behaviour, learning, and memory functions in rats.

The Elevated Plus Maze (EPM) model was used to evaluate anxiety-related behavior and memory performance. The apparatus is based on the natural conflict between the tendency of rodents to explore new environments and their fear of open elevated spaces. Increased transfer latency observed in stressed animals indicated impairment in learning and memory due to chronic stress exposure. Treatment with Manilkara zapota fruit peel extract significantly reduced transfer latency, suggesting improvement in cognitive performance and anxiolytic activity. The EPM is a well-established model for assessment of anxiety and memory in rodents (Walf et.al, 2007).

The Morris Water Maze model was used to evaluate spatial learning and memory. It is one of the most widely accepted models for studying hippocampus-dependent memory and cognitive function. In the present study, stressed animals exhibited increased escape latency and decreased retention time, indicating impaired spatial memory and learning ability. Administration of Manilkara zapota fruit peel extract significantly improved these parameters, suggesting enhancement of cognitive function. The Morris Water Maze is considered a sensitive tool for evaluating learning and memory deficits associated with neurodegenerative disorders (Morris, 1984).

The Open Field Test was employed to evaluate locomotor activity, exploratory behaviour, emotionality, and anxiety-like behaviour in animals. Chronic stress generally reduces locomotor and exploratory activity due to increased anxiety and fear responses. In the present study, head dipping behaviour was selected as the major parameter to assess exploratory activity. Reduced exploratory behaviour in stressed animals indicated anxiety and cognitive dysfunction, whereas treatment with the extract improved exploratory activity, indicating anxiolytic and Neuroprotective effects. The Open Field Test is widely used for assessing emotional and exploratory behaviour in rodents (Prut et.al. 2003).

The Hole Board Test was also used to assess exploratory behaviour and anxiety-related responses in experimental animals. Head dipping behaviour is considered an important parameter for evaluating curiosity and emotional reactivity in rodents. A reduction in head dipping frequency in stressed animals indicated increased anxiety and reduced exploratory tendency, while treatment with Manilkara zapota fruit peel extract significantly increased head dipping behaviour, suggesting reduction of stress-induced anxiety and improvement in exploratory activity. The Hole Board Test is a reliable behavioural model for evaluating anxiety and exploratory behaviour in rodents (Micale et al., 2023).

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Chronic stress also caused significant reduction in body weight in negative control animals, which may be due to altered metabolism and reduced food intake during stress exposure. Treatment with the extract improved body weight in a dose-dependent manner, indicating protective effects against stress-induced physiological changes.

The Neuroprotective activity of Manilkara zapota fruit peel extract may be attributed to the presence of flavonoids, phenolic compounds, tannins, and antioxidants. These phytoconstituents may help reduce oxidative stress, prevent neuronal damage, and improve cognitive functions.

Among the treatment groups, the higher dose exhibited better Neuroprotective activity compared to the lower dose, while the standard drug showed maximum improvement in behavioural and cognitive parameters. Overall, the findings suggest that Manilkara zapota fruit peel extract possesses significant Neuroprotective potential against chronic stress-induced Alzheimer-like alterations in rats.

II. CONCLUSION

The present study demonstrated that chronic restraint stress produced significant impairment in learning, memory and cognitive function in rats, indicating Alzheimer-like neurodegenerative changes.

The Manilkara zapota fruit peel extract exhibited dose-dependent protective effects, with the higher dose showing better improvement compared to the lower dose. Overall, Manilkara zapota fruit peel extract demonstrated promising protective activity against chronic stress induced cognitive dysfunction and memory impairment in rats.

Future Scope of the Research

Based on your study on the neuroprotective activity of Manilkara zapota fruit peel extract in chronic stress-induced Alzheimer's disease in rats, the following future perspectives can be included:

1. Further studies can be carried out to isolate and characterize the specific phytoconstituents responsible for the neuroprotective activity of Manilkara zapota fruit peel extract.
2. Detailed molecular and biochemical investigations may be performed to understand the exact mechanism of action of the extract on oxidative stress, Neuroinflammation, amyloid beta deposition, and cholinergic dysfunction in Alzheimer's disease.
3. Future research can evaluate the effect of the extract on biomarkers of Alzheimer's disease such as amyloid-β, tau protein, acetylcholinesterase activity, and inflammatory cytokines.
4. Long-term toxicity and safety studies are necessary to establish the safe therapeutic dose and chronic administration profile of the extract.
5. The neuroprotective potential of Manilkara zapota fruit peel extract can be explored in other experimental models of neurodegenerative disorders such as Parkinson's disease, dementia, and age-related cognitive decline.
6. Clinical studies in human subjects may be conducted in future to confirm the efficacy and safety of the extract for the management of stress-associated cognitive impairment and Alzheimer's disease.
7. Development of herbal formulations, nutraceuticals, or Nano formulations containing Manilkara zapota fruit peel extract may improve bioavailability and therapeutic effectiveness.
8. Combination studies with standard anti-Alzheimer drugs such as donepezil may help determine possible synergistic effects and reduction in adverse effects.
9. Since the fruit peel is generally considered agricultural waste, future studies may also focus on its economical utilization as a value-added neuroprotective herbal product.
10. Additional behavioral, histopathological, and neurochemical studies can further validate the memory-enhancing and neuroprotective effects observed in the present work.

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