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Neuroprotective Potential and Memory Retention Effects Of *Aegle Marmelos* On Scopolamine-Induced Amnesia In Swiss Albino Mice

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ABSTRACT

Background: One major neurodegenerative disease that interferes with memory development is Alzheimer's disease (AD). Impaired encoding, consolidation, or retrieval of episodic memory is the cause of amnesia in early AD. Because of its anticholinergic properties, scopolamine mimics dementia by causing cognitive deficiencies**.** This study aimed to assesses the neuroprotective potential and memory retention effect of ethyl acetate fraction of *Aegle marmelos* (EFAM) scopolamine-induced amnesia in mice.

Methods: EFAM (200 and 400 mg/kg, p.o.) was administered to Swiss albino mice for 30 days and scopolamine (3 mg/kg, i.p.) was injected to induce amnesia. Behavioural models such as elevated plus maze, hebb williams maze, and novel object recognition and biochemical indicators such as reduced glutathione and malondialdehyde were measured. Brain tissue histopathological analysis was also carried out.

Results: Scopolamine-induced memory deficits were significantly restored by EFAM (200 mg/kg and 400 mg/kg) as indicated by decreased transfer latency (TL), time to reach the reward chamber (TRC) and increased recognition index (RI), and indicating an improvement in behavioural parameters. And also improved brain antioxidant defence (GSH, MDA levels), improved histopathological damage

Conclusion: Based on the findings, this study suggests that EFAM may have a therapeutic function in the treatment of Alzheimer's disease by demonstrating neuroprotective potential against scopolamine-induced alzheimers through behavioral, biochemical, and histological changes.

Keywords: *Alzheimer's disease, Scopolamine, Aegle marmelos, Neuroprotection, Memory retention, Antioxidants*.

1. INTRODUCTION

The neurological ailment known as Alzheimer's disease was first described in 1906 by a German doctor named Alois Alzheimer. A long-term, degenerative neurological condition with a gradual beginning, Alzheimer's disease eventually results in dementia, strange behaviour, personality changes, and death. Dementia is a term used to represent a group of symptoms that can include thinking and memory loss, understanding issues, language or problem-solving challenges (Schachter & Davis, 2000). The cortex and hippocampus regions of the human brain have a much lower amount of acetylcholine (Ach), according to neurochemical studies of Alzheimer's disease. In both rats and humans, centrally acting anti-muscarinic drugs impair memory and learning (Ballard et al., 2011). The buildup of neurofibrillary tangles and the

deposition of sensile plaques in the brain are associated with AD. It is thought that the accumulation of amyloid B (AB) starts a pathogenic chain reaction that leads to AD. AB-induced neurotoxicity has a complicated process that involves multiple signaling channels. The ability of fibrillar forms of amyloid B to stimulate inflammation in brain cells is now well known, and several research teams have pinpointed the signaling pathways that underlie this effect. It is thought that neuroinflammation, a subsequent outcome of brain aggregation in Alzheimer's disease, causes microglia to become activated and releases cytokines, chemokines, reactive oxygen and nitrogen species, and proteolytic enzymes, all of which lead to neuronal degeneration. Increased cerebral ventricles and brain shrinkage are the conditions and morphological hallmarks. Reduce the levels of choline acetyltransferase and other cholinergic indicators from a biological perspective. Histologically, extracellular deposits called cerebral plaques are indicative of AD. AD is also frequently associated with neurofibrillary tangles in neurons. Alzheimer's disease is not inherited, even if certain genes may act as risk factors (Ferreira et al., 2014) .However, family types of autosomal dominant (non-sex-linked) inheritance account for only 0.1 percent of cases, and symptoms typically appear before age 65. A person's medical history, family history, and behavioural observations are typically used to diagnose Alzheimer's disease. At this time, there is not enough evidence to draw the conclusion that any particular course of action will successfully prevent AD. For mild to moderate conditions. Symptoms of Alzheimer's illness Galantamine, Rivastigmine, and Donepezil are examples of acetylcholinesterase (ACE) inhibitors that can assist manage Alzheimer's disease. Alzheimer's disease (AD) is a major neurological illness. From the molecular level to the structure of brain networks and evolutionary elements of human cognition, the primary pathophysiology of AD disrupts memory formation. Disrupted encoding and consolidation of episodic information, or a deficit in retrieving stored memory information, are the causes of amnesia in the early stages of AD. Because of its anticholinergic properties, the well-known medication scopolamine is used to cause cognitive impairments in experimental animals. Animals given scopolamine show memory problems similar to those seen in people with dementia. Since herbal therapy has multiple target regulation rather than single-target antagonists, it may be a novel treatment approach for AD. Many herbal plants include anti-inflammatory and antioxidant qualities that serve to reduce inflammation and oxidative stress in neurons. The study is appropriate for assessing the potential therapeutic benefits of Aegle marmelos, a herbal plant that contains bioactive compounds like coumarins, tannin, alkaloids, pectin’s, and flavonoids that help with dementia, learning, and amnesia. These compounds also have antioxidant activity and AchE inhibitory properties, which may help treat Alzheimer's disease. As a crucial component of contemporary clinical methods to neuroprotection, the current study investigates the neurobehavioral and memory-enhancing effects of Aegle marmelos on scopolamine-induced amnesia (Tian, Shi, Zhang, & Wang, 2010) .

2. MATERIALS AND METHODS:

Plant extraction:

Dried powder (3 kg of) of *Aegle marmelos* leaves was thoroughly extracted using 6 L of n-hexane over the course of 48 hours in order to eliminate gums, waxes, and non-polar chemical components. The residue further extracted using methanol (6 L) for one week by cold maceration method. A 50 g crude methanol extract was obtained after solvent evaporation (Parekh, Jadeja, & Chanda, 2005).

Percentage yield of methanol extract was calculated by: $\frac{\text{Theoretical yield}}{\text{Practical yield}} \times 100$

Liquid-Liquid Fractionation Extraction:

To improve polarity, the dried methanol extract was fractionated using a liquid-liquid partition method. After dissolving the methanol extract in water, fractionated using n-hexane, chloroform, ethyl acetate and butanol. The resulting fractions were designated as follows: n-hexane fraction (HFAM), chloroform fraction (CFAM), ethyl acetate fraction (EFAM) and butanol fraction (BFAM) (Abubakar & Haque, 2020).

Assessment of Antioxidant activity:

The ability of each fraction to scavenge DPPH was tested. The freshly prepared DPPH solution was incubated at room temperature for 30 minutes with different concentration of methanol extract and its fractions. The absorbance of solution was read at 517 nm (Deng, Cheng, & Yang, 2011). The DPPH scavenging ability of the test extract was calculated using the formula below:

Percentage of DPPH radical scavenging activity= $\frac{A0-A1}{A0} \times 100$

Animals:

Male Swiss albino mice weighing 25-30 g were employed. They were housed in polypropylene cages in a room with standard laboratory conditions (Uddin et al., 2016). The Institutional Animal Ethics Committee gave its approval for this protocol with approval number IAEC/XV/0/RIPER/2020.

Experimental protocol:

Five groups of six animals each were randomly selected from among all the animals.

Group 1: Received only vehicle
Group 2: Received vehicle and scopolamine (3 mg/kg i.p) (Kwon et al., 2010).
Group 3: Received donepezil (1 mg/kg p.o) (Malik, Karan, & Vasisht, 2016).
Group 4: Received EFAM (200mg/kg,p.o) (Mustafa et al., 2019).
Group 5: Received EFAM (400mg/kg, p.o) (Gohil, Pathak, Jivani, Devmurari, & Patel, 2010).

The animals were given the aforementioned treatment for 30 days. To produce amnesia, a single dosage of scopolamine (3 mg/kg) was injected into all groups except group 1. Following 30 minutes of scopolamine injection, behavioural alterations were noted.

Assessment of behavioural parameters

Elevated plus maze

Each mouse was placed at the end of an open arm, facing away from the central platform, during the practice session prior to the scopolamine injection in order to evaluate the transfer latency time. To evaluate the memory retention of this learned task, the transfer latency time was measured on the 30th day at the end of therapy (Singh, Kahol, Singh, Saraf, & Shri, 2016).

Hebb's William - Maze

Each of Hebb's William-maze's three halves has a detachable guillotine door. During the training period, the individual mouse was put in the start box and the time taken to reach reward chamber from the start box was noted. Before going back to its own cage, each animal was given three minutes to explore the maze with all of the doors open. On the 30th day following the scopolamine injection, the memory retention of this acquired task was assessed (Bala, Khanna, Mehan, & Kalra, 2015).

Novel Object Recognition test (NOR)

Mice were tested for recognition memory using the NOR test. An open field apparatus of a 40 cm × 40 cm × 25 cm square piece of plywood was used for this test. Each mouse was put in the apparatus separately to become familiar with two similar objects for five minutes on the day before the test (day 29) and an hour later, they were all put back in their home cage. On 30^{th} day, after 30-minute of scopolamine injection further animal placed in the apparatus and time to explore the new object (tB) and the familiar object (tA) was noted (Bhuvanendran, Kumari, Othman, & Shaikh, 2018) .

The discrimination index (DI) was calculated using following formula: $\frac{tB}{tB+tA}$

Assessment of biochemical parameters

After behavioural parameters, brain samples were isolated and homogenate was prepared in phosphate-buffered saline (0.1 M, pH 8.0). Brain tissue acetylcholine esterase (AChE) activity and antioxidant levels were estimated in tissue homogenate (Ahmed & Gilani, 2009).

AChE activity

The brain tissues AChE activity was estimated as per established protocol. Briefly, 400 µL of supernatant, 0.15 mL of 0.1 M PBS (pH 8.0) and 100 µL of DTNB were added into a cuvette. To this 20 µL of acetyl thiocholine (75 mM) was added as a substrate. This solution was incubation at 37°C for 10 minutes and then absorbance was read by spectrophotometer at 412 nm (Perry, Houghton, Jenner, Keith, & Perry, 2002)

Estimation of Antioxidant markers

Malondialdehyde (MDA) estimation

Aliquot of tissue sample (0.1 mL) boiled with thiobarbituric acid (1 mL) for 30 minutes in a water bath. To this 1 mL of

trichloro acetic acid was added to stop the reaction and let it cool for 10 minutes on an ice bath. Centrifuge this cooled reaction mixture for ten minutes at 5000 rpm. The absorbance of the supernatant was read at 532 nm using UV-vis spectrophotometer. The concentration of MDA was using an extinction coefficient of 1.56×10^5 M^{-1} cm^{-1}. (Sharma & Gupta, 2001).

Glutathione (GSH) estimation

The equal amounts of tissue homogenate and trichloroacetic acid (10%w/v) was incubated for 20 minutes. To the 1mL of supernatant, 0.5 mL of the DTNB reagent (0.6 mM in 0.2 M phosphate buffer) was added to initiate the reaction. Measure the absorbance with a UV-vis spectrophotometer at 412 nm. Determine the GSH levels using an extinction coefficient of 1.36×10^3 M^{-1} cm^{-1} (Mandal, Saharan, Tripathi, & Murari, 2015; Owens & Belcher, 1965).

Histopathological studies

The brain was carefully separated and immediately preserved in a 10% formalin solution. The tissue was cleaned with xylene, dehydrated with ethanol, and kept in a block of paraffin wax. Sections of 5 µm thick were stained with haematoxylin and eosin for photo microscopy analysis (Higgins, Holtzman, Rabin, Mobley, & Cordell, 1994).

Statistical Analysis

All data were expressed using the mean ± SEM. The data was statistically analysed using the Tukey multiple comparison test and a one-way ANOVA. (Keselman & Rogan, 1977).

3. RESULTS

Quantitative yield of extraction

Liquid-liquid fractionation of methanol extract yield different fractions such as n-hexane fraction of *Aegle marmelos* (HFAM), chloroform fraction of *Aegle mermelos* (CFAM),ethyl acetate fraction of *Aegle mermelos* (EFAM) and butanol fractions of *Aegle mermelos* (BFAM). It is observed that ethyl acetate fraction (EFAM) had shown better quantitative yield when compared to all other fractions (Table 1).

Table 1: Quantitative yield of methanol extract and its fractions

Fractions	Quantity (g)
Methanol extract of *Aegle marmelos* (MEAM)	50gm
n-Hexane fraction of *Aegle marmelos* (HFAM)	6.10gm
Chloroform fractions of *Aegle marmelos* (CFAM)	7.20gm
Ethyl acetate fraction of *Aegle marmelos* (EFAM)	8.50gm
Butanol fraction of *Aegle marmelos* (BFAM)	7.50gm

DPPH scavenging activity

Methanol extract and its fractions with different concentration (25, 50, 75,100 µg/ml) were subjected to DPPH scavenging activity. When compared with all, the EFAM has shown good DPPH scavenging activity with 87.99% inhibition. Whereas, standard drug ascorbic acid shown 72.1% inhibition. So, it is observed that EFAM has shown better DPPH scavenging activity (Table 2).

Table 2: DPPH scavenging activity of methanol extract and its fraction

Test sample	Concentration (µg/ml)	Percentage inhibition (Mean±SD)
MEAM	25	17.18±2.10
	50	21.81±1.09
	75	30.5±2.10
	100	45.6±0.74

HFAM	25	20±2.10
	50	29±1.25
	75	43.32±0.85
	100	77.2±1.25
CFAM	25	19.41±2.10
	50	27.1±1.05
	75	31.1±0.22
	100	45.21±0.99
EFAM	25	87.99±0.95
	50	32.5±2.10
	75	55.6±0.74
	100	87.99±0.95
BFAM	25	17.21±0.55
	50	25.1±1.55
	75	27.21±0.55
	100	65.11±0.55
Ascorbic acid (Standard reference)	25	21.44±1.10
	50	26.1±0.88
	75	34.21±2.55
	100	72.1±0.55

Elevated plus maze

Transfer latency time in increased in scopolamine treated mice significantly than normal control it indicate memory dysfunction with scopolamine. Whereas, mice treated with EFAM had shown dose dependent shorten transfer latency time. Higher dose (400mg/kg) had shown more improvement in transfer latency time (Table 3).

Table 3: Results of behavioral parameters

Groups	**Elevated plus maze (EPM)** **Transfer latency time (TL)**	**Hebb Williams maze (HWM)** **Time to reach reward chamber (TRC)**	**Novel object recognition method (NOR)** **Recognition Index (RI)**
1. Normal	166.4±17.76	34.24±9.54	20.342±0.151
2. Scopolamine	178.1±25.31***	40.22±10.22**	6.895±0.035**
3. Donepezil	152.5±5.156*	28.60±3.763*	17.097±0.3128***
4. EFAM (200mg/kg)	142.5±4.23*	26.40±3.265*	12.876±0.124***
5. EFAM (400mg/kg)	138.9±2.16**	19.15±1.30***	15.967±0.248***

All values are expressed Mean ±SD one way ANOVA followed by Dunnett's method *P<0.05 or **P<0.01 and ***P<0.001

Hebb's Williams maze

The mice were placed at start box and observed for the time taken by the mice to reach the reward chamber from start box. It is observed that the mice treated with scopolamine taken more time to reach the reward chamber. Whereas, the mice treated with EFAM (400mg/kg) had taken less time to reach the reward chamber. So, it is concluded that EFAM (400mg/kg) improves memory deficit (TRC) (Table 3).

Novel object recognition test

This test is used to assess recognition memory in mice and this is expressed as recognition index. Higher the index better the recognition memory During this study it is observed that the mice treated with scopolamine explored time for the novel objects is decrease so recognition index is also less and whereas mice treated with EFAM dose dependent manner significantly explore for novel object which is indicated by higher recognition index (400mg/kg). This indicate memory dysfunction associated with scopolamine efficiently antagonized by test extract (Table 3).

Malondialdehyde (MAO) levels

Lipid peroxidation of brain tissue has been observed during scopolamine treatment and is indicated by increase in malondialdehyde (MAO) levels in brain tissue compared to normal control. Whereas, EFAM treated antagonize the lipid peroxidation with scopolamine and is observed that malondialdehyde quantity is greatly decreased in treated group compared to scopolamine group (Table 4).

Table 4: Levels of oxidative stress markers in brain homogenate

Groups	Malondialdehyde (MDA) nmol/g protein	Glutathione (GSH) nmol/g protein	AChE levels nmol/g
1. Normal	**14.26 ±0.5887**	**0.4800±0.0803**	**29.12±1.85**
2. Scopolamine	**17.98±0.9487*****	**0.2017±0.0351****	**35.84±0.15*****
3. Donepezil	**14.16±0.8664*****	**0.4233±0.0371****	**19.35±2.15*****
4. EFAM (200mg/kg)	**11.70±0.8602*****	**0.5317±0.0560*****	**26.62±0.98****
5. EFAM (400mg/kg)	**10.60±0.9274*****	**0.5717±0.0627*****	**22.53±1.57****

All values are expressed Mean ±SD one way ANOVA followed by Dunnett's method *P<0.05 or **P<0.01 and ***P<0.001

Reduced glutathione (GSH) levels

The brain tissue reduced glutathione (GSH) was significantly decreased in scopolamine treated mice indicate defect in oxidative defensive factor during scopolamine induced oxidative stress. On other hand, EFAM (200 & 400mg/kg) treated mice had shown restoration of reduced glutathione of glutathione (GSH) levels indicate protective effect against scopolamine induced oxidative stress (Table 4).

Brain tissue AChE activity

Scopolamine treatment induce acetylcholinesterase activity and in indicated by significant elevation of acetylcholinesterase levels as compared to normal control. This reflect central alteration of cholinergic transmission lead to memory dysfunction. Which is reflect in behavioral changes. EFAM (200 & 400 mg/kg) treatment has shown significant reduction in acetyl cholinesterase levels compared to scopolamine which reflect improvement cholinergic transmission there by improve behavioral changes in mice (Table 4).

Histopathology observations

Under a light microscope, the CA1 area of the hippocampus of control group exhibits typical structures with the right density and normal architecture. Sscopolamine treatment group displayed degeneration of neuronal cells, altered neuronal cell shape, and loss of nuclear features. The donepezil treated group displayed typical pyramidal cell nuclear characteristics. The pyramidal neuronal cells were preserved in mice given 200 mg/kg of EFAM and also in still improvement in 400 mg/kg treated mice comparable to those in the control group.

4. DISCUSSION

Alzheimer's disease is typified by broad structural abnormalities in the brain along with gradual memory loss, cognitive impairment, and personality flaws. Many cognitive impairments brought on by neuronal death, damage, and synapse failure.

The clinical illness known as amnesia is typified by the emergence of changes in neurotransmitters, inflammation, oxidative stress, and cholesterol buildup all contribute to this cycle, which is implicated in brain dysfunction (Akbarzadehmoallemkoalei et al., 2025) . Examining the effect of *Aegle marmelos* as a cognitive enhancer in mice with scopolamine-induced amnesia is the study's goal. In order to investigate possible therapeutic drugs that could mitigate cognitive deficits, scopolamine-induced cognitive dysfunction is often used (Wesnes, Simpson, & Kidd, 1988). After undergoing solvent-solvent fractionation of methanol extract lead to get various fractions such as n-hexane, chloroform, ethyl acetate and butanol. The potent antioxidant effect of the ethyl acetate fraction of *Aegle marmelos* (EFAM) than other fractions might be good choice to study its anti-amnesic effect. So EFAM used to assess the *in vivo* anti-amnesic effect of scopolamine-induced amnesia in mice, taking into account the findings of the antioxidant results (Lanni et al., 2008). A single intraperitoneal injection of scopolamine at a dose of 3 mg/kg results in memory loss, as determined by many behavioral models. When compared to scopolamine-treated groups, mice treated with EFAM at 200 and 400 mg/kg for 30 days showed improved memory, as evidenced by shorter transfer latency (TL) , shorter time to reach reward chamber (TRC) values, and higher discrimination index in the Novel Object Recognition method (NOR). It implies the reversal of amnesia induced by scopolamine. The basis of memory impairment by scopolamine is due to impairment of cholinergic transmission due to induction of acetylcholinesterase. Ethyl acetate improves memory impairment by inhibiting cholinesterase, which enhances cholinergic transmission in the mouse brain (Katta SS, 2022). Scopolamine also induced neurodegeneration of cholinergic neurons due to oxidative stress which cause memory deficit in mice. It depletes reduced glutathione, an endogenous antioxidant that protects cholinergic neurons from oxidative damage, and increases malondialdehyde (MDA), an indicator of lipid peroxidation of cholinergic neurons (Wahid F, 2022). In the current study, low levels of GSH and a higher level of MDA in the mice's brains of scopolamine treatment demonstrate stress-associated brain injury. Reduced glutathione (GSH) levels and malondialdehyde (MDA) levels in the mouse brain homogenate are dose-dependently increased and decreased by the EFAM at two distinct doses of 200 mg/kg and 400 mg/kg, protecting against the neurotoxicity linked to scopolamine-induced oxidative stress (Ionita R et al., 2018). Because of its antioxidant properties, it demonstrates the neuroprotective impact on cholinergic neuron dysfunction. The decrease of density and arrangement of pyramidal cells in the hippocampus is the final histopathological observation that demonstrates the loss of neuronal cells in the CA1 area of the hippocampus in the scopolamine-treated group (Samir SM et al., 2024). Similar to the control group, the EFAM preserve typical hippocampal neuronal structures against scopolamine induced CA1 region neurodegeration in mice. It added up confirmative neuroprotective effect of *Aegle marmelos* ethyl acetate fractions.

5. CONCLUSION

In this study, we are using a mouse model of scopolamine-induced neurotoxicity to examine the neuroprotective potential and memory retention effects of *Aegle marmelos*. Mice with scopolamine-induced amnesia benefit from the memory retention properties of *Aegle marmelos* ethyl acetate fraction (EFAM). This may be because of anti-cholinesterase, and antioxidant properties. This supports the long-standing usage of *Aegle marmelos* to treat memory dysfunction.

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Conflict of interest

The authors declare that there is no conflict of interest.

List of abbreviations

S.NO	Abbreviation	Full form
1	AG	Aegle marmelos
2	EFAM	Ethyl acetate fraction of Aegle marmelos
3	BFAM	Butanol fraction of Aegle marmelos
4	CFAM	Chloroform fraction of Aegle marmelos
5	HFAM	n-Hexane fraction of Aegle marmelos
6	AD	Alzheimer’s disease
7	Ach	Acetylcholine
8	DPPH	α, α-diphenyl-β-picrylhydrazyl

9	ATCI	Acetylthiocholine iodide
10	DTNB	5,5'-Dithiobis (2-nitrobenzoic acid)
11	AChE	Acetylcholinestrase enzyme
12	TL	Transfer latency
13	NOR	Novel Object Recognition Model
14	DMSO	Dimethyl sulfoxide
15	MDA	Malondialdehyde
16	TCA	Trichloroacetic acid
17	TBA	Thio barbituric acid
18	GSH	Glutathione

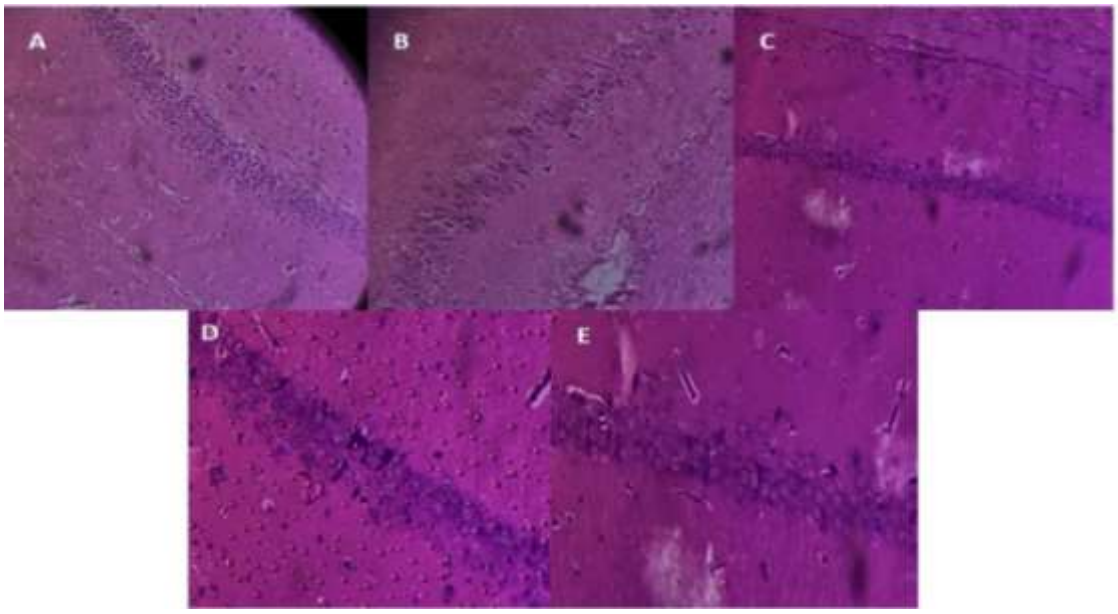

Figure 1: Histopathological study of mice CA1 region of hippocampus

A: control group; B: scopolamine; C: donepezil; D: EFAM group (200mg/kg); E: EFAM group (400mg/kg).

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