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RESEARCH ARTICLE

Studies on Therapeutic Potential of Essential Oils of *Nepeta Cataria* in Treatment of Alzheimer's Disease.

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ABSTRACT

Nootropic acitivity of essential oil of *Nepeta cataria* (EONC) was studied in mice. Elevated plus maze and passive avoidance paradigm were employed to evaluate learning and memory parameters. Scopolamine (0.4 mg/kg, i.p.) was used to induce amnesia in mice. The essential oil (1gm/kg) significantly attenuated amnestic deficits induced by scopolamine (0.4 mg/kg, i.p.) and natural aging. Also exhibited decreased the transfer latencies and increased step down latencies significantly in the aged mice and scopolamine induced amnesic mice as compared with Piracetam (200 mg/kg, i.p.). To delineate the possible mechanism through which *Nepeta cataria* elicits the anti-amnesic effects, we studied its influence on central cholinergic activity by estimating the whole brain acetylcholinesterase activity. EONC significantly decreased acetyl cholinesterase activity in mice. The results indicate that essential oil of *Nepeta cataria* might prove to be a useful memory restorative agent in the treatment of dementia seen in elderly. The underlying mechanism of action may be attributed to its anti acetylcholinesterase property.

Keywords: Nootropic activity, *Nepeta cataria,* Memory, anti acetylcholinesterase.

1. INTRODUCTION

Memory is ability of an individual to record event, information and retains them over short or long periods of time and recalls the same whenever. Alzheimer's disease (AD) first described by a Bavarian psychiatrist and neuropathologist named Alois Alzheimer in 1907. AD is a progressive neurodegenerative brain disorder that occurs gradually and results in memory loss, unusual behavior, personality changes and ultimately death. It is a chronic, progressive disabling organic brain disorder characterized by disturbance of multiple cortical functions, including memory, judgment, orientation, comprehension, learning capacity and language[1]

Nootropics, popularly referred to as "smart drugs", are substances, which boost human cognitive abilities (functions and capacities of the brain). Typically these are thought to work by increasing the brain's supply of neurochemicals (neurotransmitters, enzymes and hormones) improving brain's oxygen supply or by stimulating nerve growth[2].

Learning is defined as the acquisition of information and skills. Memory comprises of registration, consolidation and retrieval. Cholinergic neurons in forebrain and brainstem send diffused projections to hippocampus and cortex. Degeneration of the above, nucleus basalis of meynert and septohippocampal nucleus is involved in AD and in learning and short term memory. Neurotransmitters involved in learning and memory process are glutamate, N-methyl-D-aspartate (NMDA), acetylcholine, dopamine, serotonin, noradrenaline, GABA, neuropeptides and neurosteroids[3].

N. cataria in folk medicine used for antispasmodic, carminative, stimulant, and tonic properties. Moreover, traditionally, the tea made of its leaves is known as sedative and soporific and also is used to relive gastrointestinal and respiratory disorders such as colic, diarrhea, cough, asthma, and bronchitis. It has been shown that many medical properties of *Nepeta* species are the characteristic of its essential oil (EO) and flavonoids and have been reported to have antibacterial, antifungal, insecticidal and antioxidant activities [4].

2. MATERIALS AND METHODS

2.1. Plant Materials:

Nepeta cataria was procured from local herb suppliers and was authenticated by Dr. Kempegowda, Botanist

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Department of Botany, Bangalore University. Voucher specimen has been deposited at the herbarium for further reference.

2.2. Isolation of the essential oil:

Plant material was subjected to hydro distillation for 3 h using a Clevenger type apparatus. The oil will be dried over anhydrous Na2SO4 and preserved in a sealed vial at 4 0C until further analysis56 All the doses were prepared in distilled water using 5% Tween 80 solution as suspending agent and administered orally. In all cases, the concentrations were prepared in 1 ml/100g of body weight. The test substances were administered in a single dose using a gastric intubation tube after fasting for 3 to 4 h.

2.3. Drugs and Chemicals: Scopolamine Hydrobromide IP (Cadila health care Ltd Goa), Piracetam (Normabrain® Torent Pharmaceuticals LTD, vill, India), DTNB (5,5-dithiobis-2- nitro benzoic acid), Acetylcholine iodide, Sodium dihydrogen phosphate, Dipotasium hydrogen phosphate (Hi-Media, India). Scopolamine hydro bromide was dissolved separately in normal saline and injected i.p., volume of i.p. injection was 1 ml/100 g of mouse.

2.4. Acute Toxicity Studies*: Nepeta cataria* at different doses (50-2000 mg/kg) was administered orally to mice with the help of a specially designed oral needle connected to a polythene tube. ECCO was administered at the same time on each day. During the first four hours after the drug administration, the animals were observed for gross behavioral changes if any, for 7 days. Parameters such as hyperactivity, grooming, convulsions, sedation served. The dose 1gm/kg/day was selected.

2.5. Animals*:* Swiss mice of either sex weighing around 18 g (younger ones, aged 8 weeks) and 25 g (older ones, aged 28 weeks) were used in the present study. Animals were procured from disease free. They were acclimatized to the laboratory conditions for 5 days before behavioral studies. The animals had free access to food and water and were maintained under 12:12 h light and dark cycles. Institutional Animals Ethics Committee (IAEC) had approved the experimental design and care was taken as per guidelines of CPCSEA, Dept. Govt. of India.

2.6. Behavioral Models:

2.6.1. Elevated plus Maze (EPM)[5,6]:

The elevated plus maze served as the exteroceptive behavioral model (where stimulus existed outside the body) to evaluate learning and memory in mice. The apparatus consisted of two open arms (16 cm × 5 cm) and two covered arms (16 cm × 5 cm × 12 cm). The arms extended from first day, each mouse was placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) was taken as the time taken by the mouse to move into any one of the covered arms with all its four legs. The mouse was allowed to explore the maze for 10 sec and then re-turned to its home cage. Memory retention was examined.

2.6.2. Passive shock avoidance paradigm[7,8]:

Passive avoidance behavior based on negative reinforcement was recorded to examine long-term memory. The apparatus consisted of a box (27 × 27 × 27 cm) having three walls of wood and one wall of Plexiglas, featuring a grid floor (3 mm stainless steel rods set 8 mm apart), with a wooden platform (10 × 7 × 1.7 cm) in the center of the grid floor. The box was illuminated with a 15 W bulb during the experimental period. Electric shock (20V AC) was delivered to the grid floor. Training was carried out in two similar sessions. Each mouse was gently placed on the wooden platform set in the center of the grid floor. When the mouse stepped down and placed all its paws on the grid floor, shocks were delivered for 15 sec and the step-down latency (SDL) was recorded. SDL was defined as the time taken by the mouse to step down from wooden platform to grid floor with its entire paw on the grid floor. Animals showing SDL in the range (2-15 sec) during the first test were used for the second session and the retention test. The second-session was carried out 90 min after the first test. When the animals stepped down before 60 sec, electric shocks were delivered for 15 sec. During the second test, animals were removed from shock free zone if they did not step down for a period of 60 sec. Retention was tested after 24 h in a similar manner, except that the electric shocks were not applied to the grid floor. Each mouse was again placed on the platform, and the SDL was recorded with an upper cutoff time of 300sec.

2.7. Experimental Protocol

The animals were divided into 9 (6+3) groups and each group consisted of six animals. Separate animals were used for each experiment.

2.7. A. Young groups:

Group 1: Control (normal saline was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, again after 24 h, i.e. on the 9th day.)

Group 2: Scopolamine (0.4 mg/kg, i.p.) Was injected intraperitonially and TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.

Group 3: Only Piracetam (200 mg/kg, p.o.) was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.

Group 4: Piracetam (200 mg/kg, p.o.) + Scopolamine (0.4 mg/kg, i.p.): Piracetam was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, after 45 min injected Scopolamine intraperitonially for 1

days. TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.

Group 5: EONC (1gm/kg) + Scopolamine (0.4 mg/kg, i.p.): EONC was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, after 45 min injected Scopolamine intraperitonially for 1 day. TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.

Group 6: EONC (1gm/kg) was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.

2.7. B. Aged groups:

Group 1: Control (normal saline was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.)

Group 2: Piracetam (200 mg/kg, p.o.) was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.

Group 3: EONC (1gm/kg) was administered orally for 8 days. TL was noted after 45 min of administration on the 8th day, again after 24h, i.e. on the 9th day.

2.8. Estimation of Brain Acetyl Cholinesterase (AChE) Activity[9,10] :

On the 9th day the animals were killed by cervical dislocation carefully to avoid any injuries to the tissue. Mice brains were isolated quickly and placed in ice-cold saline. The tissues were weighed and homogenized in 0.1 M Phosphate buffer (pH 8). 0.4ml aliquot of the homogenate was added to a cuvette containing 2.6 ml Phosphate buffer (0.1M, ph 8) and 100µl of DTNB. The contents of the cuvette were mixed thoroughly by bubbling air and absorbance was measured at 412 nm in a UV spectrophotometer. When absorbance reaches a stable value, it was recorded as the basal reading. 20µl of substrate i.e acetylthiocholine was added and change in absorbance is recorded for a period of 10 min at interval of 2 min. Change in the absorbance per minute is thus determined. Acetyl cholinesterase (AChE) activity was determined on 9th day, and calculated using following formula.

$R = 5.74\times 10^{-4} \times A / CO$

Where,

R = Rate in moles of substrate hydrolyzed / minute / gm tissue

A = Change in absorbance / min

CO = Original concentration of the tissue (mg / ml).

3. STATISTICAL ANALYSIS

All the results were expressed as mean ± Standard error. The data was analyzed using one-way ANOVA followed by multiple range tests was used for the analysis of non-normally distributed data. p <0.05 was considered as significant.

4. RESULTS

4.1. Acute Toxicity Study:

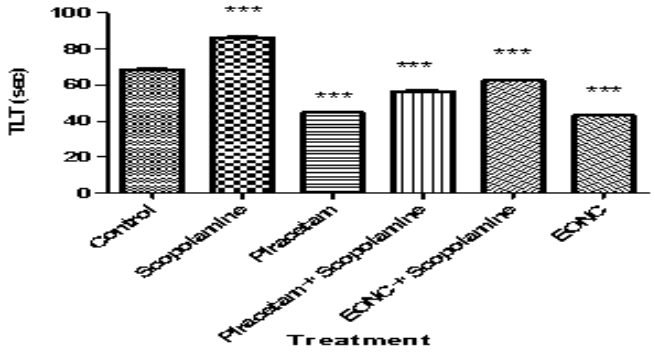
No mortality was observed following oral administration of EOCN even with the highest dose (2000 mg/kg). However EOCN at doses more than 2000 mg/kg produced profuse watery stools in animals. Both the doses of EONC had no toxic effect on the normal behavior of the rats.

4.2. Effect on Transfer Latency Using EPM

Aged mice showed higher transfer latency (TL) values on first day and on second day (after 24 h) as compared to young mice (fig 3 &4), indicating impairment in learning and memory (i.e. ageing-induced amnesia). Piracetam (200 mg/kg, i.p.) pretreatment for 8 days decreased transfer latency of the 8th day 9th days as compared to distilled water treated group, indicating improvement in both learning and memory. Scopolamine (0.4 mg/kg) increased TL significantly (p < 0.001) in young mice as compared to control, indicating impairment of both learning and memory (Fig 1 and Fig 2).

Group No.	Treatment	Dose	TLT (sec) mean ± S.E.M [n=6]
I	Control	10 ml/kg	68.67 ± 0.3333
II	Scopolamine	0.4 mg/kg	86.33 ± 0.3333***
III	Piracetam	200 mg/kg	44.83 ± 0.3073***
IV	Piracetam + Scopolamine	200 mg/kg + 0.4 mg/kg	56.67 ± 0.4216***
V	EONC + Scopolamine	1 gm/kg + 0.4 mg/kg	62.50 ± 0.5627***
VI	EONC	1 gm/kg	43.17 ± 0.4014***

Table No.1. Effect of EONC on Anxiety in EPM : (Young) 8th Day n=6 in each group. Data expressed as mean ± S.E.M.. statistical analysis were performed using one-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control



FigureNo.1. Effect of EONC on Anxiety in EPM: (Young) 8th Day

4.3. Effect of essential oil *of Nepeta cataria* on TLT in young mice (9th Day):

The young animals treated only with EONC (1gm/kg, p.o.) showed significant ($p<0.001$) reduction in TLT of both learning and memory task as compared to normal control group. EOCN + Scopalamine group showed significant ($p<0.001$) reduction in TLT of both learning and memory task as compared to scopolamine induced group.

Piracetam + Scopalamine group as expected showed significant ($p<0.001$) reduction in TLT of both learning and memory task as compared to scopolamine induced group. Only Piracetam (200 mg/kg, p.o.) treated group shown significantly ($p<0.001$) reduction in TLT of both learning and memory, as compared with normal control group (Table:1 & 2)

Group No.	Treatment	Dose	TLT (sec) mean ± S.E.M [n=6]
I	Control	10 ml/kg	62.67 ± 0.2108
II	Scopolamine	0.4 mg/kg	84.67 ± 0.3333***
III	Piracetam	200 mg/kg	40.67 ± 0.3333***
IV	Piracetam + Scopolamine	200 mg/kg + 0.4 mg/kg	52.17 ± 0.4773***
V	EONC + Scopolamine	1 gm/kg + 0.4 mg/kg	60.67 ± 0.4216**
VI	EONC	1 gm/kg	41.33 ± 0.3333***

n=6 in each group. Data expressed as mean ± S.E.M.. statistical analysis were performed using one-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control

Table No.2. Effect of EONC on TLT in EPM : (Young) 9th Day

4.4 Effect of EONC on Anxiety in EPM : (Young) 9th Day

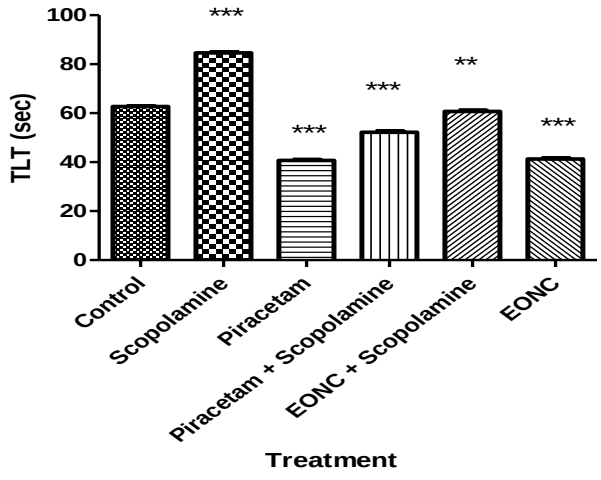


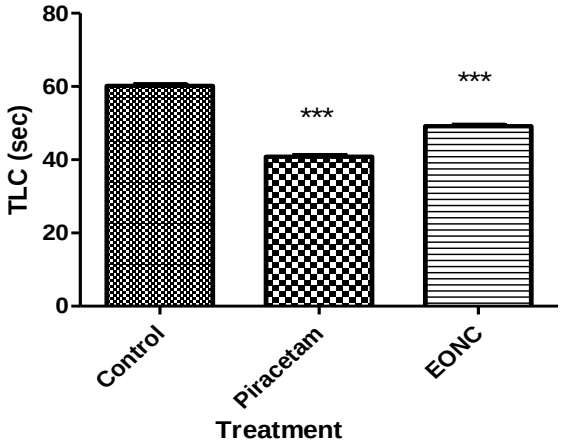
Figure No.2. Effect of EONC on Anxiety in EPM: (Young) 9th Day

Group No.	Treatment	Dose	TLT (sec) mean ± S.E.M [n=6]
I	Control	10 ml/kg	60.17 ± 0.3073
II	Piracetam	200 mg/kg	40.83 ± 0.4014***
III	EONC	1 gm/kg	49.17 ± 0.3073***

n=6 in each group. Data expressed as mean ± S.E.M.. statistical analysis were performed using one-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control

Table No.3. Effect of EONC on Anxiety in EPM : (Aged) 8th Day

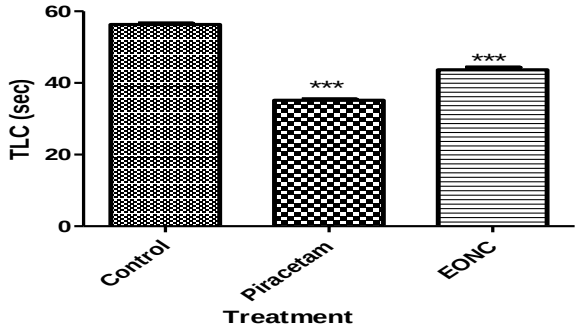
4.5. EPM – Aged – EONC – 8th day :



FigureNo.3. Effect of EONC on Anxiety in EPM : (Aged) 8th Day

EONC (1gm/kg, p.o.) decreased TL on the 8th and 9th days in both young and aged mice ($p < 0.001$) when compared to respective control groups. dose of EONC (1gm/kg, p.o.) improved learning and memory of aged and young mice as reflected by marked decrease in TL on the 8th and 9th days, when subjected to elevated plus maze tests (Fig 3 & 4). EONC pretreatment for 8 days protected the young as well as the old mice ($p < 0.05$) against scopolamine induced amnesia.

EPM – Aged – EONC – 9th day :



FigureNo.7. Effect of EONC on Anxiety in EPM : (Aged) 9th Day

Group No.	Treatment	Dose	TLT (sec) mean ± S.E.M [n=6]
I	Control	10 ml/kg	56.33 ± 0.3333
II	Piracetam	200 mg/kg	35.17 ± 0.3073***
III	EONC	1 gm/kg	43.67 ± 0.7149***

n=6 in each group. Data expressed as mean ± S.E.M.. statistical analysis were performed using one-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control

Table No.4. Effect of EONC on Anxiety in EPM : (Aged) 9th Day

4.6. Effect on SDL Using Passive Avoidance Paradigm

EONC (1gm/kg, p.o.) treatment profoundly increased step down latency (SDL) as compared to control group on the second day indicating improvement in memory of young mice. Scopolamine hydrobromide (0.4 mg/kg, i.p.) decreased SDL on second day after training, indicating impairment of memory. EONC (1gm/kg, p.o.) administered orally for 8 days significantly reversed amnesia induced by scopolamine and natural ageing (Fig 5).

Group No.	Treatment	Dose	Latency to reach SFZ in 15 min (Sec) (Acquisition / Learning)	No of mistakes (SDE) in 15 min (Consolidation / Memory)
I	Control	10 ml/kg	35.17 ± 0.3073	7.50 ± 0.2236
II	Scopolamine	0.4 mg/kg, i.p	40.33 ± 0.4216***	8.16 ± 0.4014
III	Piracetam + Scopolamine	250 mg/kg + 0.4 mg/kg, i.p	10.67 ± 0.3333***	3.66 ± 0.2108***
IV	EONC + Scopolamine	1 gm/kg +0.4 mg/kg, i.p	11.67 ± 0.4216***	3.667 ± 0.2108***
V	Piracetam	200 mg p.o	8.167 ± 0.3073***	3.00 ± 0.2582***
VI	EONC	1 gm/kg	11.67 ± 0.3333***	5.667 ± 0.2108***

n=6 in each group. Data expressed as mean ± S.E.M.. statistical analysis were performed using one-way ANOVA followed by Dunnett's test. *P < 0.05, **P < 0.01, ***P < 0.001 vs. control

Table No.5 : Effect of EONC on Learning and Memory in Passive avoidance response model :

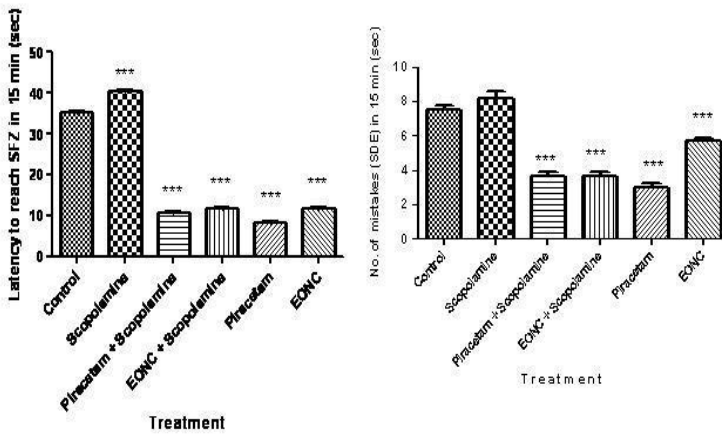


Figure No.5a & 5b: Effect of EONC on Learning and Memory in Passive avoidance response model

4.7. Effect on Acetylcholinesterase Activity:

The acetylcholiesterase activity of whole brain was markedly elevated (p < 0.05) after scopolamine (0-4 mg/kg, p.o.) treatment. Piracetam (200 mg/kg, p.o.) and EONC (1gm/kg, p.o.) significantly lowered AChE activity (Fig 6 & 7).

Group	Treatment	Dose	AChE (µM)
I	Normal control	10 ml/kg	0.12±0.0020
II	Scopolamine	0.4 mg/kg (i.p)	0.18±0.0046***
III	Piracetam+Scopolamine	200 + 0.4(mg/kg)	0.12±0.0025###
IV	***EONC*** +Scopolamine	1 gm + 0.4(mg/kg)	0.13±0.0023###
V	***EONC***	1gm/kg(p.o.)	0.11±0.0013aaa
VI	**Piracetam**	200mg/kg(p.o.)	0.09±0.0036***

Each group consists of 6 animals. Values are mean ±S.E.M. ***P < 0.001 compared to normal control group. aaaP< 0.001 compared to scopolamine treated group. ###P < 0.001 compared to scopolamine treated group.

Table 6: Effect of *EONC* on whole brain acetyl cholinesterase activity on young mice using Elevated plus maze:

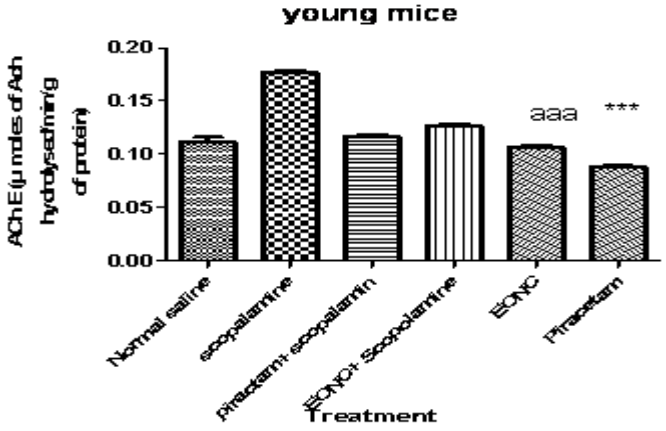


Fig 6: Effect of *EONC* on whole brain acetyl cholinesterase activity on young mice

Group	Treatment	Dose	AChE (µM)
I	Normal control	10 ml/kg (p.o.)	0.13±0.0016
II	Piracetam	200 mg/kg (p.o.)	0.08±0.0014***
III	***EONC***	1gm/kg (p.o.)	0.114±0.0002***

Values are mean ±S.E.M, (n=6). One way ANOVA followed by Dunnett's tests. ***indicates p< 0.001 as compared to normal control group of aged mice. ** indicates p< 0.01 as compared to normal control group of aged mice. * indicates p< 0.05 as compared to normal control group of aged mice

Table7: Effect of *EONC* on whole brain acetyl cholinesterase activity on aged mice using Elevated plus maze

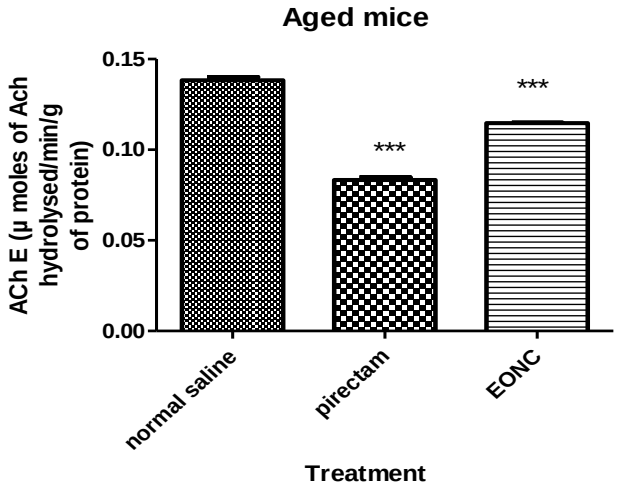


Fig7: Effect of *EONC* (1gm/kg, p.o.) Administered orally for eight successive days on Whole brain acetyl cholinesterase activity of aged mice using Elevated pluse maze (EPM). Piracetam (200 mg/kg, p.o.) was used as a standard drug.

5. DISCUSSION

Aromatic plants had been used since ancient times for their preservative and medicinal properties, and to impart aroma and flavor to food. Hippocrates, sometimes referred to as the 'father of medicine', prescribed perfume fumigations. The pharmaceutical properties of aromatic plants are partially attributed to essential oils. The term 'essential oil' was used for the first time in the 16th century by Paracelsus von Hohenheim, who named the effective component of a drug, 'Quinta essential'[11]

Cognition is that operation of mind by means of which, we become aware of our surroundings, objects and thoughts. Cognitive disorders such as delirium, dementia and amnesic disorders are common in elderly individuals. Dementia of the Alzheimer type (DAT) is a common disease with important consequences to the patients' life quality.[2] Inhibition of the enzyme acetylcholinesterase (AChE) is the basis of most drugs used clinically for symptomatic relief of the early stages of AD. Inhibition of AChE (i.e., reduction of the enzyme responsible for breaking down ACh) results in elevated levels of ACh in the brain, which is associated with improvement of cognitive function including memory[12].

The ability of cholinesterase inhibitory activity in cyclic monoterpenes was identified as the most active compounds. These include Camphor, 1, 8-Cineole, Beta-pinene, Alpha-pinene, together with their inhibitory activities. It can be seen that, of the active components, 1,8-cineole is likely to contribute most to the activity of the oil since it is present in the greatest concentration.[13,14].

It should be noted that 1,8-cineole is a relatively common compound in essential oils and is found in several other plant species. The cholinesterase inhibitory properties of these monoterpenes were only recently reported. Antioxidant effects were noted with 1,8-cineole, alpha-pinene and beta-pinene, but a pro-oxidant effect was produced by camphor, a relatively major component of the oil. It is likely that the pro-oxidant activity of camphor is eclipsed by the antioxidant compounds so that the total oil would have an overall antioxidant effect[15].

EONC also reversed the scopolamine-induced impairment in learning and memory, when assessed on passive avoidance paradigm. Piracetam, the first representation of a class of nootropic agents, has been shown to improve memory deficits in geriatric individuals. Repeated injections of piracetam had improved learning abilities and memory capacities of laboratory animals[16]. Passive avoidance behavior is based on negative reinforcement and is used to examine long-term memory[17,18]. Both piracetam and *Nepeta cataria* meet major criteria for nootropic activity, namely improvement of memory in absence of cognitive deficit[19,20].

In the present study, *Nepeta cataria* significantly inhibited the AChE activity in the mice whole brain homogenate, indicating its potential in the attenuation of symptoms of cognitive deficits. Hence, the memory improving activity of *EONC* may be attributed to its antioxidant, neuropro-tective, pro-cholinergic and anti-acetylcholinesterase properties and can be of enormous use in delaying the onset and reducing the severity of Alzheimer's disease. Further investigations using more experimental paradigms are required for further confirmation of nootropic potential of EONC in the treatment of various cognitive disorders.

6. ACKNOWLEDGEMENT:

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Conflict of Interest: None Declared

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