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NEUROPROTECTIVE EFFECT OF *MADHUCA LONGIFOLIA* LEAF EXTRACT AGAINST COLCHICINE: AN EXPERIMENTAL STUDY ON COGNITIVE DYSFUNCTION AND BIOCHEMICAL ALTERATIONS IN MICE

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ABSTRACT: The goal of the research was to explain as a cognition enhancer the traditional claim of *Madhuca longifolia* (Sapotaceae) leaves. Dementia was activated by intracerebrovascular colchicine administration for 28 days. *Madhuca longifolia* leaves ethanolic extract was evaluated in mice for cognition-enhancing activity in colchicine-induced dementia using elevated plus maze (EPM), actophotometer, and biochemical estimation of brain AChE and MDA levels. Piracetam (200 mg/kg p.o.) was used as standard medicine. Transfer latency (TL) was observed in the colchicine-induced mice using EPM, showing a significant increase ($p<0.01$) in TL compared to the regular control group. No major effect was found on the locomotor activity of the mice. In colchicine-induced mice, a significant increase ($p<0.01$) in AChE and a decrease in MDA levels relative to normal control were observed. These results formed the standard argument, and *Madhuca longifolia* can therefore be a memory enhancer because of the presence of flavonoids.

INTRODUCTION: Alzheimer's disease is a chronic, liberal neurological disorder that steadily triggers memory loss, changes in behavior, personality, and ability to think. Dementia is usually caused by Alzheimer's disease in older adults. The period of time between the onset of symptoms and death is around 8.5 years. About 15 million world population suffer from Alzheimer's disease [1]. Alzheimer's disease usually affects people around the age of 65 years [2]. More free-radical generations mostly weaken the central nervous system. Neuronal degradation of DNA, membrane lipids, and proteins may result from the excessive formation of free radicals.

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There is a marked reduction in cholinergic neurotransmission in the elderly due to reduced brain concentrations of acetylcholine [3]. Alzheimer's disease (AD), where neuron loss happens in different regions of the brain, is the most significant cause of dementia [4]. Neurotic plaque formation involving amyloid β protein is characterized by AD. Cholinergic cell dysfunction is responsible for the development of dementia in the forebrain and acetylcholine [5]. The main risk factors for neurodegenerative diseases are toxins, stress, and genetic predilection [6]. Conventional medicine is widely used for the prevention, diagnosis, recovery, and treatment of different illnesses and diseases. The treatment of various diseases by herbal plants is based on observations, and previous experiences contained in or taught verbally in books [7]. The therapeutic strategies that can postpone or repair neuronal harm include neuroprotection. Herbalism is now as effective, safer and cheaper as it is in trend [8].

Madhuca longifolia belongs to the Sapotaceae family and is classified as Mahua as well [9]. The name Madhuca derives from "Madhu", *i.e.* honey, and is also referred to as the butter tree of India. Mahua, found in India, Nepal and Srilanka, is a deciduous and medium-sized tree [10]. Mahua has many medicinal qualities in every aspect of it. Fruit-refrigerant, aphrodisiac, tonic and anti-ulcerative. Leaf-healing wounds, anthelmintic, emollient and rheumatism. Seed- Diuretic, refrigerant, liquor, hepatoprotective, increased production of woman's milk and antihelmintic. Bark-tonsillitis, stomach upset, anti-venom in snake-poisoning [11]. It consists of various phyto-constituents including flavonoids, triterpenoids, glycosides, saponins and steroids [12]

MATERIALS AND METHODS:

Plant Sample: The fresh leaves of *Madhuca longifolia* were collected from Shri Ram Murti Smarak (College of Engineering and Technology), Bareilly (U.P.), India. They were identified (specimen number- RU/PS/2016/415) by Prof. A.K. Jaitly, Head, Department of Plant Science, Mahatma Jyotiba Phule Rohilkhand University, Bareilly, Uttar Pradesh. A voucher specimen of collected sample was deposited in the institutional herbarium for future reference.

Extract Preparation: *Madhuca longifolia* leaves were washed carefully in tap water, dried in the shade and powdered. This powder was packed into a Soxhlet column and extracted for 24 hours with petroleum ether (60°-80°C). For 24 hours, the same marc was extracted with chloroform (50°-60°C) and then ethanol (68°-78°C). On a water bath (50°C), the extracts were concentrated. The dry powder extract was kept at room temperature after being concentrated. The yield was 0.83 percent (w/w), 1.73 percent (w/w), 25.5 percent (w/w), 28.1 percent (w/w) and 25.9 percent (w/w), respectively, for extracts of petroleum ether, chloroform extract, extract of methanol, extract of ethanol and water extract. For the study, ethanolic leaf extract was used.

Drug Treatment: The test pharmacological made the extract obtained to be suspended at doses of 100, 200 mg/kg p.o. Distilled water which double comprises carboxymethylcellulose (1 percent w/v CMC).

The prescriptions and dosages were administered to every mouse in sets and group 4,5,7,8 based on earlier researches of the ethanolic extract of *Madhuca longifolia* extract. Up to the end of the study period there was no mortality due to medication. During the course of the treatment, the drug excerpt and extract of *Madhuca longifolia* caused no abnormality or death.

Animals: Animals were collected from Animal House, Pharmacy Department, SRMS CET (Pharmacy), Bareilly, U.P. Animals were approved for this study by the Institutional committee responsible for Animal Ethics of the Pharmacy Department, SRMS CET (Pharmacy), Bareilly, U.P. Approval number (715/PO/Re/S/02/ CPCSEA). Swiss albino strains of undeveloped healthy adult mice of both sexes in equivalent numerical for every group (n=6) were taken for the study. The weight differences of the used animals were kept nominal at the start of the research and did not exceed ± 20 percent of the average weight of each and every species. Mice usually weighed 25-30 gm. The experimental animal house temperature of 22°C was maintained. Relative humidity must be between range from 50 to 60%. The lighting was artificial; the sequence was 12 light hours, 12 dark hours. We used traditional laboratory diets ad libitum provided with drinking water. Animals of the same group had been kept together in one cage. Healthy young adult mice were indiscriminately assigned to the control, standard and treatment sets and group the animals were marked by labeling at the base of the tail and accustomed in their cages for at least 5 days before the research was initiated.

Chemicals and Drugs:

Drugs: Sigma Aldrich had purchased piracetam and colchicine.

Chemicals: Ethyl acetate, petroleum ether, methanol, ethanol, and chloroform were gotten from the laboratory of Central Drug House.

Vehicle: *Madhuca longifolia* extract (MLE) has been suspended in 1% w/v CMC and administered through oral means to mice. Colchicine and Piracetam were liquefied distinctly in normal saline and injected i.c.v. and i.p. respectively. The capacity administered orally and i.p. injection was 1ml/100 g of the mouse.

Studies with Serious Toxicity: *Madhuca longifolia* ethanolic extract has been tested for severe oral toxicity in compliance with revised OECD guidelines No.425. When given by oral route in dosages of up to 2000 mg/kg, the extract was without any toxicity in mice. Therefore, the experiment used 200 and 400 mg/kg of ethanolic leaf extract.

Group I: It was a control set. The vehicle was orally administered for 28 successive days, and the transfer latency was assessed on 28th and again on 29th day after 90 minutes of administration.

Group II: It denoted the positive control set. Piracetam was given to the underdeveloped mice for 28 consecutive days, and transfer latency was calculated and on 28th day after 60 min of administration and again on 29th day after 24 h.

Class III: This was a negative control group. Colchicine was injected i.c.v to underdeveloped mice, and transfer latency being was assessed 45 min after inoculation and also again after 24 hours (*i.e.* on the 29th).

Class IV and V: MLE was orally given to the underdeveloped mice for 28 successive days. TL was reported on 28th day after 90 minutes of exposure and similarly after a period of 24 hours on the 29th day.

Group VI: Young mice received inoculation of piracetam for 28 successive days. Colchicine 1 mg/kg, i.p., at 60 min after 28th-day piracetam injection was given in. TL was reported after 45 minutes of colchicine administration and once more on the 29th day after 24 hr.

Group VII, VIII: MLE were orally given to the underdeveloped mice for 28 consecutive days and colchicine (1 mg/kg) was inoculated i.p. to small aged mice at 90 min. after administration of excerpt on day 28th. TL was reported 45 min. once the inoculation is done and after 24h.

Exteroceptive Behavioral Models:

Elevated Plus Maze: The structure consists of a 10×10 cm-sized central platform attached to two 50×10 cm open arms and two 50×40×10 cm-sized closed arms and raised 50 cm above the floor. The research was using mice weighing 20 to 25 g. The experiment was carried out in 2 steps. On day 14, the day of acquisition testing, each mouse was fixed at the last position of an open arm pointing away from the middle point. The period of time consumed through only one locked arms was noted and documented, then later calculated as transfer latency [TL]. All four legs were counted as an entry within the closed arm. For each mouse, the cut-off time was 180 s. Animals who did not reach closed arms during the time of cut-off were excluded from the analysis. Retention testing was carried out on the 15th day, and transfer latency was reported in the same manner as previously stated. Shortening of transfer latency depicted improvement of memory [6].

Actophotometer: Actophotometer comprises six built-in photo-sensors and 4 optical counters showing the operation of the locomotive activity. It indicated the behavior digitally. Most locomotive movements in man & animals are affected by CNS acting drugs. The locomotive activity (horizontal activity) can be measured easily by an actophotometer that functions on photoelectric cells that are linked to a counter in the circuit. When the beam is cut off by an animal of light falling on the photocell, a count is registered. An actophotometer may possess either a round or a square region where the animal roams about. We initially weighed and numbered the mice, then switched on the equipment and placed each and every mouse in the activity birdcage individually for 10 min. We noted down all the animal's basal activity score [13].

Biochemical Analysis: On the 28th day after Colchicine injection, the biochemical parameters for oxidative stress such as MDA and AChE were calculated in mice's brain.

Brain Tissue Preparation: Using ether anesthesia the mice were killed. After the cranium was cut and the brain was removed. The brain was cleansed using regular (chilled) saline solution. 10 percent (w/v) homogeneous brain sample was obtained with 0.03 M sodium phosphate buffer (pH 7.4) at 10 strokes at 2000 rpm. MDA and AChE may be measured using a homogenized preparation of brain tissue.

MDA Measurement: MDA is a test of peroxidation of lipids. MDA can be measured spectrophotometrically using standard 1,1,1,3,3-

tetraethoxypropane, using the technique defined by Colado *et al*., 1997. MDA is typically articulated by nanomoles per mg protein. For 10 minutes, homogenized brain tissue was centrifuged at 700 g. Approximately 500 µl of homogeneous brain tissue in phosphate buffer (pH 7.4) was added to 300 µl 30% trichloroacetic acid (TCA), 150 µl 5N HCl, and 300 µl 2% (w / v) 2-thiobarbituric acid (TBA), respectively. The mix was then boiled at 90°C for 15 min by placing aluminum foil in the mouth of the test tube. The tubes were withdrawn after 30 min and held in ice-cold water for 30 min. The supernatant was obtained in pink colour. The 12,000g mixture was centrifuged for 10 min; the resultant supernatant was spectrophotometrically calculated at 532 nm [14].

Acetylcholinesterase (AChE) Activity: Acetyl-cholinesterase action is considered as a marker for the brain's prolonged depletion of the cholinergic system of the brain. The Ellman's test conducted a quantitative analysis of the acetylcholinesterase levels in the brain. 0.1 ml of DTNB, 0.1 ml of acetylthiocholine iodide, 0.05 ml of supernatant, and 3 ml of 0.01 M sodium phosphate buffer (pH 8) were taken using this process. The absorbance shift at 412 nm was assessed at a 30 s interval for 2 min. Outcomes got calculated through the utilization of the chromophore's molar extinction coefficient ($1.36 \times 10^4\ M^{-1}cm^{-1}$) and expressed as acetylcholine hydrolysed/min/mg protein micro-moles [15].

$$R = \delta\ OD \times Volume\ of\ Assay \times 1000 / E \times mg\ protein$$

Where, R is the rate of enzymatic action in 'micro' mole of acetylthiocholine iodide hydrolyzed per minute per mg of protein. δ OD is the variation or change in absorbance per minute E is the coefficient of extinction ($1.36\times10^4\ M^{-1}cm^{-1}$) [16, 17].

Protein Estimation: In all brain samples, the protein was calculated utilizing Lowry's technique where bovine serum albumin (BSA) (1 mg/ml) was used as standard [18].

Reagents:

1. Alkaline Solution

- **a.** 2% (w/v) Sodium carbonate in 0.1 M NaOH.
- **b.** 1% (w/v) Copper Sulphate
- **c.** 2% Sodium Potassium tartrate

Working alkaline solution: 48ml of A + 1ml of B + 1ml of C

2. Stock Std. Bovine Serum Albumin (BSA) – 1mg/Ml

3. Working Standard BSA (1000µg/Ml) Diluted The Stock 20 Times.

4. Folin-Phenol Reagent (Ice-Cold) Diluted With Equal Amount Of Water At The Time Of Use.

Test Method: 0.1ml of supernatant was added to 0.9ml DDW and 5ml of working alkaline reagent. The mixture was well mixed and then incubated at the temperature of the surrounding for 10 min. Following this, 0.5 ml Folin-phenol reagent was applied and hatched at the temperature of the surrounding for thirty minutes. The absorbance had been calculated against blank at 750 nm. A standard and typical curve (50-1000µg) were then plotted accompanied by an estimate of the sample's protein content as mg/ml [17].

Statistically Done Analysis: All of the findings were represented as an average ± SEM and assessed by One-way ANOVA followed by Dunnett's multiple post-hoc evaluation studies. A 'P' value of < 0.05 has been recognized as statistically important. Graph Pad Prism software analyzed data.

RESULTS AND DISCUSSION: Elevated Plus Maze Test:

TABLE 1: EFFECT OF *MADHUCA LONGIFOLIA LEAF* EXTRACT ON TRANSFER LATENCY IN ELEVATED PLUS MAZE

Treatment	Before (Mean ± SEM)	After (Mean ± SEM)
Control	30.15±0.68	21.91±0.65
Piracetam (200mg/kg, i.p.)	26.28±0.57**	16.95±0.67***
Colchicine (1mg/kg, i.c.v.)	40.53±1.02***	43.78±0.69***
Low dose *Madhuca longifolia,* (100mg/kg, p.o.)	24.75±0. 73***	21.36±0.62*
High dose *Madhuca longifolia*, (200mg/kg, p.o.)	22.03±0.93***	18.46±0.60**

Piracetam+ Colchicine, (200mg/kg, i.p+1mg/kg, i.c.v.)	26.36±0.71**	16.51±0.52***
Low dose *Madhuca longifolia* + Colchicine, (100mg/kg, p.o.+ 1mg/kg, i.c.v.)	24.48±0.47***	22.05±0.34
High dose *Madhuca longifolia* + Colchicine, (200mg/kg, p.o.+ 1mg/kg, i.c.v.)	21.68±0.52***	19.50±0.67*

Results are expressed as MEAN ± SEM (n=6), *P<0.05, **P<0.0 1, ***P<0.001 when compared to control group by One way ANOVA followed by Dunnett's test.

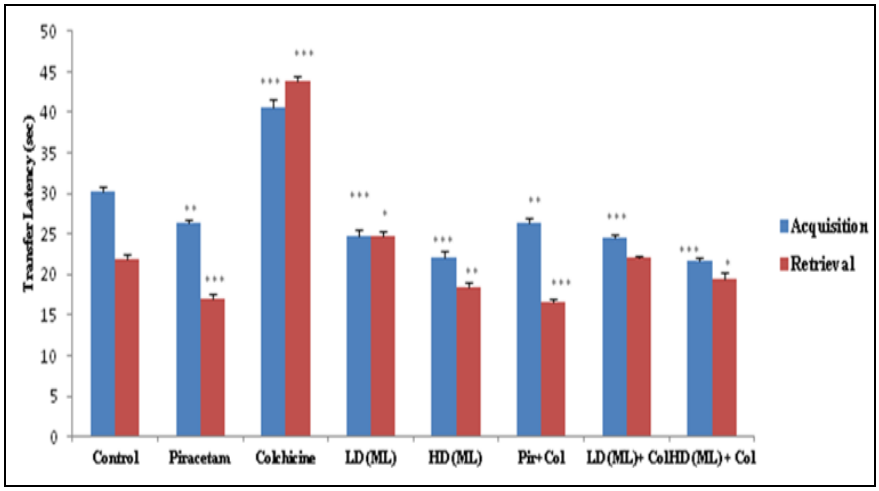

FIG. 1: EFFECT OF *MADHUCA LONGIFOLIA* EXTRACT ON TRANSFER LATENCY IN ELEVATED PLUS MAZE

The result of the *Madhuca longifolia* leaf extract on elevated plus maze apparatus is shown in **Fig. 1**. The Initial Transfer Latency was conducted on the 14th day; *i.e.*, acquisition trial, and no significant variation was found. Outcome are characterized as average ± SEM (n=6), *P<0.05, **P<0.01, *** P<0.001 when one-way ANOVA was followed by Dunnett's tests compared with a control group. In the leaf extract, an increase in transmission latency was found and therefore, nootropic activity was proven. The 200 mg/kg dosage of the *Madhuca longifolia* leaf extract showed substantial improvement in the mice's transfer latency. This shows the action on the leaf by the nootropic excerpt of *Madhuca longifolia*.

Actophotometer:

TABLE 2: EFFECT OF *MADHUCA LONGIFOLIA* LEAF EXTRACT ON BASAL ACTIVITY SCORE IN ACTOPHOTOMETER

Treatment	Day 2 (Mean ± SEM)	Day 7 (Mean ± SEM)	Day 14 (Mean ± SEM)	Day 29 (Mean ± SEM)
Control	237.40±0.54	234.18±0.70	228.90±0.54	219.31±0.61
Piracetam (200mg/kg, i.p.)	242.21±0.74***	239.03±0.48***	240.53±0.66***	214.50±0.59***
Colchicine (1mg/kg, i.c.v.)	234.18±0.70**	235.61±0.66	231.56±0.39*	240.53±0.66***
Low dose *Madhuca longifolia*, (100mg/kg, p.o.)	235.61±0.66	235.61±0.96	231.56±0.39*	219.31±0.61
High dose *Madhuca longifolia*, (200mg/kg, p.o.)	237.70±0.70	237.40±0.54*	232.90±0.66***	216.45±0.60*
Piracetam+ Colchicine, (200mg/kg, i.p+1mg/kg, i.c.v.)	234.00±0.73*	234.00±0.73	231.56±0.39*	215.38±0.69**
Low dose *Madhuca longifolia* + Colchicine, (100mg/kg, p.o.+ 1mg/kg, i.c.v.)	235.61±0.66	232.90±0.66	228.90±0.54	223.11±0.54**
High dose *Madhuca longifolia* + Colchicine, (200mg/kg, p.o.+ 1mg/kg, i.c.v.)	238.03±0.54	235.61±0.66	230.90±0.43*	220.15±0.67

Results are expressed as MEAN ± SEM (n=6), *P<0.05, **P<0.0 1, ***P<0.001 when compared to control group by One-way ANOVA followed by Dunnett's tests.

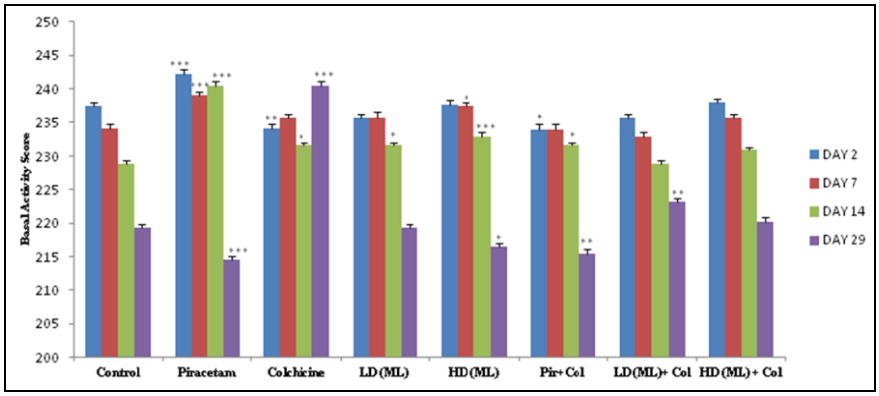

FIG. 2: EFFECT OF *MADHUCA LONGIFOLIA* LEAF EXTRACT ON BASAL ACTIVITY SCORE IN ACTOPHOTOMETER

The effect of the *Madhuca longifolia* leaf extract on an actophotometer is shown in **Fig. 2**. Results are characterized as an average ± SEM (n=6), *P<0.05, **P<0.0 1, *** P<0.001 when one-way ANOVA was followed by Dunnett's test to compare with control group. The leaf extract did not show any CNS depressant effect on mice.

Estimation of MDA:

TABLE 3: EFFECT OF *MADHUCA LONGIFOLIA* EXTRACT ON MDA LEVEL

Treatment	MDA (nM/mg of protein)
Control	1.44±0.18
Standard	2.49±0.31
Colchicine	71.19±1.70***
LD ML	3.28±0.33
HDML	3.10±0.53
Pir+col	2.90±0.45
LdML+col	4.19±0.17
Hd ML+col	2.75±0.25

Results are expressed as mean ± SEM, (n=6), analysed by one-way Anova followed by Dunnett's test. *P<0.05, **P<0.01, ***P<0.001, when treated groups are compared with control group.

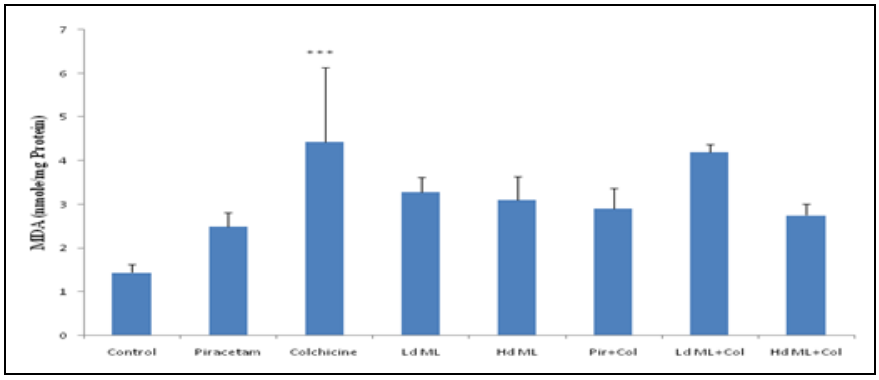

FIG. 3: EFFECT OF *MADHUCA LONGIFOLIA* EXTRACT ON MDA LEVEL

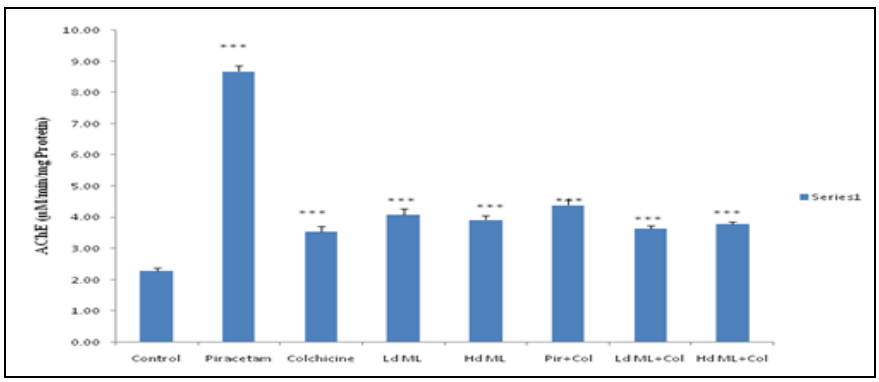

FIG. 4: EFFECT OF *MADHUCA LONGIFOLIA* EXTRACT ON AChE LEVEL

The effect of *Madhuca longifolia* leaf extract on AChE level of mice's brain homogenate is shown in **Fig. 4**. The mice were sacrificed on the 29th day, and brain homogenate was prepared to estimate improvements in the amount of AChE. Outcomes are calculated as average ± SEM (n=6), *P<0.05, **P<0.01, ***P<0.001 when one-way ANOVA which is then by Dunnett's test compared with control group. In the leaf extract an increase in AChE level was observed, suggesting nootropic activity. Alzheimer's ailment and disease is a gradual onset neurodegenerative condition. A satisfactory drug for the complete cure of Alzheimer's disease is yet to be developed in the allopathic system of medicine. Now we should look forward to treating this illness with the herbal medicines. In the current research, *Madhuca longifolia* extract for 28 days was given orally which showed an improvement in mice's learning behavior.

Throughout this analysis, the higher dose of *Madhuca longifolia* extract (200 mg/kg) significantly enhanced mice's memory as there was a decrease throughout transfer latency in the case of elevated plus maze and didn't affect the locomotor activity of mice. The *Madhuca longifolia* ethanolic leaf extract decreased MDA and increased the level of AChE. *Madhuca longifolia* extracted pretreatment for 28 days and sheltered the animals from the shortfalls of the memory generated by colchicine. These findings indicate the potential role of *Madhuca longifolia* extract in neuroprotecting.

CONCLUSION: It has been concluded from this study that *Madhuca longifolia* extract is effective nootropic drug with 200 mg/kg dose as it decreased the transfer latency of mice in elevated plus maze apparatus. It also reduced MDA and AChE level in brain homogenate of mice. *Madhuca longifolia* is a potent herbal drug that can be used in the treatment of Alzheimer's disease.

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CONFLICTING INTEREST: Writers assert that they don't have conflicting interest.

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