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Madhuca indica Leaf Extract: A Promising Candidate for the Treatment of Neuroprotective Effects

Vidhan Chand Bala[1,*], Bhawna Diwakar[1], Arvind Kumar Patel[2], Sushil Kumar[1]

[1]School of Pharmaceutical Sciences, Faculty of Pharmacy, IFTM University, Moradabad, Uttar Pradesh, 244102, India
[2]Narayan Institute of Pharmacy, Gopal Narayan Singh University, Rohtas, Bihar, 821305, India

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Abstract The recent trend worldwide is searching for plant extracts to prevent neurodegenerative disorders. The aim of this study is to conduct the phytochemical screening to explore neuroprotective effects of *Madhuca indica leaf* ethanol extract (MLE) in rats.. Chemical composition was screened by using phytochemical screening tests and HPTLC methods. The neuroprotective effect was analyzed by Immobilized stress tolerance test, Elevated plus maze test, and Morris water maze test. The result of this study reflected that ethanolic extract from *Madhuca Indica* leaves was valuable in all methods in the dose-dependence approach. The findings show that, in comparison to the amnesia control group, the MLE significantly lowered the levels of metabolic markers like glucose, cholesterol, urea, and nitrogen increased escape latency (EL), and lowered the transfer latency (TL). Based on the aforementioned useful animal study, we have determined that MLE considerably affects neuroprotective activity compared to the amnesia control group. We may therefore conclude that *Madhuca indica* is highly successful in all test models and that it may be utilized to treat CNS illnesses by enhancing their effects and minimizing their negative effects in combination with currently marketed medications.

Keywords Neuroprotective Effect, Alzheimer's Disease, *Madhuca indica*, HPTLC, Escape Latency, Transfer Latency, Oxidative Stress

1. Introduction

Among dementias, Alzheimer's disease (AD) is the most ordinary. Degeneration of the forebrain's basal cortical cholinergic neurons coexists with memory deficits [1,2]. Plaque formation, neurofibrillary tangles, decreased calcium balance, oxidative stress, inflammatory cytokine fabrication, deficiencies in energy metabolism, and neurotransmitter disturbances are among the pathological characteristics of the CNS in Alzheimer's disease [3]. Cholinergic impairments appear to be the cause of the association between amnesia and neuropathological alterations in the severity of Alzheimer's disease [4]. Because it helps to restore cholinergic activities by extending the availability of acetylcholine at the synapse, acetylcholinesterase (AChE) is involved in the breakdown of neurotransmitters [5-7].

All stress is just our body's response to something that throws us off balance, mentally or physically. While chronic stress can have detrimental consequences on health, acute stress can be thrilling and help us stay focused and energized [8]. In therapeutic settings, nootropic medications like piracetam and AChE blockers are used to treat neurodegenerative illnesses by enhancing mood, behavior, and cognitive function [9,10]. One of the primary mechanisms behind the pathophysiology of neurodegenerative illnesses, such as AD, is oxidative stress. Reduced cellular intrinsic antioxidant defense may result from elevated production of lipid peroxide and reactive oxygen species (ROS). In AD, it also precipitates cognitive

deterioration [11].

Grown extensively in the deciduous forests of Indian states, *Madhuca is* a herbal medicinal plant that is a member of the Sapotaceae family [12,13]. *Madhuca indica* has been utilized as a medicinal herb for several uses for millennia. Because of the free radical scavenging properties of the bark of the *Madhuca indica* species, an astringent, and emollient derived from the bark extract is used to treat leprosy by treating wounds, swelling, itching, and fractures [14]. Another use for the bark is as a coolant for gum disease, bleeding gums, inflammation, and mouth ulcers. Leaves can help with hemorrhoids, damaged cartilage, eczema, burns, vomiting, and emollients [12]. Flower-distilled juice is used as an expectorant, stimulant, diuretic, helminths, antihelmintic, verminosis, strangury, cough, and bronchitis. It is regarded as a nutritious cooling tonic. In native groups, the entire bloom is utilized to promote lactation [10]. The fruits are constrictive and are mostly used as a lotion to treat acute tonsillitis, pharyngitis, and chronic ulcers [15,16]. In addition to being a laxative, seed oil is used to treat rheumatism, headaches, and skin conditions [12].

2. Methods and Methods

2.1. Anthology and Validation of Plant Material

Madhuca indica leaves were collected from a local garden in the northern part of India (Moradabad District, Uttar Pradesh, India). The samples were chosen according to the quality and freshness of the leaves.

2.2. Preparation of Extract

The young leaves were divided and allowed to air dry. After being dried and ground into a coarse powder, the plant materials will go through a 20-mesh sieve. The plant material that has been coarsely ground will first be defatted using petroleum ether, and a Soxhlet apparatus will next extract the substance in stages. After filtering and distilling off the solvents, the extracts will be concentrated and dried using a rotary vacuum evaporator.

2.3. Method of Extraction

Petroleum ether was used to extract the dried leaves of *Madhuca indica* for up to 72 hours at 60–80 degrees Celsius. Following the extraction process, the solvent was extracted, and dark recall oil was collected and stored. Following the extraction of petroleum ether, the marc was dried and subsequently extracted for up to 72 hours in a soxhelet apparatus using a hydroalcoholic solvent (alcohol 99% v/v, distilled water). A lower pressure was used to evaporate the extract to get an average yield. After that, the solvent was extracted under low pressure, leaving behind a sticky residue with a brownish-black color that was utilized to detect the substance's effect on memory and learning. To provide a specific concentration, CMC (1% w/v) was used as a suspending agent in the preparation of the MLE test solution.

2.4. Phytochemical Screening

The phytoconstituents present in extracts produced from ethanolic solvent will be determined by a battery of chemical assays [17].

2.5. High-Performance Thin-Layer Chromatography (HPTLC)

In a 7 x 10 cm pre-coated silica gel 60 F 366 plate (E.MERCK KGaA) was used to perform HPTLC analysis. The sample solution was injected to the plate tn bands using a CAMAG Linomat applicator adjoin 100 nl micro syringe, at a constant flow rate of 159 nl/s. In a mechanical development chamber, the sample loaded plate was kept in a mobile phase mixture of ethanol, ethyl acetate, and formic acid (5:4:1 v/v/v). Densitometry scanning was examined using CAMAG TLC scanner-4 and winCATS software. Short-wavelength UV radiation with a wavelength of 366 nm will cause UV-sensitive compounds to experience fluorescence quenching and come into view as black patches on a light backdrop. Chemicals that take up a UV beam at 366 nm, on the additional furnish, will show up as intense patches on a dark background [18].

2.6. Animals

Westar albino rats are 10-12 weeks old, both sexes, in good physical condition, and weigh about 150g approximately chosen from animal house facilities for *in-vivo* experiments. At temperature 25 ^{0}C and relative humidity 40-80%, the animal chamber should be kept for 12/12 hours inter ball. Rat's pellets and water feed from day/night rhythm and fame. The plan of the laboratory experiment has been permitted by IAEC regulation, IAEC license no. 837/PO/ReBiBt/S/04/CPCSEA.

2.7. Grouping of Animals

The Wister albino rats (150–200 g) of either sex were used in the experiments. Animals were equally and randomly separated into five separate groups (n = 6): 1) VEH (vehicle control group) received 10 ml of distilled water per os and 2) ACC (Amnesia or stress control group) received vehicle + scopolamine 0.4 mg per kg intraperitoneal, induction of disease, 3-4) MLE (Teats group) received 200 and 400 mg per kg per os dosage of MLE for 7 days, before the scopolamine administration, 5) WS (Standard drug treated group) received *Withania somnifera* 100 mg/kg per os for 30 min before the scopolamine injection, which will be taken into

consideration for all screening activities.

2.8. Oral Toxicity Study

Oral toxicity experiments were examined using female rats in accordance by way of OECD guideline. The planned rats were separated into four experimental groups, and each group contained three animals after they had fasted for the whole night. Following feeding, the animals were observed every hour for one hour, then every four hours on occasion, and every seven days on average [19].

2.9. Immobilize Stress Tolerance Test (IST)

Five groups of six rats each were used in the immobilized stress tolerance test model. The animals were preserved inside an adaptable acrylic semi-cylindrical plastic cylinder (2.25 cm radius, 12 cm length), which caused stress. For seven days in a row, the rats were kept in individual confinements and exposed nonstop for 150 minutes each day. On the seventh day, following the final stress exposure, blood samples were collected from the retro-orbital while the subjects were under anesthesia. After a fixed amount of time, the animals were slaughtered, and the organ weights were recorded [20].

2.10. Elevated Plus Maze Test (EPMT)

This study used the EPMT, which consists of two open arms (50 x 10 cm) interlinked with two closed arms (50 x 10 x 40 cm). A central square that measured 10 cm x 10 cm was connected to the arms. The tools were installed to a length of 70 cm in a dimly lit room. The EPM was located in a room with light and sound attenuations. The study entailed timing the amount of time it took the rat, one at a time, to move from the end of an open arm of the EPMT to either of the closed arms while having their backs on the square platform. The Transfer Latency (TL), a metric for estimating the memory improvement property, was calculated.

The time taken by the rat to travel into the covered arms using all four arms was measured as the transfer latency (TL), and 90 seconds was attributed to this TL. After ten seconds of exploration at the EPM, the mouse was allowed to return to its cage. Memory retention was assessed 24 h after the first or second day of the trial. The first trial was administered on the ninth days, sixty min gone after the last dose of medication, and the second time (i.e., the ninth day) TL was measured after 24 hours. Using this formula, the inflection ratio (IR) was determined [21].

2.11. Morris Water Maze Test (MWT)

The working memory of rats was measured using the Morris water maze (MWMT), a flexible tool that can be used for a variety of tasks. The MWMT comprises a large circular tank (35-39 inc in radius and 18-20 inc in height) painted white on the exterior and constructed from opaque black PVC and resin. Water at 20-22 degrees Celsius was poured into the pool to a depth of 12-15 inc. To make the water opaque, a small quantity of milk or a non-hazardous white dye was added. The floor of the surrounding tank was divided into 4 equivalent quadrants, labeled arbitrarily as north, south, east, and west. The escape platform was constructed using plexiglass. A 13 cm × 13 cm platform was fastened to a 34 cm long, cylindrical, clear plexiglass pedestal with a 3 cm radius. The rats had a firm grip as they climbed on the platform because of the grit-covered top. To complete the hidden platform challenge, water was added to the circular tank until it reached 2 cm above the top of the platform. The easiest way to gauge performance is to look at how long it takes to get out of the water and the unseen raised area during the entire training session. Each animal was subjected to four separate trials for four days. During each trial, the animal was free to escape into the unseen raised area and was permitted to stay nearby for 20 s.

Escape latency is the time taken to find the invisible platform in the MWT and it is used as a gauge of learning or acquisition. If the animal did not find the invisible platform in 120 s, it was led by the hand to the platform and left for 20 s. The platform was removed on the ninth days, sixty min gone after the last dose, and the amount of time each animal spent looking for the invisible platform in the target quadrant was recorded [22].

3. Results

3.1. Analysis of Phytochemicals in a Qualitative Manner

The numerous phytochemical screening results show various phytochemical constituents in the leaves of Amaranthus tricolor. The research finding that the phytochemical study consists of presence of Alkaloids, Saponins, Flavonoids, Steroids, Sterols, Carbohydrates, Protein, Amino Acids, and Tannins in the LEAT shown in Table 1. According to the Shinoda test and zin chloride test, the presence of flavonoids with a crimson red or occasionally green to blue color was found to be in ethanolic leaves extracts. The foam formation in ethanolic extract indicated the presence of saponins in the test. In Mayer's, Dragendroff's, Wagner's, and Hager's tests, the presence of alkaloids was found in the ethanolic extracts. In the Salkowski and Liberman-Burchard test, the presence of steroids with bluish red to cherry color in the chloroform layer and bluish-green color, was found to be in ethanolic extracts. The Ninhydrin, Biuret, and Millon's tests exhibited the existence of amino acids and protein. Molisch's, Benadich's, and Fehiling's test shows the presence of carbohydrates, with orange-red precipitate. The ferric chloride and lead acetate test exhibits the presence of tannins in ethanolic extracts.

Table 1. Test performed for photochemical compounds with procedure, observation, and outcome

Tests	Procedure	Observation	Outcome
Alkaloids	a. Mayer's Test: Sample solution + Mayer's reagent b. Dragendroff's Test: Sample solution + Dragendroff's reagent c. Wagner's Test: Sample solution + Wagner's reagent d. Hager's Test: Sample solution + Hager's reagent	Yellow color Brown/reddish precipitate Red precipitate Yellow precipitate	+++
Saponins	a. Foam Test: Extract + distilled water and shake in a graduated	Foam to show the existence of Saponins	++
Flavonoids	a. Shinoda Test: Sample solution + few magnesium turnings and concentrate HCL dropwise b. Zinc hydrochloride test: Sample solution + zinc dust + conc. Hydrochloric acid	Crime red color appears Red color	+++
Steroids	a. Salkowski test: extracts in chloroform and conc. H_2SO_4 b. Libermann-Burchard Test: Test sample + chloroform + acetic anhydride + glacial acetic acid	Cherry color in chloroform layer Blue color	++
Carbohydrates	a. Molisch's Test: Sample solution + 2 drops of alcoholic α-naphthol b. Benedict's test: Sample solution + Benedict's reagent c. Fehling's Test: Sample solution + dil. HCl + fehling's A & B solutions	Violet ring at the junction Orange-red precipitate Red precipitate	+++
Proteins	a. Millon's Test: Sample solution + sulphuric acid + million's reagent	Yellow precipitate	+
Amino acids	a. Ninhydrin Test: 2 drops of freshly prepared 0.2% ninhydrin reagent + sample solution b. Biuret test: Sample solution + 4% sodium hydroxide and 1% copper sulfate solution	Blue color Violet or pink color	++
Tannins	a. Sample solution + 5% ferric chloride b. Sample solution + Lead acetate	Dark blue or black White precipitates	++

'+' indicates the bioactive chemical component present, '–' indicates the bioactive chemical component absent, ++' and '+++' indicate the moderate and strong presence of bioactive chemical components

3.2. HPTLC Analysis

As seen in the figures and tables below, the HPTLC analysis of MLE indicated the presence of a variety of phytochemicals. Peak tables were produced and the retention time plots (Figures 1, 2, 3, and 4) were obtained after scanning at UV 366 nm. Tables 2, 3, and 4 list the unknown chemicals' Rf values, peak height, peak area, and % area.

3.3. Acute Toxicity Study

Acute toxicity of MLE at dosages of 2000 mg/kg was investigated. In treated animals, the extract was determined to be completely safe and to have no harmful effects. As a result, 200 and 400 mg/kg were preferred for further experiments.

3.4. Biochemical Assessment

In this experiment, MLE (200 mg) demonstrated a significant impact ($p < 0.001$) on cholesterol and glucose levels, while showing no noticeable effect on blood nitrogen. Conversely, the conventional treatments of MLE (400 mg) and WS exhibited more pronounced effects ($p < 0.001$) on these parameters. The WS showed extensively higher levels ($p < 0.001$) compared to the VEH group, while glucose and cholesterol levels were notably lower ($p < 0.01$). The exception was blood nitrogen, which was reduced by the 400 mg dose. As shown in Table 5, the drug's effects at both the MLE (400 mg) WS(100 mg) doses were virtually identical.

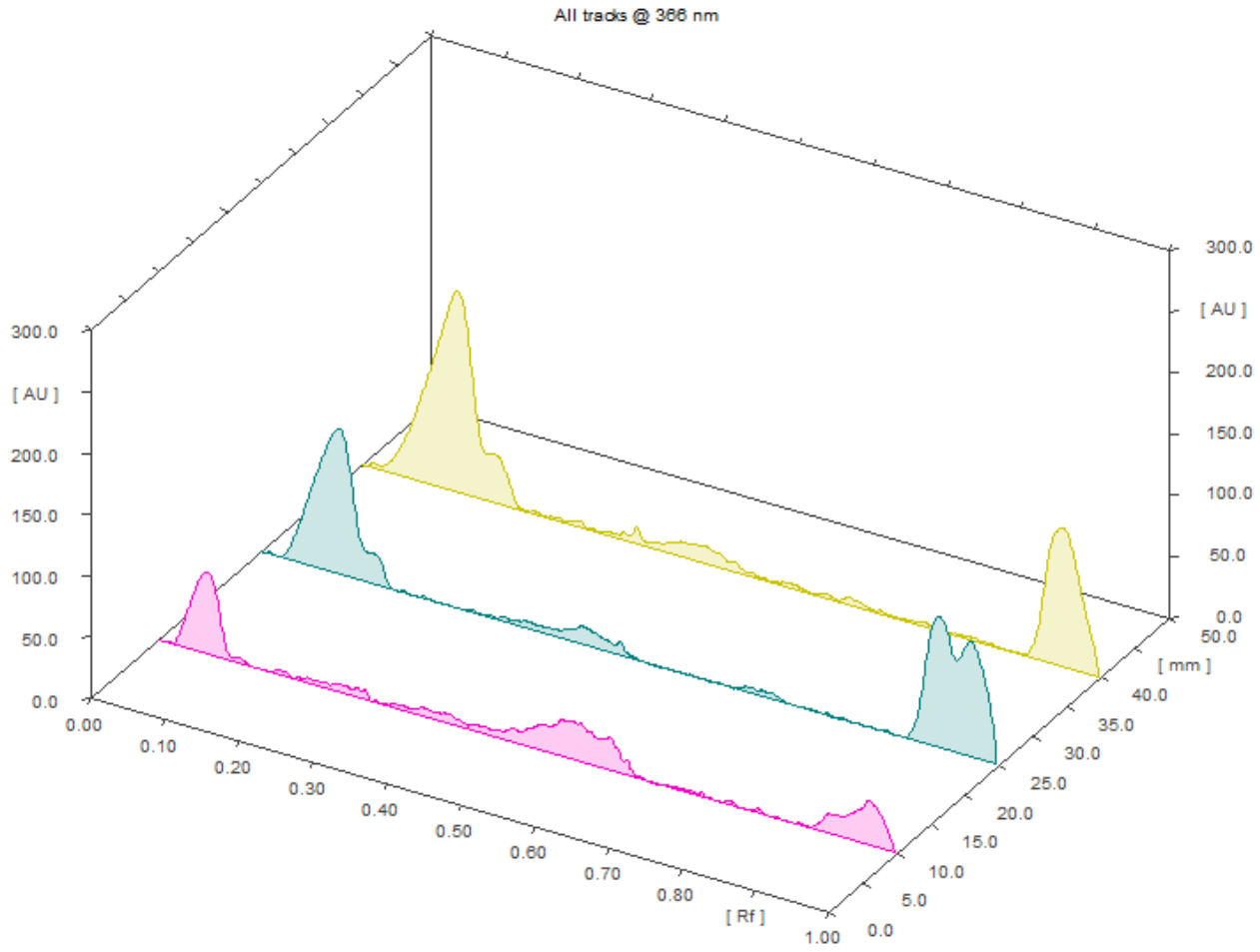

Figure 1. 3D overlay of HPTLC retention time plot of all tracks, at 366 nm

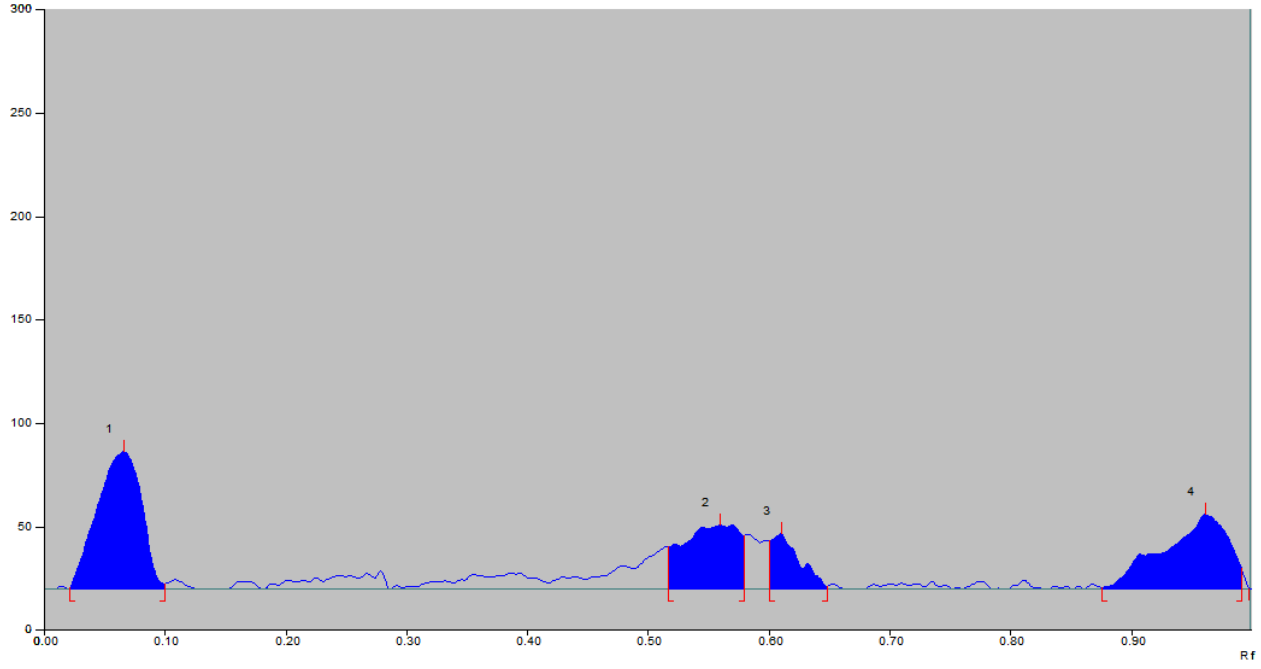

Figure 2. HPTLC retention time plot at 366 nm (tracks 1)

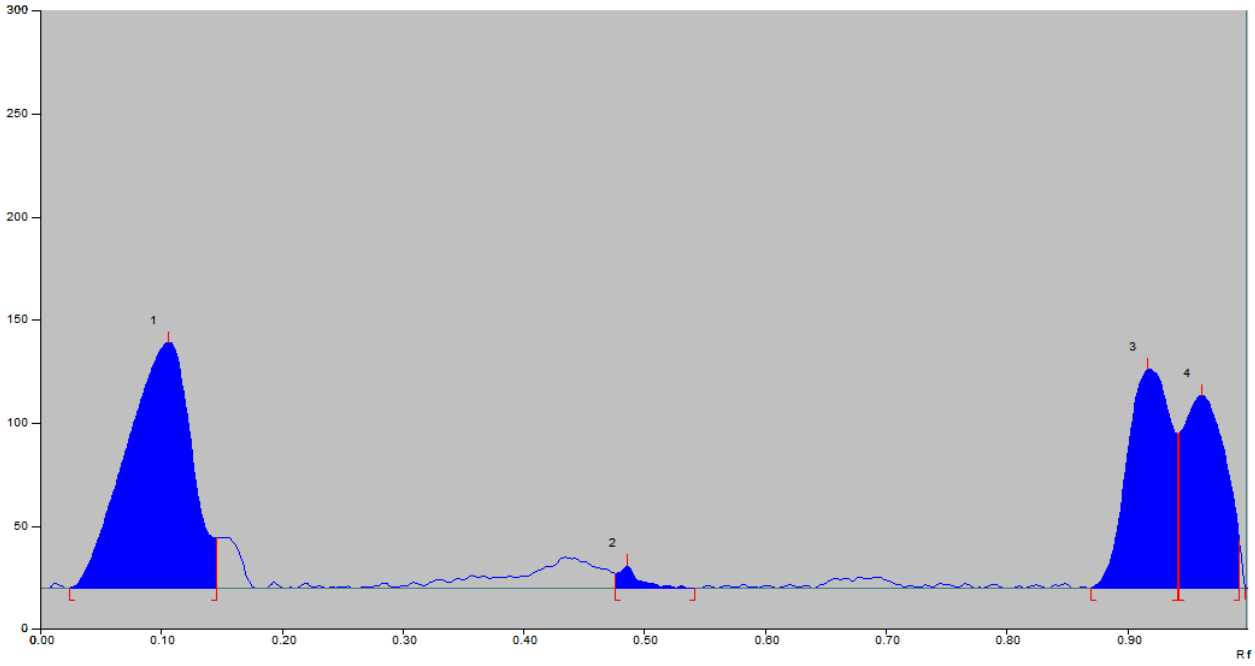

Figure 3. HPTLC retention time plot at 366 nm (tracks 2)

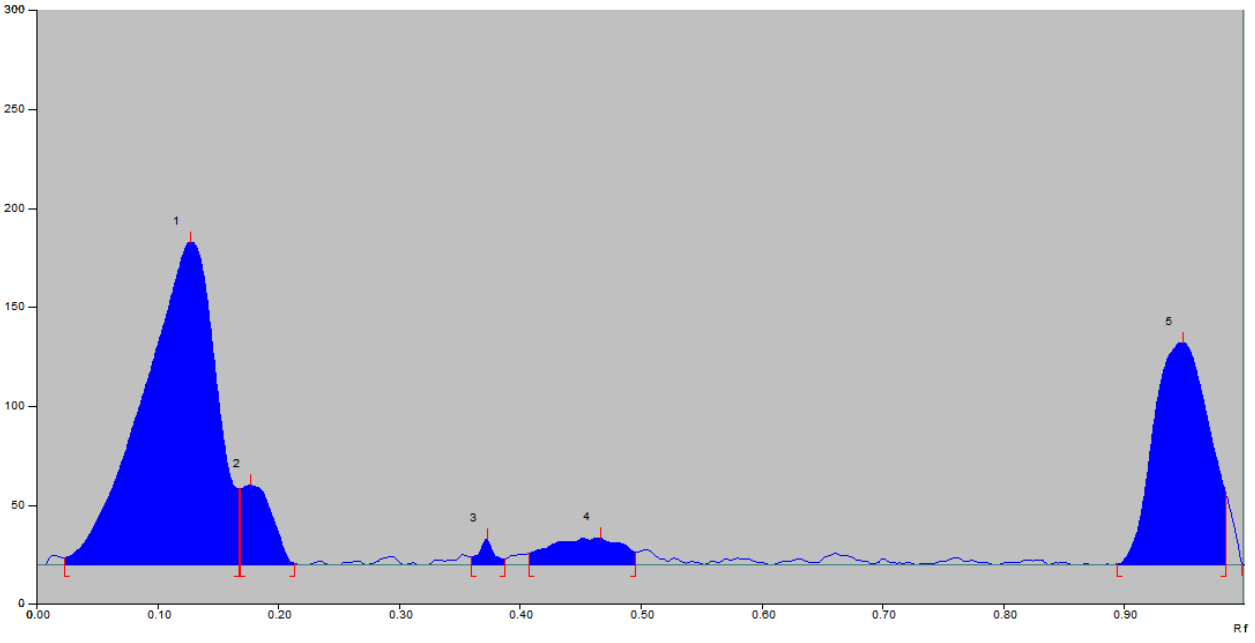

Figure 4. HPTLC retention time plot at 366 nm (tracks 2)

Table 2. HPTLC profiling of ethanolic extract of *M. Indica* Leaves (at 366 nm, tracks 1)

Peak	Start Rf	Start Height	Max Rf	Max Height	Max %	End Rf	End Height	Area	Area %	Assigned substance
1	0.02	0.6	0.07	66.3	41.48	0.10	2.5	1982.5	37.68	unknown
2	0.52	20.4	0.56	30.9	19.34	0.58	25.8	1202.3	22.85	unknown
3	0.60	23.5	0.61	26.6	16.66	0.65	1.3	524.9	9.97	unknown
4	0.88	0.7	0.96	36.0	22.52	0.99	9.8	1552.4	29.50	unknown

Table 3. HPTLC profiling of ethanolic extract of *M. Indica* Leaves (at 366 nm, tracks 2)

Peak	Start Rf	Start Height	Max Rf	Max Height	Max %	End Rf	End Height	Area	Area%	Assigned substance
1	0.02	0.1	0.11	119.3	36.16	0.15	24.2	5179.2	46.56	unknown
2	0.48	7.0	0.49	10.9	3.32	0.54	0.0	151.7	1.36	unknown
3	0.87	0.1	0.92	106.3	32.22	0.94	74.9	3129.1	28.13	unknown
4	0.94	75.1	0.96	93.4	28.30	0.99	22.5	2663.0	23.94	unknown

Table 4. HPTLC profiling of ethanolic extract of *M. Indica* Leaves (at 366 nm, tracks 3)

Peak	Start Rf	Start Height	Max Rf	Max Height	Max %	End Rf	End Height	Area	Area%	Assigned substance
1	0.02	3.7	0.13	163.1	47.72	0.17	38.4	7905.1	57.93	unknown
2	0.17	3.8	0.18	40.1	11.74	0.21	0.8	825.2	6.05	unknown
3	0.36	4.2	0.37	13.1	3.82	0.39	2.8	129.7	0.95	unknown
4	0.41	5.7	0.47	13.5	3.95	0.50	6.4	663.3	4.86	unknown
5	0.89	0.5	0.95	112.0	32.77	0.98	35.4	4121.9	30.21	unknown

Table 5. Impact of MLE on biochemical markers in IST

Groups	Biochemical marker		
	Glucose	Cholesterol	Nitrogen
VEH	61.50 ±1.52	63.83 ±1.24	19.33 ±1.22
ACC	135.00 ±2.88	73.50 ±1.60	12.00 ±1.06
MLE 200 mg	94.66 ±2.51***	67.50 ±0.76***	16.33 ±0.55^{ns}
MLE 400 mg	73.16 ±1.53***	43.16 ±2.44***	17.00 ±0.51**
WS	82.00 ±1.86***	60.16 ±2.49***	17.66 ±0.55***

The values are written by one-way ANOVA analysis; average ± SEM; **p < 0.01, ***p < 0.001 represent statistic significance, ns = no significance

3.5. Elevated Plus Maze Test (EPMT)

Both MLE (200 mg) and MLE (400 mg) significantly ($p < 0.05$) decreased the memory transfer latency (TL), with the WS (100 mg) exhibiting a more pronounced drop in TL than the ACC group, as indicated by the data in Table 6.

3.6. Morris Water Maze Test (MWMT)

The results of this test are shown in Table 7, where it was found that while MLE 200 mg significantly increase, the escape latency (EL), MLE 400 mg, and WS 100 mg significantly ($p < 0.01$) and significantly ($p < 0.001$) increase EL, as compared with the ACC group.

Table 6. Impact of MLE on learning performance assessed by EPMT

Groups	TL on 7th Day	TL after 24 h	IR
VEH	16.50 ±0.42	14.00 ±0.68	0.14 ±0.04
ACC	24.33 ±0.76	29.83 ±1.30	0.17 ±0.06
MLE 200 mg	17.00 ±0.85	15.00 ±0.96**	0.05 ±0.03
MLE 400 mg	13.50 ±0.42	13.00 ±0.73***	0.05 ±0.03
WS	11.50 ±0.61	10.16 ±0.47***	0.15 ±0.04

The values are written by one-way ANOVA analysis; average ± SEM; **p < 0.01, ***p < 0.001 represent the statistic significance

Table 7. Impact of MLE on learning performance assessed by MWMT

Groups	EL on 7th Day	EL after 24 h	IR
VEH	14.50 ±0.42	10.50 ±0.76	0.21 ±0.06
ACC	23.66 ±0.84	40.00 ±1.29	0.70 ±0.08
MLE 200 mg	19.83 ±0.54	18.16 ±0.47***	0.09 ±0.01
MLE 400 mg	18.00 ±0.36	15.33 ±0.42***	0.12 ±0.02
WS	16.50 ±0.76	13.00 ±0.36***	0.18 ±0.02

The values are written by one-way ANOVA analysis; average ± SEM; ***p < 0.001 represent the statistic significance

4. Discussion

Neurotransmitters are generated in reaction to stress to harden organisms by giving resistance against stressful events, a process known as adaptation. Neurotransmitters are functionally involved in regulating stress responses. Extended periods of high stress result in poor adaptability, which lowers mood and energy levels. Studies such as the scanning test, the hypoxia tolerance test, and the stabilizing exercise test have revealed decreased amounts of adrenaline or epinephrine in the brains of stressed animals [23]. The production and use of these amino acids are enhanced in several brain regions during stressful situations. However, amines are utilized in their composition and eventually depleted if the stress persists since it is uncontrollable [24].

Stress is hypothesized to raise blood cholesterol by activation of the hypothalami-hypophyseal axis, which leads to enhanced liberation of catecholamines and corticosteroids because adrenaline mobilizes lipids from adipose tissues [24]. Since BUN is a consequence of protein metabolism, immobilization stress models showed higher BUN concentrations. Urea excretion rises as a result of increased protein metabolism brought on by excessive adrenocortical activity [25]. On the other hand, MLE increased BUN levels in contrast to stress control, indicating that stress decreases protein catabolism. Learning is the process of gaining knowledge, whereas memory is the ability to retain knowledge that has been learned and retrieve it [26].

Transfer latency (TL) can be used to measure acquisition (learning) on the seventh day of enhanced plus trials. Transfer latency dropped in the positive control group but it increased in the group receiving scopolamine, suggesting the onset of amnesia. Improved cognitive function and resistance to memory loss are indicated by reduced TL (treatment group) [27]. MWM learning is a fairly good test of long-term memory and cognitive functioning. MWM was used to increase escape latency. Because of cognitive function, escape latency was higher in the group treated with extract and *Bacopa monnieri*. The animal's capacity to recognize the concealed platform might be related to long-term memory. MWM is used to determine escape delay. Because of their cognitive impairment, the AC control group's escape latency was reduced.

5. Conclusions

Since people have been using medicinal plants for centuries, we have concluded from the above valuable animal study that the MLE (Ethanolic extract of Madhuca indica leaves) showed significant effects on anti-stress, anti-cataleptic, and nootropic activity when compared to the control group. We may therefore conclude that *Madhuca indica* is highly successful in all test models and that it may be utilized to treat CNS illnesses by enhancing their effects and minimizing their negative effects in combination with currently marketed medications.

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Competing of Interest

The authors confirmed no competing of interest.

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