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Nootropic Effects of *Neolamarckia cadamba* Leaves on Scopolamine-Induced Amnesia in Rats

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Abstract

This study evaluated the memory-enhancing potential of *Neolamarckia cadamba* (Roxb.) Bosser ethanolic extract (200 and 400 mg/kg, orally) in scopolamine-induced amnesic rats, with piracetam as a standard. Cognitive function was assessed using the elevated plus maze, hole board test, and Morris water maze, along with locomotor activity and brain acetylcholinesterase (AChE) levels. Phytochemical analysis revealed 0.515 g% phenolics (gallic acid equivalents) and 2.129 g% flavonoids (quercetin equivalents). GC–MS profiling identified 11 major bioactive compounds with reported antioxidant, anti-inflammatory, and neuroprotective activities. In vitro antioxidant evaluation by the DPPH assay demonstrated concentration-dependent radical scavenging, with an IC_{50} of 337.42 µg/mL. Oral administration of *N. cadamba* extract for 14 days significantly reversed scopolamine-induced memory deficits. The extract reduced transfer latency in the elevated plus maze, shortened escape latency in the Morris water maze, and increased exploratory behavior in the hole board test. It also enhanced locomotor activity and decreased AChE levels, indicating improved cholinergic function. The high dose (400 mg/kg) consistently produced superior effects, suggesting dose-dependent efficacy. These findings suggest that N. cadamba ethanolic extract exhibits nootropic and neuroprotective effects, likely through antioxidant and cholinergic mechanisms, and may be a promising candidate for managing cognitive impairments, including Alzheimer's disease.

Keywords: Alzheimer's disease; Dementia; Neolamarckia cadamba; Nootropic Activity; Neuroprotective.

1. Introduction

Neurodegenerative disorders cause impairment of nerve cells and disrupt nervous system function, potentially impacting locomotion, language, perception, cognition, and mental functions [1]. Dementia is a growing global public health issue, particularly among older people. The

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World Health Organization estimates that 450 million individuals worldwide are afflicted with a mental or behavioural illness [2]. Alzheimer's disease (AD) is a type of dementia that causes an increase in amyloid beta (Aβ) and phosphorylated tau protein, leading to changes in the central nervous system. Memory degradation is caused by the irreversible loss of cognitive function in the cholinergic system [3].

Acetylcholine is a neurotransmitter found in the central nervous system, playing a crucial role in cognitive and memory functions. The cholinergic system is a key neurotransmission channel in the brain that affects memory and cognitive function [4]. The first pathophysiological factor linked to AD was the marked decrease in cholinergic activity. Memory function is gradually reduced as a result of changes in acetylcholine production or presynaptic recapture that causes the neurodegeneration of cholinergic neurons [5]. Reduction of acetylcholine causes other memory-related diseases such as anxiety, depression, mania, schizophrenia, psychosis, and overactivity [6]. There is a high level of oxidative stress in AD, primarily caused by reactive oxygen species. The role of oxidative stress in neurodegeneration is that it leads to the release of free radicals that attack neural cells. Although oxygen is imperative for life, imbalanced metabolism and excess reactive oxygen species (ROS) generation contribute to a range of disorders such as AD, Parkinson's disease, aging, and many other neural disorders [7].

For the treatment of this disease, the nootropic drugs are used [8]. These are a diverse class of substances that are sometimes referred to as "smart drugs" in English-language publications. Cornelius E. Giurgea coined the word "nootropic" in 1972/1973 to refer to drugs that mainly stimulate cognitive functions, such as learning and memory. Therefore, they also give an enhancing effect [9]. The synthetic drugs such as rivastigmine, piracetam, galantamine, donepezil, and citicoline are used in the treatment of AD, but they have low efficacy and more side effects. The plant-based herbal medicines are used as an alternative to avoid problems associated with synthetic medicines [10].

Ayurveda states that imbalances in vata, pitta, and kapha lead to AD. Herbal remedies are often the most effective in treating AD [11]. Certain herbal remedies, such as Medhya Rasayanas (drugs that function as nerve tonics), such as *Shankhpushpi* [11], *Glycyrrhiza glabra* (Liquorice) [12], *Celastrus paniculatus (*Jyotishmati*)* [13], *Garuga pinnata Roxb.* [14], *Prosopis cineraria* [15], *Acorus calamus Linn.*(Vacha) [11], *Bacopa monnieri* [16] is used to treat memory impairments.

The tree *Neolamarckia cadamba*, also known as *Anthocephalus cadamba*, *Anthocephalus indicus*, or *Sarcocephalus cadamba* (Roxb.), belongs to the family Rubiaceae and is commonly referred to as Kadamba or cadamba in Marathi [17,18]. *Neolamarckia cadamba* is a tree of great economic significance, primarily exploited in the paper, pulp, and wood industries. Beyond its industrial uses, various parts of the *Neolamarckia cadamba* tree have a history of traditional use in folk medicine to treat a diverse range of health issues [19]. These traditional medicinal applications encompass the management of conditions such as fever, uterine problems, blood disorders, skin ailments, tumors, anemia, eye inflammation, and diarrhea [14, 17]. Furthermore, *Neolamarckia cadamba* has been associated with various therapeutic properties in traditional medicine. These reported benefits include its potential as an antihepatotoxic (liver-protective) agent, an antimalarial, analgesic (pain-relieving substance), anti-inflammatory, antipyretic (fever-reducing agent), diuretic (promoting urine production), and laxative (promoting bowel movements) [19, 20]. Chemical analyses have revealed the presence of various phytochemicals, including cadambine and its derivatives (dihydrocadambine and iso-dihydrocadambine) in the leaves, as well as indole alkaloids known as Neolamarckine. The bark of *Neolamarckia cadamba* has also been found to contain quinovic acid derivatives [19, 21].

In the aforementioned studies on *Neolamarckia cadamba*, it has been reported that high doses of the plant are well-tolerated and safe in experimental animals. Furthermore, an *in-silico* study on the anti-Alzheimer's effects of the methanolic extract of *Neolamarckia cadamba* suggests that the phytoconstituents present in the plant material can be tested for their potential to combat AD and could also serve as novel leads for drug development [17].

In the search for safe and novel therapeutic agents to combat memory impairment in AD, this study investigates the nootropic potential of an ethanolic

extract derived from *Neolamarckia cadamba* leaves against scopolamine-induced amnesia in a rat model.

In this study, the nootropic potential of *Neolamarckia cadamba* was evaluated using scopolamine-induced amnesia in rats. Cognitive function was assessed through established behavioral models, including the elevated plus maze (to evaluate learning and memory), hole board test (for exploratory behavior and memory), and Morris water maze (for spatial learning and memory). Locomotor activity was measured using an actophotometer to assess the effect of treatment on general activity levels, ensuring that observed cognitive changes were not due to altered motor function.

2. Materials and Methods

2.1. Plant material

The plant material was collected from the local region of Katyayani, Kolhapur. To ensure its authenticity, the collected plant material was authenticated at Balwant College, Vita, Sangli, Maharashtra, India. The voucher specimen (MA 001) of plant material was placed in the Department of Botany, Balwant College, Vita, Sangli, Maharashtra, India.

2.2. Preparation of extract

Fresh leaves of *Neolamarckia cadamba* were shade-dried and manually separated from extraneous material. The dried leaves were pulverized using a mechanical grinder to obtain a coarse powder (50 g). Ethanol (300 mL) extraction was performed using a Soxhlet apparatus, with the powder loaded in a muslin cloth thimble. The extraction proceeded through 18 complete cycles at a controlled boiling temperature until the powder was exhausted (resulting in a colorless solution). The resultant extract was concentrated under reduced pressure using a rotary evaporator (40°C), yielding 12.38% w/w of crude extract [22].

2.3. Phytochemical screening

The ethanolic extract was subjected to qualitative phytochemical screening using standard analytical procedures. Tests were performed to detect the presence of tannins, phenolics, alkaloids, carbohydrates, flavonoids, glycosides, saponins, steroids, triterpenoids, and fixed oils [23].

2.4. Quantitative estimation of phenolics

A gallic acid stock solution (100 µg/mL) was prepared and used to generate calibration standards (20–80 µg/mL). Each standard was mixed with Folin–Ciocalteu reagent (1 mL), 7% sodium carbonate solution (10 mL), and distilled water to a final volume of 25 mL. The test extract (100 µg/mL) was treated in the same manner. After 90 min dark incubation at 23°C, absorbance was measured at 760 nm (Shimadzu UV–Vis 1800), and total phenolic content was expressed as gallic acid equivalents (GAE) [24].

2.5. Quantitative estimation of flavonoids

A quercetin stock solution (100 µg/mL in methanol) was prepared and diluted to obtain standards ranging from 25 to 300 µg/mL. Each standard was treated sequentially with distilled water, 5% sodium nitrite (0.3 mL), 10% aluminium chloride (0.3 mL), and 1 M sodium hydroxide (2mL), and the final volume was adjusted to 10 mL with water. The extract (100 µg/mL) was processed in the same way, with a reagent blank prepared without aluminium chloride. Absorbance was measured at 510 nm (Shimadzu UV–Vis 1800), and results were expressed as quercetin equivalents (QE) [25].

2.6. Gas Chromatography-Mass Spectroscopy analysis

The ethanolic extract of *Neolamarckia cadamba* was analyzed using a Shimadzu GC–MS TQ 8050 Plus system (Japan) equipped with an AOC-20i+s autosampler. The injector was operated in direct mode with a dwell time of 0.3 s, five pumping cycles, and an 8 µL wash volume (pre- and post-solvent rinses). Operating conditions included a purge flow of 3 mL/min, injection temperature of 250 °C, and column oven temperature initially set at 50 °C. Pressure was maintained at 54.4 kPa, and the carrier gas flow rate was 1.01 mL/min throughout the 4–50 min run. Data acquisition and processing were performed using Shimadzu GC–MS solution software. Compound identification was achieved by matching mass spectra against the NIST14 library [26].

2.7. Antioxidant activity

The DPPH method was used to evaluate the antioxidant activity of the extract. Briefly, 3 mL of a 0.1 mM DPPH

solution was mixed with varying volumes of the extract (1–2 mL, 100 µg/mL) and then adjusted to 5 mL with methanol. A DPPH solution without extract served as the control, while butylated hydroxytoluene (BHT, 100 µg/mL) was used as the standard. After 30 min of dark incubation at room temperature, absorbance was measured at 517 nm using a UV–Vis spectrophotometer (Shimadzu 1800), and % free radical scavenging activity was calculated using the following equation [27]:

$$\text{DPPH scavenged\% \%} = \frac{\text{A con} - \text{A test}}{\text{A con}} \times 100 \qquad (01)$$

Where,
A con = Absorbance of control
A test = Absorbance of test

2.8. Experimental animals

Albino Wistar rats (180–250 g, either sex) were used for the study. Animals were maintained in transparent cages under controlled conditions (25 ± 2 °C, 12 h light/dark cycle) with free access to standard pellet diet and water. All experimental procedures followed CPCSEA guidelines and were approved by the IAEC, Biocyte Institute of Research and Development, Sangli, Maharashtra.

2.9. Acute toxicity study

Acute oral toxicity was evaluated in accordance with OECD Guideline 423 (Fixed Dose Method). Female Albino Wistar rats (180–250 g) were fasted overnight before dosing and administered the extract at a dose of 2000 mg/kg. Animals were observed for behavioral, neurological, and physiological changes (including skin, fur, eyes, and mucous membranes), as well as tremors, convulsions, and mortality, at regular intervals up to 72 hours and daily thereafter for 14 days [28].

2.10. Drugs and chemicals

Piracetam, scopolamine hydrobromide, and normal saline were used for the study. All chemicals were procured from a local vendor and Loba Chemie, Mumbai.

2.11. Behavioural study (Training period)

All rats were trained for the behavioral study over a 7-day training period, during which they received no treatment. From these completely trained rats, a subset was selected for the study.

2.12. Experimental design

Memory impairment was induced by intraperitoneal administration of scopolamine hydrobromide (1 mg/kg). Rats were divided into five groups (n = 6):

- **Normal Control:** received distilled water, p.o. (per oros- orally).
- **Disease Control:** received scopolamine only (1 mg/kg, i.p.).
- **Standard:** received piracetam (200 mg/kg, i.p.) followed by scopolamine (1 mg/kg, i.p.).
- **Low Dose Extract:** received *Neolamarckia cadamba* ethanolic extract (NCEE) (200 mg/kg, p.o.) followed by scopolamine (1 mg/kg, i.p.).
- **High Dose Extract:** received NCEE (400 mg/kg, p.o.) followed by scopolamine (1 mg/kg, i.p.).

Scopolamine hydrobromide (1 mg/kg, i.p.) was administered to the disease control and treatment groups (Standard, Group I, and Group II) during the last 7 days of the 14-day experimental period. NCEE (orally) and piracetam (i.p.) were given 30 minutes prior to scopolamine administration. Behavioral assessments were performed 30 minutes after scopolamine injection each day to capture its acute effects on cognition, while treatments were continued throughout the 14 days.

2.13. Elevated plus maze

The elevated plus maze consisted of two open arms (50 × 10 cm) and two closed arms (50 × 10 × 40 cm), with a central platform (10 × 10 cm) elevated 50 cm above the ground. Each rat was placed at the end of an open arm facing away from the centre, and transfer latency (time to enter a closed arm) was recorded. Animals failing to enter within 90 seconds were placed in a closed arm, with latency noted as 90 seconds, followed by 20 seconds of exploration. After 14 days of treatment, acquisition (learning) was assessed on day 15, with transfer latency measured one hour post-treatment. Retention (memory) was evaluated on day 16 [29].

2.14. Hole board test

The hole board apparatus consisted of an acrylic platform (40×40 cm) with 16 evenly spaced holes (3 cm

diameter, 3 cm depth) and 10 cm high surrounding walls, elevated 5 cm above the floor. A food reward was placed beneath the board. Each rat was placed at the centre, and nose-poking behavior was recorded for five minutes. Following 14 days of treatment, animals were tested on day 15 (acquisition/learning) by recording the number of nose pokes one hour after the administration of the drug. Retention (memory) was assessed on day 16 by repeating the procedure [30].

2.15. Morris water maze

The Morris water maze was used to evaluate spatial learning and memory. The setup included a circular pool (100 cm diameter, 35 cm height) filled with water (25 cm depth, room temperature) and a hidden platform (10 × 10 cm, 20 cm height) submerged 2 cm below the surface in the target quadrant (Q4). Rats underwent four trials daily for seven days, starting from different quadrants, with a 120-second time limit to locate the platform. Those unable to find it were guided and allowed to remain for 20 s. Escape latency was recorded during training. On the last day, the platform was removed, and rats were observed for 300 s; time spent in the target quadrant was measured as the probe trial (memory index). Following 14 days of treatment, escape latency was assessed on days 15–18, and the probe trial was conducted on day 19 [31].

2.16. Actophotometer

Animals were divided based on the above-mentioned models. Before the study, all rats were fasted for 4 hours and received treatment according to their designated groups. After a one-hour treatment, every rat was individually placed in an actophotometer to measure locomotor activity for 10 minutes. The locomotor activity score was recorded [32].

2.17. Estimation of acetylcholinesterase enzyme

After behavioral testing, two rats from each group were anesthetized with thiopental sodium (40 mg/kg, i.p.) and decapitated. Brains were rapidly excised, rinsed in ice-cold saline, and dissected to isolate the frontal cortex, hippocampus, and septum. Tissues were weighed and homogenized in 0.1 M phosphate buffer (pH 8). For AChE activity, 0.4 mL of homogenate was added to 2.6 mL phosphate buffer (0.1 M, pH 8) and 100 µL DTNB in a cuvette. Absorbance was measured at 412 nm until a stable (basal) reading was achieved. Subsequently, 20 µL of acetylcholine iodide was added as the substrate, and the change in absorbance was recorded at 2-minute intervals for 10 minutes. Enzyme activity was expressed as a change in absorbance per minute [8].

The enzyme activity was calculated by using the following formula:

Acetylcholinesterase activity (M/ml) = (A/min. × Vt) / (Ɛ × b × Vs) (02)

Where,

A/min. is the change in absorbance per minute

$Ɛ = 1.361 \times 10^4\ M^{-1}cm^{-1}$

b = Pathlength (1 cm)

Vt = total volume (3.1 mL)

Vs = sample volume (0.4mL)

The final reading of enzyme activity was expressed as µ moles/mL of the Sample.

2.18. Statistical Analysis

Results were expressed as mean ± Standard Error of Mean (SEM). Data were analyzed using GraphPad Prism software version 10.1.0. Comparison between different groups was done by One-Way Analysis of Variance (ANOVA) followed by Tukey's multiple comparison test. A p-value less than 0.05 was considered statistically significant.

3. Results and Discussion

3.1. Phytochemical screening

The results of preliminary phytochemical screening of the ethanolic extract of *Neolamarckia cadamba* are shown in **Table 1**. Phytochemical tests for the ethanolic extract of *Neolamarckia cadamba* confirm the presence of alkaloids, flavonoids, carbohydrates, glycosides, saponins, triterpenoids, steroids, tannins, and phenolic compounds. Ethanolic extract shows negative results for fats and oils.

Table 1. Results of Phytochemical screening.

[Sr. No.	Phytoconstituent Name	Name of test	Result
1	Carbohydrates	Baljet test	+ve
2	Alkaloids	Dragendroff's test Mayer's test	+ve
3	Flavonoids	Shinoda test	+ve
4	Fats and Oils	Solubility test	-ve
5	Glycosides	Baljet test	+ve
6	Tannins and Phenolic Compounds	Lead acetate test Bromine water test	+ve
7	Saponin	Foam test	+ve
8	Steroids	Salkowski test	+ve
9	Triterpenoids	Liebermann Burchard test	+ve

(+ve: Present, -ve: Absent)

3.2. Quantitative estimation of phenolics

The calibration curve of gallic acid was linear over the range of 20–80 µg/mL (R^2 = 0.9977). Using the regression equation (Y = 0.0047X + 0.0383), the total phenolic content of the ethanolic extract of *Neolamarckia cadamba* was determined as 0.515 g% gallic acid equivalents (GAE).

3.3, Quantitative estimation of flavonoids

The quercetin calibration curve was linear in the range of 25–300 µg/mL (R^2 = 0.9995). Based on the regression equation (Y = 0.0011X – 0.0067), the total flavonoid content of the ethanolic extract of *Neolamarckia cadamba* was calculated as 2.129 g% quercetin equivalents (QE).

3.4. Gas chromatography-Mass spectroscopy analysis

GC–MS profiling of the ethanolic extract of *Neolamarckia cadamba* revealed 25 phytoconstituents (**Figure 1**). Among these, 11 major compounds with reported pharmacological relevance are summarized in **Table 2**. Most identified compounds are associated with antioxidant, analgesic, and anti-inflammatory activities, supporting the extract's potential neuroprotective effects.

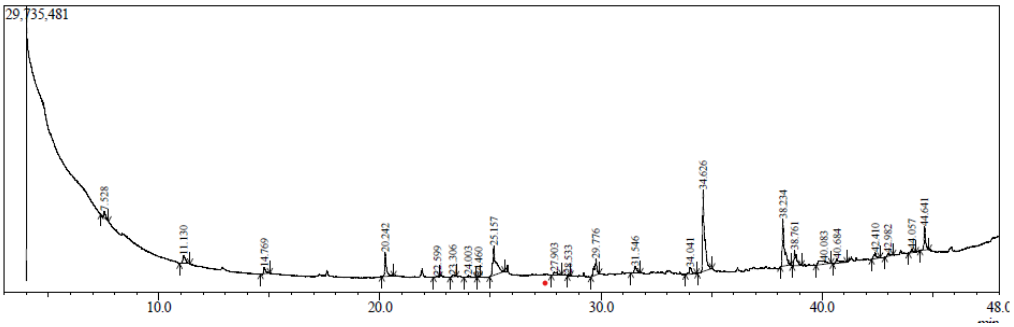

Figure 1: GC-MS Chromatogram of ethanolic extract of *Neolamarckia cadamba*

Table 2. Bioactive compounds present in the ethanolic extract of *Neolamarckia cadamba*.

RT	Compound	Class	Peak area %	Activity	References
11.130	Propane, 1,1,3-triethoxy-	Retinaldehyde	3.22	Antioxidant activity, Anti-inflammatory, Upper respiratory infections	[26]
14.769	Dodecane	Alkane	1.45	Antibacterial activity	[33]
20.242	Tetradecane	Alkane	5.57	Antimicrobial Activity, Wound healing activity, Anti-viral and Antitumor activities, Elephantiasis, asthma, throat disease, bronchitis	[34]
22.599	1-Tetradecanol	Alcohol	0.18	Antibacterial and Anti-inflammatory	[34]
23.306	Phenol, 2,4-bis(1,1-dimethylethyl)-	Phenol	0.56	Natural antifungal compound	[35]
25.157	Hexadecane	Alkane	12.61	Antibacterial, Antioxidant activities	[36]
34.626	Hexadecanoic acid, ethyl ester	Fatty acid ester	23.12	Anti-inflammatory, Hypocholesterolemic, Cancer preventive, Hepatoprotective, Nematicide, Insecticide, Antihistaminic, Antieczemic, Antiacne, Alpha-reductase inhibitor, Antiandrogenic, Antiarthritic, Anti-coronary, Antifibrotic.	[37]
38.234	(E)-9-Octadecenoic acid ethyl ester	Fatty acid ester	13.60	Steroids, fertility.	[38,39]
38.761	Octadecanoic acid, ethyl ester	Saturated fatty acid ethyl ester	4.76	Antioxidant, Anti-inflammatory, Antifungal, Antitumor, Antibacterial Activity	[38,39]
40.083	Hexadecenoic acid, 2-hydroxyethyl ester	Fatty acid ester	3.64	Antioxidant and Anti-inflammatory Activity	[37]
49.919	Squalene	Triterpene	5.78	Antioxidant, Antistatic, Antibacterial, Anticancer, Antitumor	[26]

3.5. Antioxidant activity

The ethanolic extract of *Neolamarckia cadamba* exhibited concentration-dependent free radical scavenging activity with an IC_{50} value of 337.42 µg/mL. At 400 µg/mL, the extract achieved 53.72% inhibition, compared to 74.19% for the standard BHT (200 µg/mL). The lowest inhibition observed for the extract was 40.52% at a concentration of 200 µg/mL. These findings confirm the antioxidant potential of the extract.

3.6. Acute toxicity study

The limit test for acute toxicity revealed that *Neolamarckia cadamba* ethanolic extract at 2000 mg/kg, p.o., in rats had a normal behavioral, neurological, and autonomic profile. No mortality or toxicity was observed during the 72-hour and 14-day observation periods. This indicated that *Neolamarckia cadamba* ethanolic extract at 2000 mg/kg, p.o., is relatively safe and non-toxic to rats. In animals, no toxicity signs were observed at a dose of 2000 mg/kg in the toxicity study. Therefore, at both low and high doses, a 10% dose of 2000 mg/kg, i.e., 200 mg/kg, and a double dose, i.e., 400 mg/kg, were administered for further in vivo study [28].

3.7. Elevated plus maze

The effect of treatment on transfer latency is presented in **Table 3**. The elevated plus-maze was used to evaluate learning (acquisition) on day 15 and memory (retention) on day 16. Scopolamine-treated disease control rats showed a significant ($p<0.05$) increase in transfer latency compared to the normal control, confirming cognitive impairment. In contrast, the normal control, standard (piracetam), and both extract-treated groups (200 and 400 mg/kg) exhibited a significant reduction in transfer latency compared to the disease control group. Transfer latency in the extract groups was higher than in the standard group. However, the high-dose extract (400 mg/kg) produced a greater reduction than the low-dose group, demonstrating a dose-dependent improvement. These findings indicate that both doses of *Neolamarckia cadamba* extract effectively mitigated scopolamine-induced deficits in learning and memory. Effects on acquisition and retention are illustrated in **Figure 2**.

Table 3. Effect of treatment on transfer latency

Group	Drug and dose	Acquisition day (15th day)	Retention day (16th day)
Normal Control	Normal Saline (p.o.)	43.33 ± 0.42$^{\$c}$	38.5 ± 0.45$^{\$c}$
Disease Control	Scopolamine hydrobromide (1 mg/kg)	57.02 ± 0.40$^{\#c}$	56.79 ± 0.61$^{\#c}$
Standard	Piracetam (200mg/kg) + Scopolamine hydrobromide (1 mg/kg)	19.87 ± 0.41 $^{\$c, \#c}$	16.84 ± 0.36$^{\$c, \#c}$
Low-dose extract	NCEE (200 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	33.21 ± 0.30 $^{\$c, \#c, +c}$	30.56 ± 0.47$^{\$c, \#c, +c}$
High dose extract	NCEE (400 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	25.75 ± 0.39 $^{\$c, \#c, +c, *c}$	22.09 ± 0.11 $^{\$c, \#c, +c, *c}$

Each value represents the mean ± SEM (n = 6). Statistical analysis was performed using One-Way ANOVA followed by Tukey's multiple comparison test. A p-value less than 0.05 was considered statistically significant. a: $p<0.05$, b: $p<0.01$, c: $p<0.001$, $: Data compared with disease control, #: Data compared with control, +: Data compared with standard, *: Data compared with low dose group.

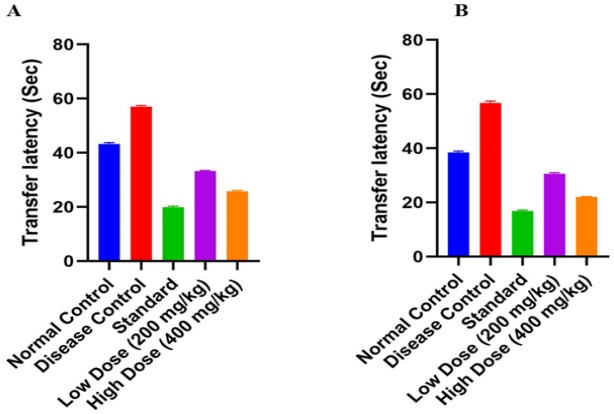

Figure 2. Effect of treatment on Transfer latency on 15th day (A) and 16th day (B)

3.8. Hole board test

The effect of treatment on nose-poking behavior is summarized in **Table 4**. The hole-board test was used to assess learning (Day 15) and memory retention (Day 16). Scopolamine-treated disease control rats exhibited a significant reduction in nose-poking entries ($p < 0.05$) compared to the normal control, indicating impaired cognitive function. In contrast, the normal control, standard (piracetam), and both extract-treated groups (200 and 400 mg/kg) showed a significant increase in nose-poking entries compared to the disease control group on both days. Compared to the normal control, the standard and low-dose extract groups exhibited a significant increase in nose-poking entries, whereas the high-dose extract group showed no significant difference ($p > 0.05$). Both extract groups had lower entries than the standard group. However, the high-dose extract (400 mg/kg) elicited significantly more entries than the low-dose group, indicating a dose-dependent improvement. Overall, oral administration of *Neolamarckia cadamba* extract for 14 days effectively mitigated scopolamine-induced deficits in learning and memory. Results for acquisition and retention are illustrated in **Figure 3**.

Table 4: Effect of treatment on nose poking entries

Group	Drug and dose	Acquisition day (15th day)	Retention day (16th day)
Normal Control	Normal Saline (p.o.)	$59.33 \pm 1.54^{\$c}$	$61.33 \pm 1.17^{\$c}$
Disease Control	Scopolamine hydrobromide (1 mg/kg)	$20 \pm 0.36^{\#c}$	$19.5 \pm 0.61^{\#c}$
Standard	Piracetam (200mg/kg) + Scopolamine hydrobromide (1 mg/kg)	$71 \pm 0.73^{\$c, \#c}$	$73.33 \pm 0.55^{\$c, \#c}$
Low-dose extract	NCEE (200 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	$51 \pm 0.81^{\$c, \#c, +c}$	$52.16 \pm 0.47^{\$c, \#c, +c}$
High dose extract	NCEE (400 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	$62.83 \pm 0.30^{\$c, +c, *c}$	$63.66 \pm 1.11^{\$c, +c, *c}$

Each value represents the mean ± SEM (n = 6). Statistical analysis was performed using One-Way ANOVA followed by Tukey's multiple comparison test. A p-value less than 0.05 was considered statistically significant. a: $p<0.05$, b: $p<0.01$, c: $p<0.001$, $: Data compared with disease control, #: Data compared with control, +: Data compared with standard, *: Data compared with low dose group.

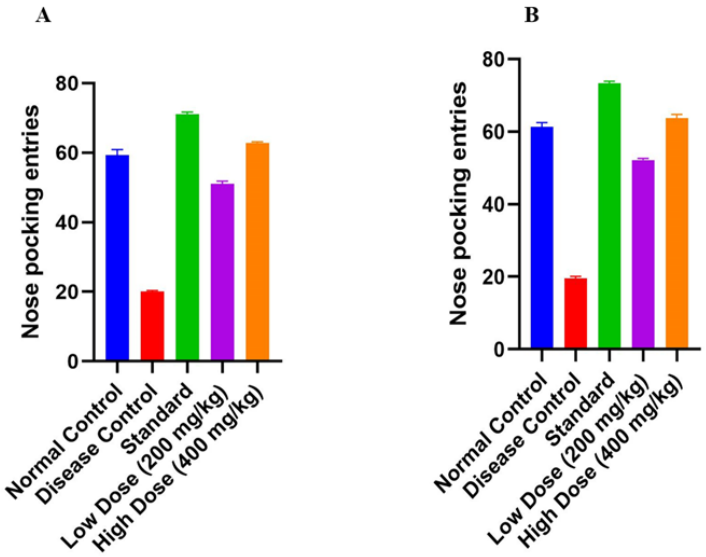

Figure 3: Effect of treatment on nose pocking entries on 15th day (A) and 16th day (B)

3.9. Morris water maze

The effect of treatment on escape latency and memory retention is summarized in **Table 5**. The Morris Water Maze was used to evaluate learning (as measured by escape latency, days 15–18) and memory retention (as indicated by the time spent in the target quadrant on day 19). Scopolamine-treated disease control rats exhibited significantly higher escape latencies ($p < 0.05$) compared to the normal control, indicating impaired learning and memory. In contrast, the normal control, standard (piracetam), and both extract-treated groups (200 and 400 mg/kg) exhibited a significant reduction in escape latency from days 15 to 18 compared to the disease control. Escape latency was lower in the standard, low-dose, and high-dose groups compared to the normal control, while both extract groups showed higher latency than the standard group. The high-dose extract (400 mg/kg) produced a significantly greater reduction in escape latency than the low-dose group, demonstrating a dose-dependent effect. On day 19, the probe trial revealed a significant increase ($p < 0.05$) in time spent in the target quadrant for the extract-treated groups, indicating enhanced memory retention. Overall, oral administration of *Neolamarckia cadamba* extract for 14 days effectively protected rats against scopolamine-induced cognitive deficits. Effects on escape latency and probe trial performance are illustrated in **Figure 4**.

Table 5. Effect of treatment on escape latency

Group	Drug and dose	15th day	16th day	17th day	18th day	Probe trial
Normal Control	Normal Saline (p.o.)	45.12 ±0.85$^{\$c}$	43.85 ±1.14$^{\$c}$	41.83 ±1.18$^{\$c}$	39.47 ±1.27$^{\$c}$	41.56 ±1.07$^{\$c}$
Disease Control	Scopolamine hydrobromide (1 mg/kg)	61.39 ±0.55$^{\#c}$	59.35 ±0.60$^{\#c}$	57.69 ±0.60$^{\#c}$	54.94 ±0.47$^{\#c}$	58.39 ±0.26$^{\#c}$
Standard	Piracetam (200mg/kg) + Scopolamine hydrobromide (1 mg/kg)	21.24 ±0.59$^{\$c, \#c}$	19.36 ±0.29$^{\$c, \#c}$	17.21±0.45$^{\$c, \#c}$	14.93±0.50$^{\$c, \#c}$	16.49 ±0.54$^{\$c, \#c}$
Low-dose extract	NCEE (200 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	32.96 ±0.32$^{\$c, \#c, +c}$	29.94 ±0.31$^{\$c, \#c, +c}$	27.87 ±0.39$^{\$c, \#c, +c}$	25.29 ±0.51$^{\$c, \#c, +c}$	25.22 ±0.78$^{\$c, \#c, +c}$
High dose extract	NCEE (400 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	26.81 ±0.18$^{\$c, \#c, +c, *c}$	24.94 ±0.27$^{\$c, \#c, +c, *c}$	22.97 ±0.45$^{\$c, \#c, +c, *c}$	20.53 ±0.51$^{\$c, \#c, +c, *c}$	22.73 ±0.49$^{\$c, \#c, +c, *c}$

Each value represents the mean ± SEM (n = 6). Statistical analysis was performed using One-Way ANOVA followed by Tukey's multiple comparison test. A p-value less than 0.05 was considered statistically significant. a: p<0.05, b: p<0.01, c: p<0.001, $: Data compared with disease control, #: Data compared with control, +: Data compared with standard, *: Data compared with low dose group.

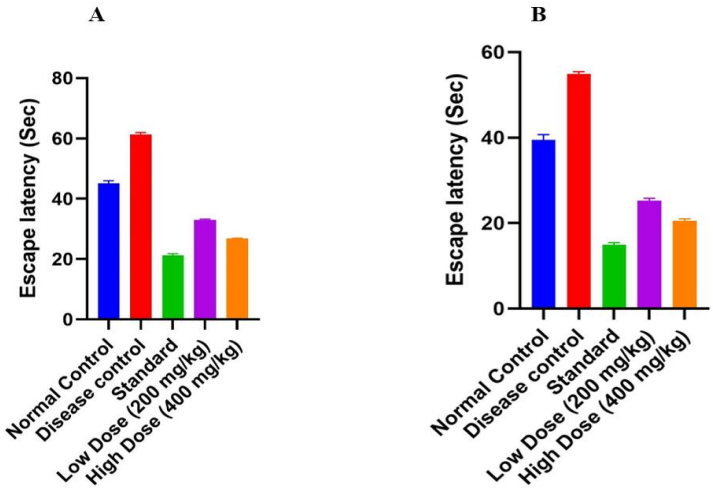

Figure 4: Effect of treatment on escape latency on the 15th day (A) and the 18th day (B)

3.10. Actophotometer

The effect of treatment on locomotor activity is presented in **Table 6**. Locomotor activity was assessed using an actophotometer as an indirect measure of learning and memory. Scopolamine-treated disease control rats exhibited a significant reduction in locomotor counts ($p < 0.05$) compared to the normal control, indicating cognitive impairment. In contrast, the normal control, standard (piracetam), and both extract-treated groups (200 and 400 mg/kg) exhibited a significant increase in locomotor activity compared to the disease control group. Compared to the normal control, the low- and high-dose extract groups showed a modest but significant decrease in locomotor counts, whereas the standard group did not exhibit a significant difference. Both extract groups exhibited lower locomotor activity than the standard group; however, the high-dose extract (400 mg/kg) produced significantly higher counts than the low-dose group, demonstrating a dose-dependent effect. Overall, oral administration of *Neolamarckia cadamba* extract for 14 days mitigated scopolamine-induced deficits in locomotor activity, indicating its potential as a nootropic agent. Effects on locomotor activity are illustrated in **Figure 5**.

Table 6. Effect of treatment on locomotor activity

Group	Drug and dose	Locomotor activity score
Normal Control	Normal Saline (p.o.)	498.5 ±3.06$^{\$c}$
Disease Control	Scopolamine hydrobromide (1 mg/kg)	217.5 ±7.30$^{\#c}$
Standard	Piracetam (200mg/kg) + Scopolamine hydrobromide (1 mg/kg)	505.83 ±4.67$^{\$c, \#c}$
Low-dose extract	NCEE (200 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	304.5 ±2.10$^{\$c, \#c, +c}$
High dose extract	NCEE (400 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	404 ±0.57 $^{\$c, \#c, +c, *c}$

Each value represents the mean ± SEM (n = 6). Statistical analysis was performed using One-Way ANOVA followed by Tukey's multiple comparison test. A p-value less than 0.05 was considered statistically significant. a: $p<0.05$, b: $p<0.01$, c: $p<0.001$, $: Data compared with disease control, #: Data compared with control, +: Data compared with standard, *: Data compared with low dose group

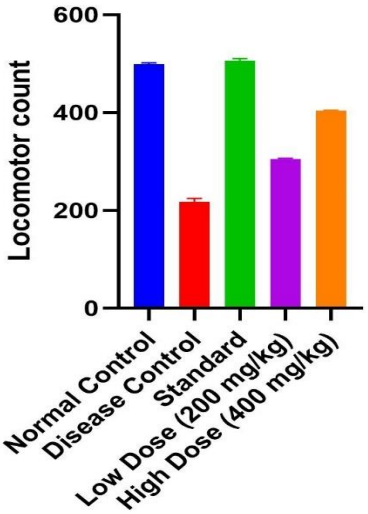

Figure 5: Effect of treatment on locomotor activity in rats

3.11. Estimation of acetylcholinesterase enzyme

Acetylcholinesterase activity is summarized in **Table 7**. Rats treated with scopolamine, a disease control, exhibited significantly elevated AChE activity, indicating impaired learning and memory. In contrast, the standard (piracetam) and both extract-treated groups (200 and 400 mg/kg) showed a marked reduction in AChE activity compared to the disease control.

While AChE activity in the extract groups remained slightly higher than in the standard group, the high-dose extract (400 mg/kg) produced a greater reduction than the low-dose group, demonstrating a dose-dependent effect. These findings indicate that oral administration of *Neolamarckia cadamba* extract for 14 days effectively mitigated scopolamine-induced cognitive deficits by reducing AChE activity.

3.12. Discussion

The present study aimed to evaluate the memory-enhancing activity of *Neolamarckia cadamba* through cholinergic pathways. Medicinal plants hold significant potential in managing memory impairment and AD due to their neuroprotective and cognitive-enhancing properties [11]. In this study, the effect of the ethanolic extract of *N. cadamba* on memory functions in scopolamine-induced amnesic rats was assessed using multiple behavioral models. The elevated plus maze was used to evaluate learning and transfer latency [29], the hole board test to assess exploratory behavior, locomotor activity, and cognitive function [30], the Morris water maze to measure spatial memory and learning [31], and locomotor activity was determined using an actophotometer [32].

Scopolamine induces memory impairment by blocking muscarinic cholinergic receptors in the brain [40]. In this study, administration of scopolamine hydrobromide (1 mg/kg, i.p.) increased transfer latency and reduced nose-poking entries, indicating impaired memory. Conversely, treatment with *N. cadamba* extract decreased transfer and escape latencies and increased nose-poking entries, demonstrating significant improvement in learning and memory. These findings suggest that the extract antagonized the effects of scopolamine, likely due to the presence of bioactive compounds, including alkaloids, flavonoids, carbohydrates, glycosides, saponins, triterpenoids, steroids, tannins, and phenolics. Flavonoids and phenolics, in particular, are known for their antioxidant capacity, which enables them to neutralize free radicals, protect neural cells, and enhance memory [14]. Quantitative analysis revealed 0.515 g/% phenolics and 2.129 g/% flavonoids in the extract, supporting its antioxidant role.

GC–MS analysis further confirmed the presence of Propane, 1,1,3-triethoxy [26],1-Tetradecanol [34], Hexadecane [36], Hexadecenoic acid, ethyl ester [37], Octadecanoic acid, ethyl ester [38,39], Hexadecenoic acid, 2-hydroxyethyl ester [37], Squalene [26]. Literature reports suggest that these compounds possess antioxidant and anti-inflammatory activities, contributing to the anti-amnesic potential of *N. cadamba*.

The elevated plus maze was used to evaluate an external perception behaviour model to assess learning and memory in rats [29]. The rats treated with scopolamine hydrobromide (1 mg/kg, i.p.) showed an increased transfer latency period, which indicates memory impairment. In contrast, the test extract showed a decrease in transfer latency, indicating that the ethanolic extract of *Neolamarckia cadamba* has a memory-improvement property.

Table 7. Effect on acetylcholinesterase enzyme

Group	Drug and dose	Acetylcholine esterase activity µM/minute/mL sample
Normal Control	Normal Saline (p.o.)	20.5
Disease Control	Scopolamine hydrobromide (1 mg/kg)	22.78
Standard	Piracetam (200mg/kg) + Scopolamine hydrobromide (1 mg/kg)	14.8
Low-dose extract	NCEE (200 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	19.36
High dose extract	NCEE (400 mg/kg) + Scopolamine hydrobromide (1 mg/kg)	15.94

The hole-board test was used to assess exploratory behavior, locomotor activity, and cognitive function in rats [30]. Rats treated with scopolamine hydrobromide (1 mg/kg, i.p.) exhibited a lower number of nose-poking entries during the period, indicating memory impairment. In contrast, the test extract showed a greater number of poking entries. The results indicated that the ethanol extract of *Neolamarckia cadamba* possesses a memory-improving property.

The Morris water maze was used to evaluate spatial memory and learning in rats [31]. The rats treated with scopolamine hydrobromide (1 mg/kg, i.p.) showed an increased escape latency period, which indicates memory impairment. The test extract showed a decrease in escape latency. The results indicated that the ethanolic extract of *Neolamarckia cadamba* possesses a memory-improving property.

Locomotor activity plays a significant role in the exploration and spontaneous behavior of rodents, which is determined by using an actophotometer [32]. The locomotor activity was significantly decreased in the group of animals treated with scopolamine hydrobromide (1mg/kg i.p.) compared to the control group, indicating an impairment of the learning and recognition process. However, the increased locomotor activity of the other groups indicated memory improvement.

Scopolamine, an anticholinergic agent, blocks muscarinic receptors, causing deficits in memory and learning, and induces oxidative stress in the brain [40]. Oxidative stress, characterized by excess reactive oxygen species (ROS), plays a central role in neurodegeneration, damaging neural cells and contributing to AD [41]. Previous studies reported that scopolamine disrupts the brain's antioxidant defense system, leading to excessive ROS generation and memory impairment [40]. In contrast, treatment with *N. cadamba* extract enhanced antioxidant enzyme activity and reduced oxidative stress, thereby restoring cognitive functions. These findings suggest that *N. cadamba* improves memory, at least in part, by suppressing ROS generation and protecting against oxidative damage [42].

Dose-dependent effects were observed, with the higher dose (400 mg/kg) producing more pronounced improvements in behavioral and biochemical parameters compared to the lower dose (200 mg/kg). Importantly, no signs of toxicity were observed in acute toxicity testing (OECD 423), confirming the safety of the compound. This highlights a therapeutic window in which *N. cadamba* maximizes cognitive benefits.

Neuroinflammation is another major contributor to AD progression, as immune-mediated neuronal damage accelerates cognitive decline. Long-term use of anti-inflammatory agents has been reported to slow AD progression [14]. Thus, the anti-inflammatory activity of *N. cadamba* may further contribute to its memory-enhancing effects [43]. The bioactive compounds identified by GC–MS, many of which possess antioxidant and anti-inflammatory properties, may act synergistically to mitigate the severity of neurodegeneration.

The cholinergic system plays a crucial role in regulating memory [44]. Reduced acetylcholine levels and increased acetylcholinesterase (AChE) activity contribute to neuronal damage and cognitive decline. Scopolamine administration causes severe cholinergic deficits by elevating AChE activity [4]. In this study, *N. cadamba* treatment significantly reduced AChE activity, thereby enhancing acetylcholine availability in the brain and improving memory.

Taken together, these results demonstrate that the ethanolic extract of *Neolamarckia cadamba* improves learning and memory by enhancing cholinergic transmission, reducing oxidative stress, and exerting anti-inflammatory effects. Its dose-dependent efficacy and safety profile suggest strong therapeutic potential for managing memory impairment and neurodegenerative disorders such as AD.

4. Conclusion

The present study demonstrates that the ethanolic extract of *Neolamarckia cadamba* leaves (yielding 14.89% w/w) possesses significant nootropic potential, as evidenced by comprehensive phytochemical and pharmacological investigations. Phytochemical analysis revealed the presence of diverse bioactive constituents, including alkaloids, flavonoids (2.129 g% quercetin equivalents), and phenolic compounds (0.515 g% gallic acid equivalents), while GC-MS profiling identified compounds with antioxidant (IC50 337.42 µg/mL) and anti-inflammatory properties. In scopolamine-induced

amnesia models, the extract exhibited marked memory-enhancing effects across multiple behavioral paradigms, reducing transfer latency in the elevated plus maze, increasing exploratory behavior in the hole board test, and improving spatial learning in the Morris water maze. These cognitive improvements were accompanied by significant acetylcholinesterase inhibition and restoration of locomotor activity, suggesting a multi-modal neuroprotective mechanism. The collective findings position *Neolamarckia cadamba* as a promising phytotherapeutic candidate for cognitive disorders, warranting further investigation into its active constituents and clinical potential for AD management.

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Conflict of interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

Authors Contributions

K.K.M: Project planning, Investigation, Data curation, Conceptualization, Review, and editing
N.H.S: Methodology, Resources, Formal analysis, Software.
M.K.A.: Methodology, Writing original draft.
N.S.M: Supervision, Resources.
R.J.D: Visualization, Formal analysis, Statistics.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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