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IN VIVO EVALUATION OF THE ANTI-ALZHEIMER'S POTENTIAL OF THE ETHANOLIC EXTRACT OF *ARTOCARPUS HETEROPHYLLUS* SEEDS IN SCOPALAMINE- INDUCED MALE ALBINO RATS

B. Soujanya, M. Nagaraju, N. Santhosh Kumar, P. Pravalika, V. Deepika, Mrs. M. Jhansi Rani*, Dr. Chandra Sekhar Rao Baru

*Associate Professor, M. Pharmacy, Department of Pharmacology, Professor & Principle, Chilkur Balaji College of Pharmacy, R. V. S. Nagar, Aziz Nagar(Post), Moinabad Road, Near T.S. Police Academy, Hyderabad.

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***Corresponding Author**
Mrs. M. Jhansi Rani
Associate Professor, M. Pharmacy, Department of Pharmacology, R. V. S. Nagar, Aziz Nagar(Post), Moinabad Road, Near T.S. Police Academy, Hyderabad.

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ABSTRACT AND KEYWORDS

KEYWORDS

Alzheimer's disease; Artocarpus heterophyllus; Scopolamine; Memantine; Neuroprotection; Cognitive impairment; Phytochemicals.

1. INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder and the leading cause of dementia worldwide. It is characterized by progressive deterioration of memory, cognition, language, executive function, and behavior, ultimately affecting activities of daily living. The increasing life expectancy of the global population has led to a rapid rise in the prevalence of AD, making it a major public health challenge with substantial social and economic impact.

Disease Pathology

The pathological hallmarks of AD include extracellular deposition of amyloid-beta plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, synaptic dysfunction, neuronal loss, oxidative stress, mitochondrial dysfunction, neuroinflammation, and cholinergic deficits. Together, these

alterations contribute to progressive cognitive impairment and neuronal degeneration.

Current therapy

Currently approved therapies, including cholinesterase inhibitors (donepezil, rivastigmine and galantamine) and the NMDA receptor antagonist memantine, primarily provide symptomatic relief and do not completely stop disease progression. Newer disease-modifying therapies have shown promise but remain limited by cost, accessibility, monitoring requirements, and adverse effects.

Need for plant-based therapeutics

Medicinal plants are an important source of bioactive compounds with antioxidant, anti-inflammatory, and neuroprotective properties. Natural products rich in flavonoids, phenolic compounds, terpenoids, and alkaloids have attracted considerable interest as potential agents for delaying cognitive decline through multiple mechanisms.

Artocarpus heterophyllus

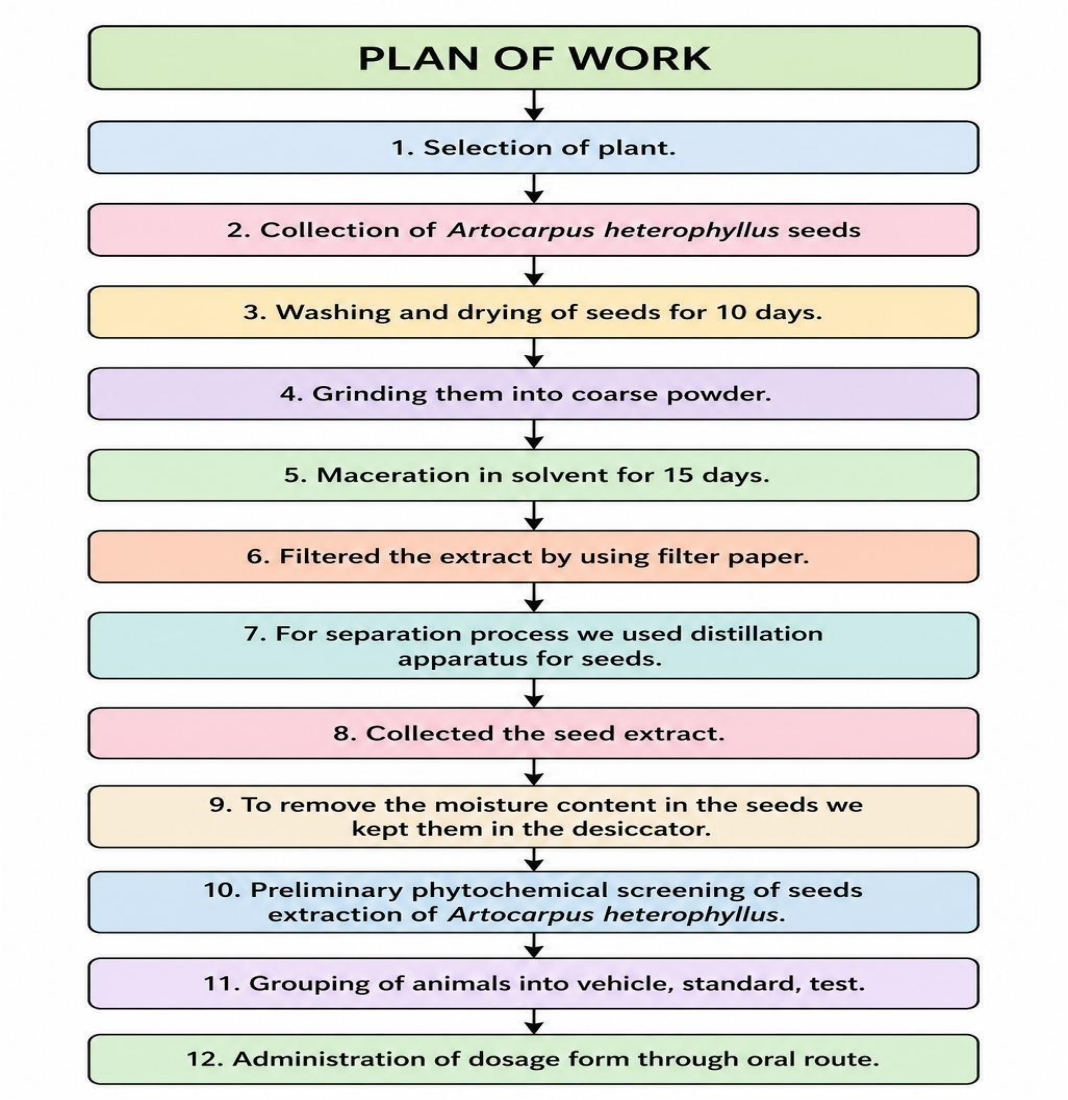
Artocarpus heterophyllus (jackfruit), belonging to the family Moraceae, is widely cultivated in tropical countries including India. Different parts of the plant have been traditionally used for nutritional and medicinal purposes. Phytochemical investigations have demonstrated the presence of flavonoids, alkaloids, glycosides, tannins, saponins, terpenoids and other constituents that may contribute to antioxidant and neuroprotective activities.

Rationale

Scopolamine-induced cognitive impairment is a well-established experimental model that mimics cholinergic dysfunction observed in Alzheimer's disease. Evaluating the ethanolic seed extract of Artocarpus heterophyllus in this model provides an opportunity to investigate its potential memory-enhancing and neuroprotective effects.

Study objective

Therefore, the present study aimed to evaluate the neuroprotective potential of the ethanolic seed extract of Artocarpus heterophyllus against scopolamine-induced cognitive impairment in male albino rats using behavioural models and phytochemical evaluation. The findings may contribute to the development of plant-derived therapeutic strategies for Alzheimer's disease.



MATERIALS AND METHODS

1. Study Design

This experimental study evaluated the neuroprotective activity of the ethanolic seed extract of Artocarpus heterophyllus against scopolamine-induced cognitive impairment in male albino rats.

2. Plant Material

Jackfruit (Artocarpus heterophyllus) seeds were collected from a local fruit market in Hyderabad, India, authenticated by the Department of Pharmacognosy, shade dried, powdered and stored in airtight containers.

3. Preparation of Ethanolic Extract

Powdered seeds (53 g) were macerated with ethanol for seven days with intermittent shaking.

The extract was filtered, concentrated at room temperature, and stored below 4°C. Percentage yield was approximately 80%.

4. Preliminary Phytochemical Screening

The ethanolic extract was screened qualitatively for carbohydrates, alkaloids, glycosides, flavonoids, saponins, proteins, amino acids, tannins and terpenoids using standard phytochemical procedures.

5. Experimental Animals

Healthy male albino rats (250–300 g) were acclimatized for one week under controlled environmental conditions with free access to food and water. Animal care followed CPCSEA/INSA recommendations.

6. Acute Oral Toxicity

Acute toxicity was evaluated according to OECD Guideline 420. No mortality or significant signs of toxicity were observed at 2000 mg/kg during the observation period.

ACUTE TOXICITY STUDIES

- Conducted as per OECD Guideline 420 (Fixed Dose Method).
- Male albino rats were fasted overnight before dosing.
- Ethanolic seed extract (AHES) tested up to 2000 mg/kg.
- No mortality or signs of toxicity observed for 14 days.
- Experimental doses selected: 100 mg/kg and 500 mg/kg.

7. EXPERIMENTAL DESIGN

Group I: Received normal saline vehicle for 15days.

Group II: Scopolamine induced Alzheimer's in male albino rats for 15 days.

Group III: Scopolamine induced +AHES -100mg in male albino rats for 15 days.

Group IV: Scopolamine induced +AHES -500mg in male albino rats for 15 days.

Group V: Scopolamine induced + Memantine -45mg in male albino rats for 15 days.

8. Drug Administration

Scopolamine was used to induce cognitive impairment. Memantine served as the standard drug. Test extract and standard drug were administered orally for 15 days.

9. Behavioural Evaluation

Learning and memory were assessed using the Elevated Plus Maze and Two-Compartment behavioural models. Transfer latency and memory retention parameters were recorded.

RESULTS

Phytochemical Screening

The qualitative phytochemical investigation of the ethanolic seed extract of Artocarpus heterophylus revealed the presence of carbohydrates, alkaloids, saponins, glycosides, flavonoids, proteins, amino acids and terpenoids, whereas phytosterols and tannins were absent. The presence of these bioactive constituents suggests that the extract may possess antioxidant and neuroprotective properties.

Table 1: Phytochemical investigation of *Artocarpus heterophyllus* seed

Phytochemical analyzed	Tests performed	Test procedure (Brief)	Results Ethanolic Extract
Carbohydrates	Molisch	2 ml extract + 2 drops alcoholic α-naphthol; add conc. H_2SO_4 along the wall. Violet ring at junction.	++
	Benedict's	2 ml extract + Benedict's reagent; boil 5 min. Brick red precipitate.	++
	Fehling's	2 ml extract + Fehling's A & B; boil 5 min. Brick red precipitate.	+
Alkaloids	Mayer's	2 ml extract + Mayer's reagent. Cream/white precipitate.	-
	Wagner's	2 ml extract + Wagner's reagent. Reddish brown precipitate.	+
	Dragendorff's	2 ml extract + Dragendorff's reagent. Orange/red precipitate.	++
Saponins	Foam Test	1 ml extract shaken with 10 ml distilled water for 15 min. Stable froth formation.	+++
Glycosides	Modified Borntrager's	Hydrolyze extract with dil. HCl, extract with benzene; add alkaline solution. Pink to red colour in alkaline layer.	+
Phytosterols	Salkowski's	2 ml extract + chloroform; carefully add conc. H_2SO_4. Reddish brown ring at interface.	-
Flavonoids	Flavonoid Test	Few drops extract + Mg turnings + conc. HCl. Pink to crimson red colour.	+
Proteins and Amino Acids	Xanthoproteic	2 ml extract + conc. HNO_3; heat. Yellow colour, turns orange with alkali.	++
	Ninhydrin	2 ml extract + ninhydrin reagent; heat. Purple/violet colour.	++
	Millon's	2 ml extract + Millon's reagent; heat. White precipitate turns red.	-
Tannins	Ferric chloride	2 ml extract + few drops of 5% ferric chloride. Blue-black or greenish black colour.	++
Terpenoids	Salkowski's	2 ml extract + chloroform; add conc. H_2SO_4. Reddish brown colour at interface.	++

- denotes absence, + denotes presence, ++ denotes average, +++ denotes abundance of phytochemicals

Acute Toxicity Study

No mortality or significant behavioural abnormalities were observed in rats up to 2000mg/kg during the acute oral toxicity study, indicating that the extract was well tolerated under the experimental conditions.

Behavioural Evaluation

Scopolamine administration produced marked cognitive impairment compared with the normal control group. Treatment with the ethanolic seed extract improved leaming and memory in a dose-dependent manner. The higher-dose treatment group demonstrated better performance than the lower-dose group and showed activity comparable to the memantine-treated group.

Elevated Plus Maze (EPM)

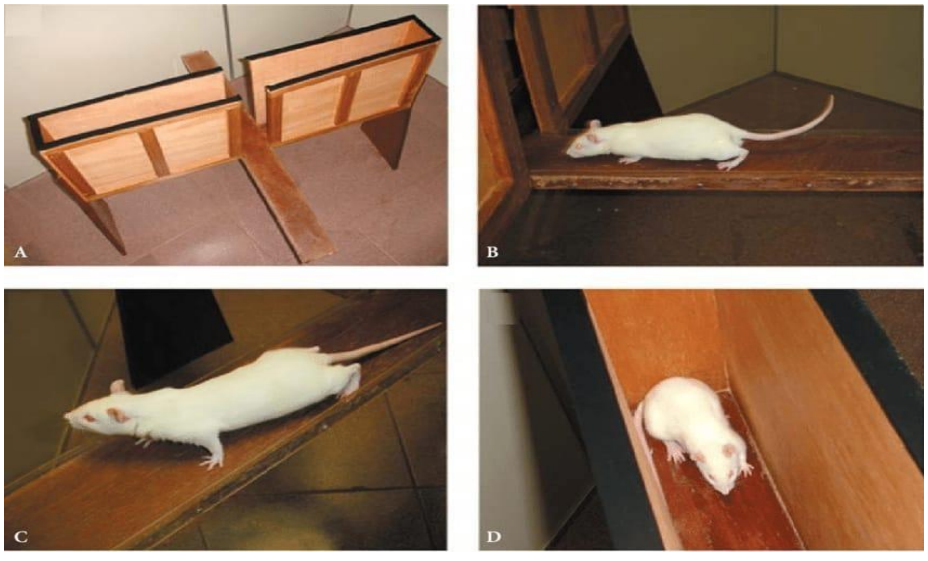
Purpose: To assess learning, memory, and cognitive function in experimental rats.

METHOD

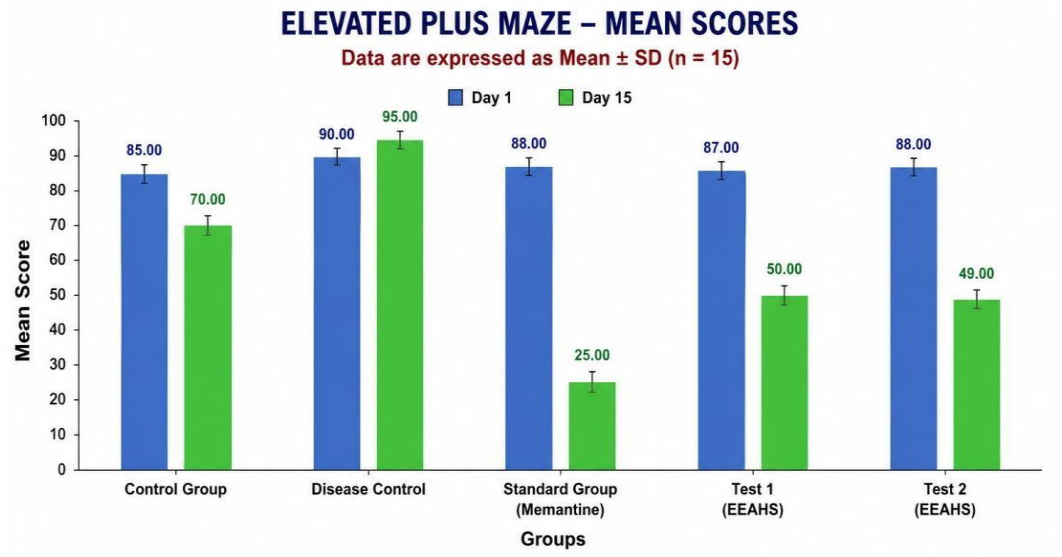
- The Elevated Plus Maze consists of two open arms and two closed arms elevated above the floor.
- Rats received the test drug 30 minutes before the experiment.
- Each rat was placed at the center of the maze facing an enclosed arm and allowed to explore for 5 minutes.
- Animal behaviour was recorded for analysis.

Parameters Evaluated

- Time spent in open arms.
- Time spent in closed arms.
- Number of entries into open arms.
- Number of entries into closed arms.
- Total arm entries.



ELEVATED PLUS MAZE ANALYSIS



Interpretation

The disease control group showed impaired memory, while the control group maintained normal memory. Memantine produced the greatest improvement. Both EEAHS Test 1 and Test 2 significantly improved memory, with EEAHS Test 2 showing slightly better activity than Test 1.

ELEVATED PLUS MAZE – DAY 1 AND DAY 15 RESULTS SUMMARY

Data are expressed as Mean ± Standard Deviation (n = 15)

DAY 1 RESULTS

GROUPS	MEAN	STANDARD DEVIATION (SD)	MEAN ± SD	% CHANGE (vs Disease Control)
Control Group	85.00	1.69	**85.00 ± 1.69**	-5.56 %
Disease Control	90.00	0.00	**90.00 ± 0.00**	—
Standard Group (Memantine)	88.00	0.00	**88.00 ± 0.00**	-2.22 %
Test 1 (EEAHS)	87.00	0.00	**87.00 ± 0.00**	-3.33 %
Test 2 (EEAHS)	88.00	0.00	**88.00 ± 0.00**	-2.22 %

DAY 15 RESULTS

GROUPS	MEAN	STANDARD DEVIATION (SD)	MEAN ± SD	% CHANGE (vs Disease Control)
Control Group	70.00	0.00	**70.00 ± 0.00**	-26.32 %
Disease Control	95.00	0.00	**95.00 ± 0.00**	—
Standard Group (Memantine)	25.00	0.00	**25.00 ± 0.00**	-73.68 %
Test 1 (EEAHS)	50.00	0.00	**50.00 ± 0.00**	-47.37 %
Test 2 (EEAHS)	28.39	0.00	**28.39 ± 0.00**	-70.11 %

Interpretation: On Day 1, all treatment groups showed scores comparable to the standard group and lower than disease control. On Day 15, Standard group showed the highest improvement, followed by Test 2 (EEAHS) which was greater than Test 1 (EEAHS) and less than Standard group.

Efficacy order on Day 15: Standard Group > Test 2 (EEAHS) > Test 1 (EEAHS) > Control Group (all vs Disease Control)

ELEVATED PLUS MAZE – SUMMARY OF RESULTS

Data are expressed as Mean ± Standard Deviation (n = 15)

GROUPS	MEAN	STANDARD DEVIATION (SD)	MEAN ± SD	% CHANGE IN MEAN (vs Disease Control)
Control Group	77.93	4.59	**77.93 ± 4.59**	-16.45 %
Disease Control	93.27	1.71	**93.27 ± 1.71**	—
Standard Group (Memantine)	58.13	19.98	**58.13 ± 19.98**	-37.66 %
Test 1 (EEAHS)	68.80	12.51	**68.80 ± 12.51**	-26.24 %
Test 2 (EEAHS)	57.13	18.45	**57.13 ± 18.45**	-38.78 %

Note: Order of efficacy (Mean values): Disease Control > Control Group > Test 1 > Standard Group > Test 2

ONE-WAY ANOVA

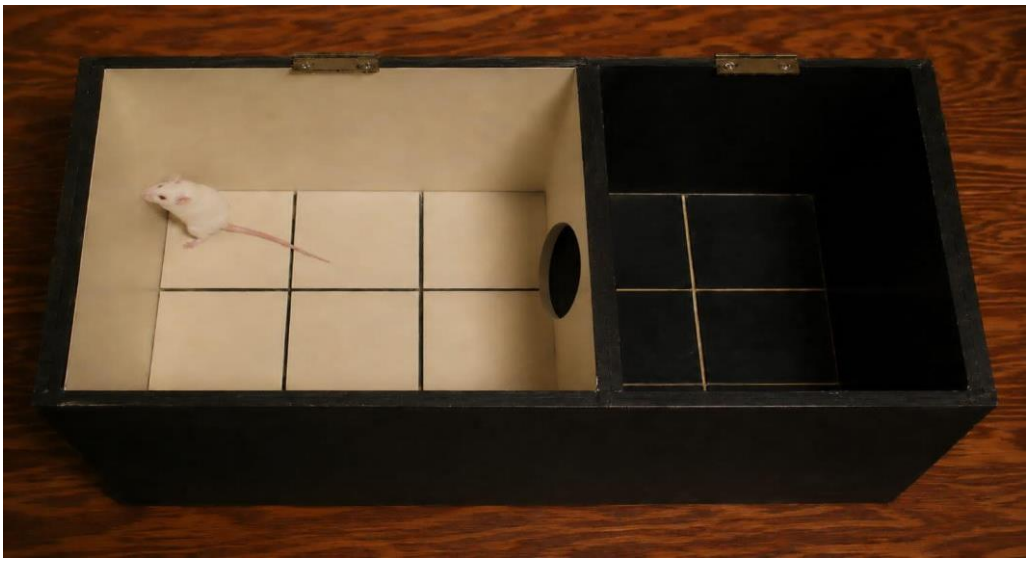
Source of Variation	Sum of Squares (SS)	df	Mean Square (MS)	F-value	P-value	Significance
Between Groups	6520.47	4	1630.12	15.21	< 0.0001	**** (Highly Significant)
Within Groups	7496.43	70	107.09	–	–	–
Total	14016.90	74	–	–	–	–

Interpretation: One-way ANOVA revealed a statistically highly significant difference among the five experimental groups ($F = 15.21$, $P < 0.0001$), indicating that the treatments significantly affected Elevated Plus Maze performance.

Post hoc analysis (Tukey's test): *Standard group vs Test 2 showed no significant difference ($p > 0.05$), Test 2 was significantly greater than Test 1 ($p < 0.05$) and significantly less than Standard group ($p < 0.05$).*

Two-Compartment Model

The two-compartment behavioural model demonstrated improved leaming and memory in extract-treated animals. The high-dose extract produced the greatest improvement among the treatment groups, suggesting significant neuroprotective activity.



Biochemical Findings

Scopolamine administration reduced acety/lcholine levels compared with the normal control group. Administration of the ethanolic seed extract restored acetylcholine levels in a dose-dependent manner. The higher dose produced results comparable to the standard drug, supporting enhancement of cholinergic neurotransmission.

Summary of Findings

Overall, the ethanolic seed extract of Artocarpus heterophyllus exhibited promising anti-Alzheimer's activity. Behavioural and biochemical findings indicated that the extract improved cognitive performance, with the higher dose showing greater efficacy.

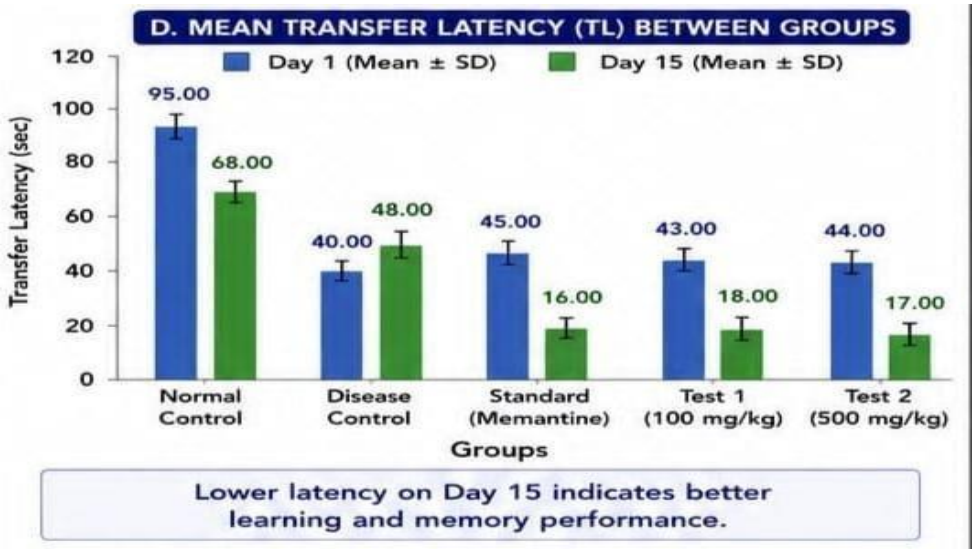
Purpose: To assess learning, memory, and cognitive function in experimental rats.

Parameters Evaluated

- Time spent in open arms.
- Time spent in closed arms.
- Number of entries into open arms.
- Number of entries into closed arms.

Total arm entries.

TWO COMPARTMENT MODEL ANALYSIS



Interpretation

One-way ANOVA showed a highly significant difference among the groups ($P < 0.0001$). All

treatment groups significantly improved memory compared to the disease control. EEAHS Test 2 showed better memory-enhancing activity than Test 1, but was slightly less effective than Memantine.

B. SUMMARY (Day 1 and Day 15 Results)

Groups	Day 1 (Mean ± SD)	Day 15 (Mean ± SD)	Difference (Day 15 – Day 1)	% Change (Day 1 to Day 15)
Normal Control	95.00 ± 3.18	68.00 ± 2.67	−27.00	−28.42 %
Disease Control	40.00 ± 2.45	48.00 ± 2.67	+8.00	+20.00 %
Standard (Memantine)	45.00 ± 2.74	16.00 ± 1.52	−29.00	−64.44 %
Test 1 (100 mg/kg)	43.00 ± 2.68	18.00 ± 1.46	−25.00	−58.14 %
Test 2 (500 mg/kg)	44.00 ± 2.46	17.00 ± 1.28	−27.00	−61.36 %

Negative difference and % change indicate reduction in latency (improvement).

C. ONE WAY ANOVA (Day 15 Results)

Source of Variation	Sum of Squares (SS)	df	Mean Square (MS)	F-value	P-value	Significance
Between Groups	7860.97	4	1965.24	126.51	< 0.0001	**** (Highly Significant)
Within Groups	1085.03	70	15.50	–	–	–
Total	8946.00	74	–	–	–	–

Since P < 0.05, the difference among the five groups on Day 15 is statistically highly significant.

DISCUSSION

The present study demonstrated that the ethanolic seed extract of Artocarpus heterophyllus possesses promising neuroprotective activity against scopolamine-induced cognitive impairment in male albino rats. Scopolamine administration produced significant memory

deficits, while treatment with the extract improved learning and memory in a dose-dependent manner. The higher dose (500 mg/kg) showed effects comparable to the standard drug, memantine.

The phytochemical screening revealed the presence of flavonoids, alkaloids, glycosides, saponins, and terpenoids, which are known for their antioxidant and neuroprotective properties. These phytoconstituents may contribute to the observed cognitive improvement by reducing oxidative stress and enhancing cholinergic neurotransmission. Overall, the findings suggest that Artocarpus heterophyllus seed extract has potential as a natural therapeutic agent for Alzheimer's disease. However, further studies are required to isolate the active compounds, investigate the molecular mechanisms, and confirm its efficacy through clinical studies.

CONCLUSION

The present study demonstrated that the ethanolic seed extract of Artocarpus heterophyllus exhibited promising neuroprotective activity against scopolamine-induced cognitive impairment in male albino rats. The extract improved learning and memory performance in behavioural models and restored acetylcholine levels in a dose-dependent manner. The higher dose showed efficacy comparable to the standard drug memantine. These findings suggest that the extract may serve as a potential source of bioactive compounds for the development of plant-based therapeutic agents for Alzheimer's disease. Further pharmacological, phytochemical and clinical investigations are required to confirm its safety, efficacy and mechanism of action.

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