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NEUROPROTECTIVE ACTIVITY OF ACALYPHA WILKESIANA IN MANAGEMENT OF NEURODEGENERATIVE DISEASES

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Abstract

To evaluate the neuroprotective activity of Ethanolic extract of leaves of *Acalypha wilkesiana (EELAW)* using Elevated Plus Maze in mice model. Neuroprotective activity in Alzheimer's disease was assessed in mice by using Elevated Plus Maze. The present study was undertaken to establish the potential of *EELAW as a* memory enhancer. The elevated plus maze was employed to evaluate learning and memory parameters. Two doses (250 and 500 mg/kg, po.) of *EELAW* were administered for 8 successive days to mice. The 200 mg/kg dose of *EELAW* has significantly improved learning and memory in mice and also reversed the amnesia induced by diazepam (1 mg/kg ip) and scopolamine (0.4 mg/kg, ip). It is observed that scopolamine-induced amnesia was reversed, i.e. an enhancement/ improvement in memory was observed may be due to the facilitation of cholinergic transmission in the brain. Hence *EELAW* might prove to be a useful memory restorative agent in the treatment of dementia conditions seen in elderly persons. The underlying mechanism of action can be attributed to its antioxidant properties of the phytoconstituents present in the extract.

Keywords: Alzheimer's disease, *Acalypha wilkesiana (EELAW)*, Elevated Plus Maze.

Introduction

Many modern medications are still derived from plants, which have been used as a source of medicine throughout history. Although plant medicine gave rise to the contemporary pharmaceutical industry, synthetic methods of drug development have since become the norm. However, this contemporary method has resulted in a decrease in new drug development in recent years and a rising market for botanical treatments, which are currently offered as dietary supplements, medications, or botanical pharmaceuticals. Medicinal plants that have been cultivated for higher yields of bioactive components are the source of the majority of botanical therapies. Many plants have undergone changes in their phytochemical makeup over time, with some bioactive chemicals becoming more abundant as a result of agricultural crops becoming domesticated and others becoming less abundant. [1]

Natural ingredients have always offered an infinite supply of medication. For thousands of years, practically without competition, plant-derived products have dominated the human pharmacopoeia.[2]

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Aspirin was the first synthetic medication produced in 1897 by Arthur Eichengrun and Felix Hoffmann when they were employed by Friedrich Bayer. Salicylic acid, a key component of herbal analgesics, was used to create aspirin (acetylsalicylic acid). An era dominated by the pharmaceutical business began with this achievement. When Alexander Fleming discovered penicillin in 1928, he added bacteria to the list of crucial sources for new medications. Recent advancements in combinatorial chemistry, computer (in silico) drug design, and structure activity guided organic synthesis have reduced the importance of naturally occurring substances derived from plants in drug development.

Natural products from plants and other biological sources continue to be an unabated supply of new pharmaceuticals, despite the diversity of drug discovery technologies and decreased funding for natural product-based drug discovery.

For centuries people have used plants for healing. Plant products – as parts of foods or botanical potions and powders – have been used with varying success to cure and prevent diseases throughout history. Written records about medicinal plants date back at least 5000 years to the Sumerians[12], and archaeological records suggest even earlier use of medicinal plants. The broken link between plants and health was felt throughout all medical fields. . The pharmaceutical business eliminated the historical link between diet and the treatment of disease by offering a pill choice. The proverb "an apple a day keeps the doctor away" is typically given by mothers rather than medical authorities. Although while functional foods, nutritional supplements, and the production of recombinant proteins are some areas of human health where plants are progressively making a comeback, they are still losing ground in other areas, like the conventional drug discovery process. [11]

Objectives

The main objectives of the present work are:

- To prepare the Ethanolic extract of leaves of *Acalypha Wilkesiana*
- Evaluation of the *EELAW* for its neuroprotective activity in Alzheimer's Disease by using Elevated Plus Maze test in mice

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Plant Profile

Figure 1: Leaves of *Acalypha wilkesiana wilkesiana*

Scientific classification

Kingdom:	Plantae
Order:	Malpighiales
Family:	Euphorbiaceae
Genus:	*Acalypha*
Species:	*A. wilkesiana*

Common name: fire fiji plant, Beef steak plant, fire dragon

Distribution: Vanuatu and Pacific Islands are home to the naturally growing tropical and subtropical plant known as *Acalypha wilkesiana*. It prefers a protected, shaded location and light, well-drained soil. Both dryness and frost have the potential to harm it. It requires a temperature of at least 10° C (50° F). Hardiness zones 10-12 are where it performs best

Botanical description:

Parts	Description	Size
Flowers	In the same plant, both the male flowers are in long spikes which hang downwards while the female flowers are in short spikes	Flowers stalks are 10–20 cms long.
Stem and branches	closely arranged crown, with an erect stem and many branches	3 meters (9.8 ft) high and 2 meters (6 ft 7 in) across
Leaves	flat or crinkled and are large and broad with teeth around the edge.	10–20 cm (3.9–7.9 in) long and 15 cm (5.9 in) wide leaves are coppery green with red splashes giving them a mottled appearance

Traditional uses

Many different illnesses, including diabetes, jaundice, hypertension, fever, liver inflammation, schistosomiasis, dysentery, respiratory issues like bronchitis, asthma, and pneumonia, as well as a skin condition, are traditionally treated and managed with plants from the Acalypha genus. In Africa and the Mascarene Islands, a number of Acalypha species are employed as medicinal plants.

Methodology

Chemicals

Piracetam, Diazepam, Scopolamine and ethanol used as a solvent

Plant material and extraction

Acalypha Wilkesiana's fresh leaves were obtained in and around the Mysuru area of India; a botanist helped identify and authenticate the leaves. The leaves are dried in the shade, ground into a coarse powder, and then extracted with 100% ethanol using the Soxhlet apparatus. The powdered leaves were wrapped in paper and placed in the Soxhlet. As the solvent in the Soxhlet became colorless, the presence of steroids extraction was complete. The extract was filtered to yield the extract, which was then given to the mice orally and behavioral testing was done.

Instruments

Elevated Plus Maze Apparatus
Soxhlet apparatus
Electronic weighing balance
Oral feeding needle.

Animals

For experimental purposes, Swiss albino mice weighing 18–22 g young mice were kept in the animal house at Sarada Vilas College of Pharmacy in Mysuru.
Number of animals per group: 6
Acclimatization: One week in experimental room

Selection of animals

The animals had a thorough inspection following *acclimatization* to make sure the chosen animals were in good health. They were then chosen at random for the study's final allocation.

Environmental conditions

Room temperature of 25 ± 10 C; relative humidity 45-55% and a 12:12 hrs. light/ dark cycle.

Diet

The animals had free access to standard mice pellet (Venkateshwara agencies, Bengaluru) with water supplied ad libitum under strict hygienic conditions.

Approval

Approval from the Institutional Animal Ethical Committee (IAEC) of Sarada Vilas College of Pharmacy, Mysuru (Karnataka) was taken prior to the experiments.

All the protocols and the experiments were conducted in strict compliance according to ethical principles and guidelines provided by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Experimental Design

Albino Swiss mice eight groups of 20–25gm animals were created based on age, weight, and size, with each group containing a minimum of six animals.

Group I: For young mice, it served as the control group; 10ml/kg (p.o.) of distilled water was given orally for 8 days. On the eighth day, TL was noticed after 45 minutes after administration, and again after 24 hours, or on the ninth day.

Group II: Mice were given 200 mg/kg (i.p.) of piracetam. TI. was noted 45 minutes after injection and once more 24 hours afterwards.

Group III: Young mice were given diazepam (I mg/kg i.p.) and TL was observed after 45 minutes of injection on the eighth day and again after 24 hours, i.e. on the ninth day.

Group IV: Young mice were given scopolamine hydrobromide (0.4 mg/kg) intravenously. From the 11th to the 14th day following drug administration, ELT was measured, and TSTQ was recorded after 24 hours (i.e., on 15th day)

Group V: For 8 days, young mice received 250 mg/kg (p.o.) of *Acalypha Wilkesiana* orally. The final dose was administered 45 minutes before the animals underwent the elevated plus maze test. On the seventh day and again 24 hours later, TL was detected.

Group VI: Young mice were given oral *Acalypha Wilkesiana* for 8 days at a dose of 500 mg/kg p.o. in. The final dose was administered 45 minutes before the animals underwent an elevated plus maze test. On the seventh day and again after 24 hours, TL was detected.

Group VII: Young mice were given *Acalypha Wilkesiana* for 8 days at doses of 250 and 500 mg/kg orally. On the eighth day, 45 minutes after the previous dose was administered. The medication diazepam (1 mg/kg ip) was given. After 45 minutes of Diazepam administration and again after 24 hours, or on the ninth day, TL was detected.

Group VIII: During 8 days, young mice received *Acalypha Wilkesiana* (250 and 500 mg/ kg p.o.). On the eighth day, 45 minutes after the previous dose was administered. A dose of scopolamine hydrobromide (0.4 mg/kg) was given. After 45 minutes of Diazepam administration and again after 24 hours, or on the ninth day, TL was detected.

Experimental design for Elevated Plus Maze Test for Alzheimer's disease activity

Groups	Treatment	Dose	No
Group 1	Control	10ml/kg (p o)	6
Group 2	Piracetam (positive control)	200mg/kg (i p)	6
Group 3	Diazepam	1mg/kg (i p)	6
Group 4	Scopolamine	0.4mg/kg (i p)	6
Group 5	AW Extract 1	250mg/kg (p o) Low Dose	6
Group 6	AW Extract 2	500mg/kg (p o)High Dose	6
Group 7	AW Extract+ Diazepam	250mg/kg (p o) + 1mg/kg (i p)	6
Group 8	AW Extract+ Scopolamine	250mg/kg (p o) + 0.4mg/kg (i p)	6
	Total		48

Effect of ethanolic extract of *Acalypha Wilkesiana* leaves from elevated plus maze test of mice

Elevated plus maze paradigm

The raised plus maze is made up of two opposed open arms (5010 cm), which are intersected by two closed arms with walls that are 40 cm high. The central square, which measures 10 by 10, connects the arms. On day 13, when the scopolamine and diazepam mice were each positioned at one end, facing the open arm and away from the middle square, memory acquisition was evaluated. It was timed how long it took to move from an open arm and how long it took to enter a closed arm. EPM is based on the observation that rodents have a natural aversion to high, open spaces and a predisposition to spend more time in enclosed spaces. After five minutes of observation. The definition of an arm entry was entry of all four paws into the arm.[105]

The following parameters were calculated for each animal.

a. Total time spent in open arms

b. Total time spent in closed arms

c. No of entries into open arms

d. No of entries into closed arms

Results

Elevated plus maze method record

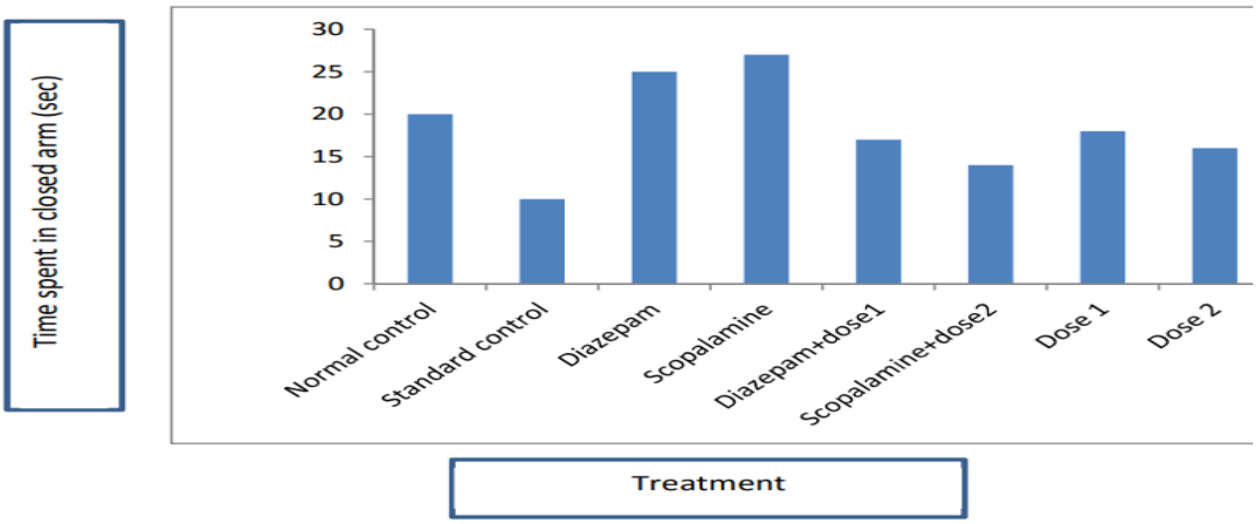

Figure 2: Total time spent in open arm (sec) in EPM

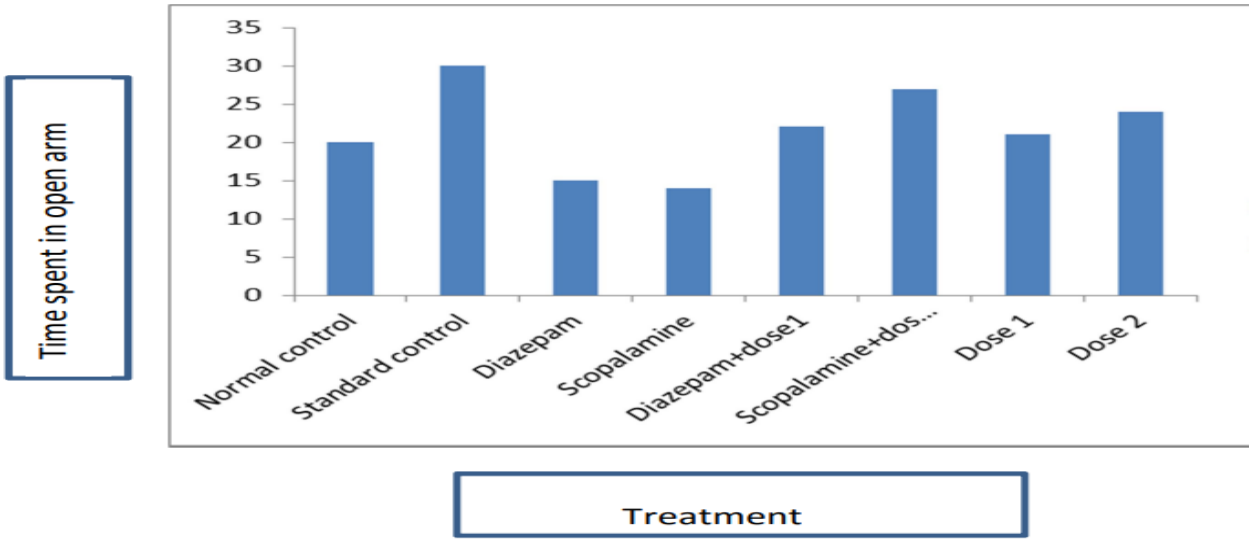

Figure 3: Total Time spent in closed arm (sec) in EPM

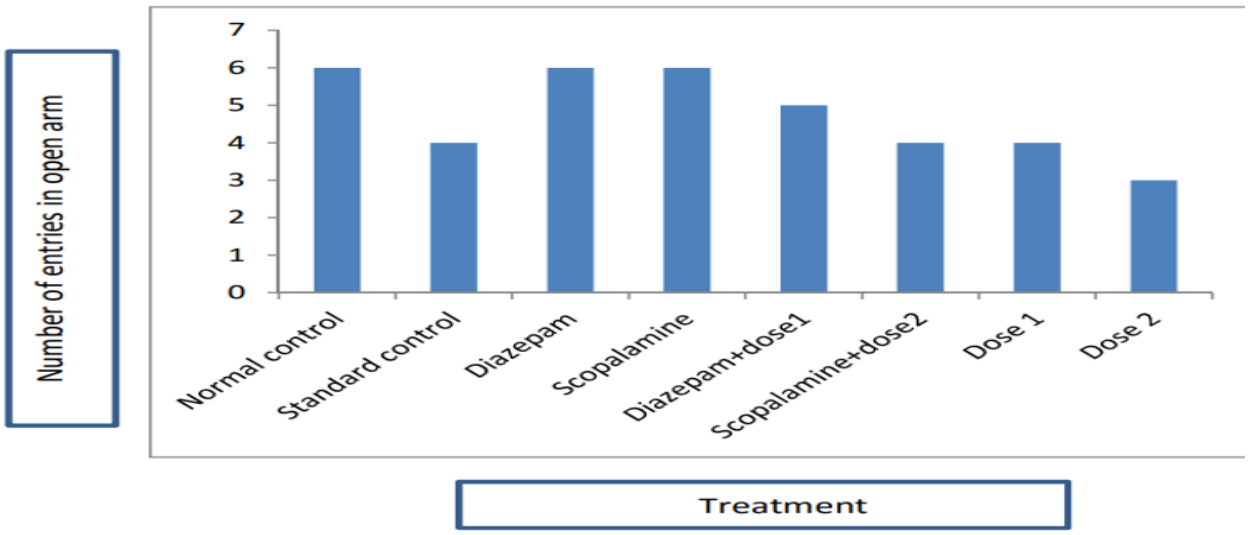

Figure 4: Number of entries into open arm

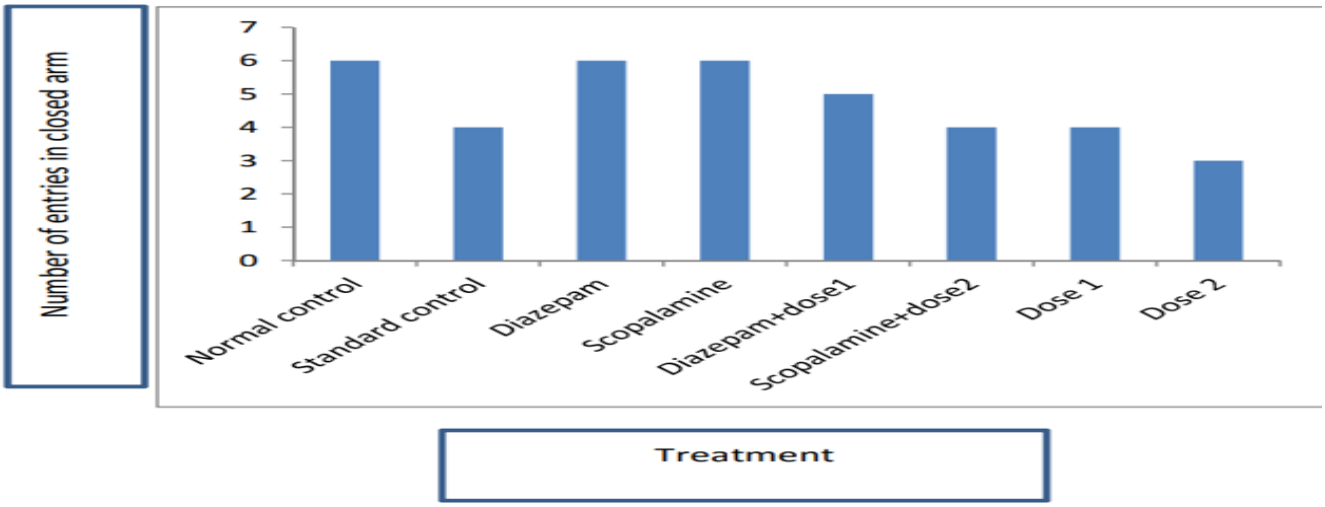

Figure 5: Number of Entries in closed arm

Note: **D**ose 1 - 250mg/kg low dose of EELAW
Dose 2 - 500mg/kg high dose of EELAW

Discussion

Alzheimer's disease (AD) is a neurological condition that worsens with time and produces substantial dementia in the elderly. The neuropathological signs of AD include the presence of aberrant tau protein filaments in the form of neurofibrillary tangles and deposits of amyloid fibrils in senile plaques. The main organs involved in the pathophysiology of AD are the hippocampal, limbic, and cortical systems. Oxidative stress has been implicated in the initiation and development of AD, and the etiopathogenesis of the disease is multifaceted. It has been established that -amyloid aggregates induce oxidative damage by producing free radicals when considering the mechanistic elements**.** In present study, we investigated the effect of *EAW* (250 and 500 mg/ kg po.) in the prevention of sporadic dementia of Alzheimer's type by using scopolamine and diazepam induced mice. *EAW* (250 and 500 mg/ kg p.o.) Significantly ameliorated the cognitive deficit neurotoxin in mice. Salient findings of this study are that pre and post- scopolamine and diazepam treatment with *EAW* (250 and 500 mg/ kg p.o.) improved cognition, In the present study, scopolamine and diazepam when given centrally resulted in significant memory impairment in elevated plus maze, which *EAW* (250 and 500 mg/ kg po.) were attenuated by chronic treatment. *EAW* (250 and 500 mg/ kg po) treated animals also shows significant increased time spending, in close arm in elevated plus maze test. These behavioral parameters reveal an enhanced motor function, which is usually disturbed in AD. Oxidative stress is a critical determinant in the

stimulation of neuronal cell death, and Aβ toxicity results in an increase in the and superoxide Radicals, which result in oxidative damage in within the cell. The toxicity of Aβ is attenuated by treatment with antioxidants well as agents that decrease intracellular superoxide levels. In the present study, scopolamine and diazepam caused a significant increase in the acetyl cholinesterase activity thereby leading to learning and memory deficits. *EAW* (250 and 500 mg/ kg po.) was able to ameliorate the colchicine induced decrease in AChE activity.

Conclusion

In conclusion, the current investigation raises the possibility that *EAW* (250 and 500 mg/ kg po.) may be effective in preventing an Alzheimer's disease model caused by scopolamine and diazepam. Studies on the chemicals responsible for the precise process involved are required in order to understand the fundamental mechanism and characterize the active elements responsible for treating Alzheimer's disease.

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