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Original Research Article

Evalution Of Nootropic Activity Of Methanolic Extract Of Grangea Maderaspatna In Wister Albino Rats.

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ABSTRACT:
The term "dementia" refers to a group of symptoms that severely impair memory, reasoning, and social functioning. While many illnesses can cause dementia, Alzheimer's disease is the most common cause of progressive dementia.Over 55 million individuals worldwide already have dementia, and there are almost 10 million new cases diagnosed each year. Beta amyloid deposition and neuro-fibrillary tangles, which induce the loss of synapses and neurons and result in gross atrophy of the affected parts of the brain, usually starting in the mesial temporal lobe, are the underlying pathophysiological causes. In the current investigation the efficacy of the methanolic extract of Grangea maderaspatana [GM] was tested in wistar albino rats against scopolamine (4mg/kg) induced Alzheimer's disease. A dose of 200 mg/kg of piracetam is used as a standard.The doses for GM were 250 mg/kg and 500 mg/kg. The nootropic activity was evaluated using the elevated plus maze model, novel object recognition test, morris water maze, and Y-Maze, as well as biochemical tests such as Acetylcholinesterase activity, brain reduced glutathione levels, melanoldehyde, and catalase activity were measured in order to assess the level of oxidative stress. During behavioural studies, Scopolamine administration reduces learning and memory enhancement. A significant reduction in time spent in the preferred arm of the Y-maze, escape latency, time spent exploring the novel object, and discrimination index of the familiar object was also observed. Acetylcholinesterase activity increased in rats, indicating a significant impairment of the central cholinergic system. Grangea maderaspatana (250 and 500 mg/kg orally administered) significantly improved rat memory in the y-maze, elevated plus maze, and novel object recognition tests, and also improved mouse locomotion in the open field. Treatment with a methanolic extract of Grangea maderaspatana also reduces brain oxidative stress and AChE activity. We find that treatment of Grangea maderaspatana [GM] methanolic extract improves rat memory by lowering AChE activity and exhibiting antioxidant effects.The presence of phenolic chemicals and flavonoids was confirmed by the phythochemical screening of the GM, making it appear to be an effective source for improving memory and learning.

KEYWORDS: Alzheimer's disease, Dementia, Grangea maderaspatana, Scopolamine, Melonaldehyde, Novel object recognition test.

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INTRODUCTION :

Neurodegenerative disorders cause nerve cell degeneration and impair the nervous system's normal functioning. and may have an impact on a person's ability to move about, speak, perceive, think, and remember during their lifetime depending on the regions affected[1]. Alzheimer's disease is a type of dementia that worsens over time and has an impact on memory, thinking, and behaviour. Clinically, it manifests as memory loss, an inability to learn new things and recollect the past, difficulty thinking, etc. According to WHO, According to brain histology, Alzheimer's disease is the sixth leading cause of death in the United States, and approximately 450 million people worldwide suffer from a mental or behavioural problem.[2]. Neuronal loss is one of the fundamental neuropathological factors underlying Alzheimer's symptoms, and when the disease is examined under a microscope, senile plaques and neurofibrillary tangles (NFTs) are the most visible features.. A number of hypothesised processes have been proposed to better understand the pathophysiology of Alzheimer's disease, including cholinergic dysfunction, oxidative damage, beta amyloid toxicity, tau protein hyperphosphorylation, and senile plaque inflammation[3][4]. The loss of cholinergic neurons, along with a decline in their production, causes the learning and memory failure that is characteristic of Alzheimer's disease. The cholinergic system, which is made up of cholinergic neurotransmitters, is crucial for memory processing[5].Nootropic drugs, which are used to improve memory, work by specifically improving the integrative function of the central nervous system, which has an impact on cognition, learning, and memory[6].

The Indian medical system places a strong emphasis on using herbs, nutraceuticals, and lifestyle modifications to treat age-related neurodegenerative illnesses[7].Traditional medicinal plants' pharmacological and therapeutic effects have been linked to a variety of Chemical components isolated from crude extracts; in particular, active compounds with antioxidant activity have been linked to a significant role in a number of neurodegenerative diseases[8].

The current treatment strategy focuses on inhibiting the acetylcholinesterase (AChE) enzyme with drugs such as donepezil, gallantamine, rivastigmine, and memantine [9].Although these medications have a number of limitations that prevent them from being viable pharmacological candidates for the treatment of AD, including low efficacy, poor bioavailability, unfavourable peripheral cholinergic side effects, restricted therapeutic ranges, and hepatotoxicity [10].

In Indian traditional medicine, the medicinal plant Granger Maderaspatna Pior is frequently used to cure a variety of illnesses. GM, also known as madras carpet, is a weed that thrives in sandy wastelands and subtropical regions of Africa, Asia, and Baluchistan. Other important chemical elements of plants include steroidal compounds, hardwickic acid, auranamide, penta and haxamethoxyflavones. The root is diuretic, anthelmentic, astringent to the intestines, and an appetiser. The herb is said to have astringent and anti-implantation properties..[11],[12],[13].

MATERIALS AND METHODS

Drugs and chemicals:

Piracetam (sun pharamaceuticals), Scopolamine, Methanol, Carboxy methyl cellulose.

Animals:

Wistar albino rats of either sex, weighing 150–200g, were used for the screening. They were obtained from the animal house of the Dr. K. V. Subba Reddy Institute of Pharmacy, Kurnool, and were maintained under standard laboratory conditions (temperature 23–20 c, relative humidity 55–10%, and 12-hour light–dark cycle). Throughout the research period, animals were fed with the

regular laboratory food and water at their discretion. The experiments were carried out after the IAEC of Dr.K.V.Subba Reddy of the Institute of Pharmacy approved the experimental protocol.

Plant material:

G. Maderaspatana plant materials (whole plant) were collected from a field near Nandanapalle village in Kurnool district, Andhra Pradesh. And authenticated by Dr.K.V.Madhusudhan, Dept of Botany, Silver Jubilee Government Degree College for Men, Kurnool. The plant was collected in December and shade dried at room temperature before being subjected to extraction procedures.

Preparation of extract:

Methanol was utilised in the extraction procedure since almost all of the Grangea maderaspatana whole plant's constituents are soluble in it. A free-flowing powder was created by electrically grinding the entire Grangea maderaspatana plant after it had been shade-dried. This powder was prepared by extracting dehydrated alcohol at room temperature. Using soxhlet, the extracted was dried at 40–50°C for 24 hours after being filtered through Whatman filter paper.

Acute toxicity study:

An acute toxicity study was carried out in accordance with OECD guideline 423. The test solution was administered to six swiss albino rats weighing 150-200g at a dose of 2000mg/kg. Rats were observed for clinical signs, gross behavioural changes, and mortality after receiving the test formulation at intervals of 30 minutes, 1 hour, 2 hours, 4 hours, 24 hours, 48 hours, and 74 hours for a total of 14 days**.**

Experimental Protocol for Nootropic activity:

Scopolamine-induced dementia model:

Scopolamine-induced acute dementia treatment protocol.

Group-I : Normal control ; Orally adminstered by CMC (0.5%w/v)

Group-II : Disease Control ; Treated with scopolamine (0.4mg/kg I.P) + CMC (0.5%w/v)in 0.5% CMC.

Group-lll : Standard: Treated with scopolamine (0.4mg/kg I.p) + piracetam (200mg/kg)

Group-IV : Low dose test ; Animals are orally adminstered by extract 250mg/kg dissloved in 0.5% CMC and + scopolamine (0.4mg/kg I.P)

Group-V : High dose test ; 500mg/kg extract orally +scopolamine (0.4mg/kg I.p) Animlas were randomly divided into 5 groups each group contains six animals. Scopolamine, used for inducing acute dementia was given 30min. Prior to the recommended treatment.

Y Maze Test:

The Y maze had three arms, each 40 cm long, 12 cm tall, 3 cm wide at the bottom, and 10 cm wide at the top, and they all converged in an equilateral triangular central area. During an 8-minute session, each rat was placed at the end of one arm and allowed to freely roam the maze. To be able to alternate, the rat must be aware of which arm they have already visited. The sequences of arm entries, including potential returns into the same arm, were visually recorded. The performance of instant working memory was measured by recording spontaneous alternation behaviour. When the rat's hind paws had completely entered the arm, entry was considered complete. On overlapping triplet sets, alternation was defined as successive entries into the three different arms (A, B, and C). % Alteration was calculated by the formula.

% Alteration = (Number of arm alteration/total arm entry-2) *100.

Elevated Plus-Maze Test :

The elevated plus maze was constructed of wood and featured two open arms (35 6 cm) and two enclosed arms (35 6 15 cm). The maze had been raised to a 40 cm height. Each rat should be positioned at the end of one arm of the elevated plus maze, facing away from the centre. The transfer latency (TL)—the length of time it took the rat to move from the open arm to one of the closed arms—was then measured. The first day the rats were allowed to explore the plus maze for 20 seconds. Rats were returned to their original cages after the first experiment's measurement of TL. Twenty-four hours later, the rats were again individually positioned on the elevated plus-maze as before, and TL was once more recorded. The first (L1) and second (L0) days' TL measurements served as the acquisition and retrieval parameters, respectively. Using the following, the inflexion ratio (IR) was calculated from these:

formula: **IR=L1/L0.**

Novel Object Recognition (NOR) Test :

The open field apparatus was made of white plywood (70x60x30 cm) with a grid floor that could be cleaned with hydrogen peroxide after each trial. The box's diagonally opposite corners were where the objects to be distinguished were placed. On the test day for the first trial (T1), two identical objects were placed in two corners of the box that were in opposition to one another, and the time it took each rat to complete a 20-second exploration was recorded. Exploration was defined as aiming the nose at an object from less than 2 cm away and/or touching it16. The time spent examining new (N) and familiar (F) objects was recorded during the second trial (T2, 90 minutes following T1). One of the objects presented during T1 was replaced with a new object during T2. (N-F)/(N+F) is the formula used to determine the discrimination index (DI). Thirty minutes before to the first trial, the animals were given the vehicle or medicines.

Morris Water Maze:

The apparatus consists of a circular pool with a smooth inner surface that is 100 cm in diameter and 45 cm high. The pool was divided into four equal quadrants, each with an equal area, and filled with opaque water (kept at 22 2 °C) to a height of 30 cm. At the centre of one of the four quadrants, there was a platform (29 cm 6 cm) that was positioned one centimetre below the water's surface (the target quadrant). Throughout the whole experiment, the platform's position remained constant. On day 10 of the treatment period, the test was started, and the rats were given time to acclimate by swimming for 120 seconds without the platform. Each animal got four 120-second learning trials separated by 60-second intertrial intervals throughout the course of the following four days. The rat was submerged for each learning trial, its back to the pool wall and diagonally across from the quadrant holding the platform. The escape latency time for each trial was calculated based on how long it took the animal to find the submerged platform.In this scenario, the escape latency time was 120 s because the animal was unable to find the platform within 120 s, it was pointed in the direction of the platform, where it was allowed to rest for 60 s. The hidden platform trials or acquisition tests took place during these sessions, which were recorded. The platform was removed from the water on day 15 (24 hours following the last learning trial), and the rats were put through a probe trial session to gauge memory recall. Each rat was dropped into the water across from the target quadrant, and given 60 seconds to swim and locate the quadrant where the platform had previously been installed. We kept track of how much time the animal spent in the target area.

Statislical Analysis :

Invivo study data were presented as the mean SEM. One-way analysis of variance was used to determine how the control and treated groups differed from one another (ANOVA). Statistics were considered to be significant at P-values under 0.05. Multiple comparisons were conducted using

Dunnet's post hoc test. The software programme graphpad prisom version No. 5.0 was used for the statistical analysis.

Estimation of biochemical parameters:

Preparation of brain sample:

Rats from each group were subjected to euthanasia using a carbon dioxide chamber after the learning and memory paradigm in scopolamine induced amnesia was evaluated. The brains were rapidly removed and stored in ice-cold saline.

Quick dissections of the frontal cortex, hippocampus, and septum were performed on a petridish with eyes crushed (this part of the brain cannot be identified in a small rat brain ;therefore, the whole brain was taken).

In 0.1M phosphate buffer, the tissues were weighed and homogenised (P^H8). The homogenates of the rat brain were collected in different test tubes and examined for various enzymes, such as acetylcholinesterase, MDA, reduced glutathione protein thioles, and catalase. Enzymatic tests employed the supernatant.

RESULTS

Acute toxicity study:

According to OECD guideline 423, the methanolic extract of dried leaves of G. maderaspatana was tested for acute toxicity. The animals were observed for signs of toxicity at differed time intervals 0,30min,1,2,4,6,8,12h and then daily for a peroid of 14 days.No signs of toxicity were obsereved in tested animals.

Nootropic activity

Y-**MAZE :** When compared to the negative control group (scopolamine), the G.M. treatment groups with methanolic extract demonstrated dose-dependent increases in percentage alteration.

S.NO	GROUP	TREATMENT	ALTERATION(%)
1.	Normal control	(CMC,P.O)	64.31 ± 2.45
2.	Negative control	Scopolamine(1mg/kg.p.o)	33.81 ± 3.19***
3.	Standard treatment	Piracetam(200mg/kg I.p)+scopolamine (1mg/kg I.p)	78.30 ± 3.61*
4.	Low dose extract	(250mg/kg p.o)+scopolamine(1mg/kg i. p)	44.25 ± 2.51**
5.	High dose extract	(500 mg/kg p.o) + scopolamine(1mg/kg i.p)	68.23 ± 2.19**

n=6, Values are Mean ±SEM, *p<0.05, **p<0.01, ***p<0.001, as compared with control group(ANOVA followed by dunnet's test)

Elevated plus maze :

The effects of elevated plusmaze are shown in table .Low dose of G.M (250mg/kg) and high dose of G.M (500mg/kg) were anticipated for 7 consecutive days.Orally treated revealed significant reduction in TL.High dose produced highly significant effect (P<0.01) and low dose produced low significance effect (P<0.05) after associated through scopolamine - induced amnesia as well as normal control group, on 6^{th}-7th days.The animals were administred with small to high dose showed a significant decline in TL of the 6^{th}-7th days as part of learning and memory. Scopolamine injected prior training considerably increased TL on the 6^{th}-7th days indicating impairment of learning and memory. Piracetam at a dose of 100mg/kg additionally revealed considerable

GROUP	TREATMENT	TL ON 6TH DAY	TL ON 7TH DAY
I	Normal Control (CMC,P.O)	25 ± 0.89	26 ± 0.72
II	Negative Control Scopolamine(1mg/kg.p.o)	56 ± 2.6	57 ± 2.7***
III	Standard Treatment Piracetam(200mg/kg I.p)+scopolamine (1mg/kg I.p)	20 ± 0.9	21 ± 0.9**
IV	Low Dose Extract (250mg/kg p.o)+scopolamine(1mg/kg i. p)	18 ± 0.54	19 ± 0.65***
V	High dose extract (500 mg/kg p.o) + scopolamine(1mg/kg i.p)	5.8 ± 0.9	5.9 ± 0.71*

n=6, Values are Mean ±SEM, *p<0.05, **p<0.01, ***p<0.001, as compared with control group(ANOVA followed by dunnet's test)

Morris Water Maze:

There is a rise in escape latency in scopolamine evoked animals when compared with the standard of each times [4,25= 66.05] (p < 0.001).

Methanolic extract of GM low dose (250mg/kg) dose not show any significance on the 6th ,7th days. Higher dose of MEGM (500mg /kg) indicates slight significance on the 6th day and high significance on 7th day.

The animals administered with the high dose MEGM showed remarkable decrease in escape latency of 6th-7th as part of learning and memory.

IMPACT OF MEGM ON ESCAPE LATENCY OF RAT USING MORRIS WATER MAZE.

GROUP	TREATMENT	ESCAPE LATENCY TIME (SECS) DAY 1	ESCAPE LATENCY TIME (SECS) DAY 2
I	Normal Control(CMC,P.O)	84.431 ± 4.0212	75.213 ± 0.5165
II	Negative Control Scopolamine(1mg/kg.p.o)	97.5 ± 2.396***	83.313 ± 0.9821***
III	Standard Treatment Piracetam(200mg/kg I.p)+scopolamine (1mg/kg I.p)	79.091 ± 3.2235*	53 ± 0.5306**
IV	Low Dose Extract (250mg/kg p.o)+scopolamine(1mg/kg i. p)	89.205 ± 0.7102***	72.320 ± 1.00313***
V	High Dose Extract (500 mg/kg p.o) + scopolamine(1mg/kg i.p)	90.506 ± 0.7724**	67.53 ± 1.1757*

n=6, Values are Mean ±SEM, *p<0.05, **p<0.01, ***p<0.001, as compared with control group(ANOVA followed by dunnet's test)

Novel Object Recognition Test:

When compared to the scopolamine-treated group, methanolic extract of GM related groups showed a dose-dependent increase in discrimination index.

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Table: Effect of methanolic extract of GM on descrimination index in scopolamine induced ammesia in albino wistar rats.

GROUP	TREATMENT	DESCRIMATION INDEX (DI)
I	Normal Control (CMC,P.O)	51.20 ± 1.062
II	Disease Control	40.16 ± 1.306*
III	Standard Treatment Piracetam(200mg/kg I.p)+scopolamine (1mg/kg I.p)	58.75 ± 1.051*
IV	Low Dose Extract (250mg/kg p.o)+scopolamine(1mg/kg i. p)	54.015 ± 1.021**
V	High Dose Extract (500 mg/kg p.o) + scopolamine(1mg/kg i.p)	57.12 ± 2.013**

n=6, Values are Mean ±SEM, *p<0.05, **p<0.01, ***p<0.001, as compared with control group(ANOVA followed by dunnet's test)

Biochemical Test :

1. Brain Acetylcholine Esterase Levels:

Comparing the methanolic extract of GM to the disease control group, the acetylcholin- esterase levels decreased in a dose-dependent manner.

Table: Effect of MEGM on acetylcholine level in scopolamine induced amnesia in albino wistar rats.

GROUP	TREATMENT	ACETYLCHOLINE LEVEL
I	Normal Control (CMC,P.O)	11.09 ± 1.34
II	Negative Control Scopolamine(1mg/kg.p.o)	29.21 ± 2.16***
III	Standard Treatment Piracetam(200mg/kg I.p)+scopolamine (1mg/kg I.p)	11.07 ± 1.06*
IV	Low Dose Extract (250mg/kg p.o)+scopolamine(1mg/kg i. p)	22.89 ± 1.08**
V	High Dose Extract (500 mg/kg p.o) + scopolamine(1mg/kg i.p)	24.12 ± 2.013**

n=6, Values are Mean ±SEM, *p<0.05, **p<0.01, ***p<0.001, as compared with control group(ANOVA followed by dunnet's test)

2. Brain Melanaldelyde Levels :

When compared to the disease control group, which received scopolamine alone, the co-administration of the methanolic extract of GM at a dose of 500 mg/kg and scopolamine significantly decreased the amount of brain melanaldehyde (p0.0001). Piracetam similarly decreased the level of MDA..

GROUP	TEARTMENT	MELANALDEHYDE
I	Normal Control (CMC,P.O)	0.14 ± 0.006
II	Disease Control	0.62 ± 0.0010**
III	Standard Treatment Piracetam(200mg/kg I.p)+scopolamine (1mg/kg I.p)	0.43 ± 0.0024*
IV	Low Dose Extract (250mg/kg p.o)+scopolamine(1mg/kg i. p)	0.20 ± 0.0010***
V	High Dose Extract (500 mg/kg p.o) + scopolamine(1mg/kg i.p)	0.18 ± 0.004**

n=6, Values are Mean ±SEM, *p<0.05, **p<0.01, ***p<0.001, as compared with control group(ANOVA followed by dunnet's test)

3. Brain Reduced Glutathione Levels:

Administration of the GM methanolic extract at doses of 250 mg/kg and 500 mg/kg significantly (P 0.0001) reduced the amount of GSH induced by scopolamine.

GROUP	TREATMENT	GSH
I	Normal Control (CMC,P.O)	21 ± 0.22
II	Disease Control	12.18 ± 1.22**
III	Standard Control (200mg/kg I.p)+scopolamine (1mg/kg I.p)	16.06 ± 0.12*
IV	Low Dose Extract (250mg/kg p.o)+scopolamine(1mg/kg i. p)	20.02 ± 0.41***
V	High Dose Extract (500 mg/kg p.o) + scopolamine(1mg/kg i.p)	20.62 ± 0.24***

n=6, Values are Mean ±SEM, *p<0.05, **p<0.01, ***p<0.001, as compared with control group(ANOVA followed by dunnet's test)

Histopathology:

In figure and table, the findings of the histological analysis are presented. While the histopathological analysis of the groups receiving standard treatment drugs (figure 1B) revealed vascular degeneration, neuronal degeneration, and gliosis that were found to be lower as compared with the negative control group, the histopathological analysis of the normal control rat revealed neuronal degeneration without vascular degeneration and gliosis. The most significant pathological alterations were seen in the scopolamine-treated groups. When compared to the normal control, the negative control, and the standard treatment, the methanolic extract of GM in both low and high doses demonstrated good regeneration scores.

DISCUSSION:

The number of AD patients is progressively increasing worldwide every day [38]. Degenerative changes in the brain cause memory loss in Alzheimer's disease [37]. Because scopolamine is an antimuscarinic agent that causes memory deficits after administration, the primary cause of AD is the loss of cholinergic neurons in the basal forebrain area.

The objective of the current investigation was to evaluate whether Grangea maderaspatana may enhance cholinergic pathways and alleviate memory impairment. Memory loss with Alzheimer's disease is managed in a substantial way by medicinal plants. In this work, we used the Y-maze, Elevated Plus Maze, NOR, and Morris Water Maze tests to assess the impact of Geangea

Maderaspatana on the memory function of amnesia rat. As was previously described [26], scopolamine caused amnesia in rats by impairing memory and blocking the brain's muscarinic cholinergic receptors. In the present investigation, prolonged scopolamine treatment to rats increased the latency time to enter the preferred arm, resulting in a reduction in the amount of time spent in the preferred arm of the y-maze. Chronic administration of GM methanolic extract, on the other hand, caused a reduction in latency time, which increased the amount of time spent in the preferred arm. According to earlier reports [27], the reduction in latency time indicated an improvement in memory. The considerable increase in entries and the length of time spent in the preferred arm reflex indicate that the memory is working well [28,29].

Neuroscience and memory studies of rat and mouse behaviour and brain functioning have been extensively exploited in an open field [30,31]. According to the results of the novel object recognition test, scopolamine increases the time it takes to find a familiar object when compared to a new one (NOR). It also reduced the amount of time spent exploring an object in relation to the frequency of investigation.The descrimination index dropped dramatically in the scopolamine-treated rats, indicating that the learning and recognition processes were impaired. Scopolamine is thus an anticholinergic drug that blocks muscarinic receptors, which have been linked to impaired learning and memory in both humans and animals.[32].

The animals' learning capacity is indicated by how long it takes them to go to the centre platform of the raised plus-maze. If the time it takes to go to the central platform is shortened, the animal is said to have learned.

The morris water maze (MWM) task was used as a behavioural task to demonstrate the mechanism by which G.M extracts show neuroprotective activity.
The findings show that, like piracetam, G.M significantly reduced the learning and retension deficits caused by repeated scopolamine doses. The time spent in the invisible platform during the retension phase was reduced by using a methanolic extract of G.M. During the retension phase, G.M also increased the amount of time spent in the target quadrant significantly. Our findings with the Morris water maze indicate that pre-treatment with G.M extract prevented scopolamine-induced learning and memory deficits, implying that G.M is neuroprotective. [33].
Memory disorders caused by scopolamine are linked to oxidative stress in the brain [34,35], as evidenced by an increase in MDA levels, a negative effect of reactive oxygen species [36]. Because the brain is composed of lipids, the action of ROS causing lipid peroxidation may directly cause brain death. The current study confirmed previous findings by Lee et al. [37] that the brain's antioxidant defence mechanism had collapsed, as evidenced by higher MDA levels and lower catalase and glutathione activity in the scopolamine-treated group versus the control group. Catalase activity, glutathione level, and MDA level in the rat brain all improved significantly after treatment with G.M. methanolic extract.

CONCLUSION

The purpose of this study was to assess whether grangea maderaspatana methanolic extract could protect against Scopolamine-induced memory loss. Scopolamine is a muscarinic acetylcholine receptor antagonist. Scopolamine-induced memory and learning deficits in Y-maze and object recognition tests resulted in an increase in oxidative stress as well as an increase in acetylcholinesterase activity.

In conclusion, Grangea maderaspatana possesses antiamnesic activity in a scopolamine rat model and enhances learning and memory in normal rats. It had a positive impact on brain levels of SOD,

CAT, and MDA, which helped to reverse the neurotoxicity and learning and memory deficits caused by scopolamine. These findings at least partially support the widespread use of Grangea maderaspatana as a neuroprotective and antiamnesic herb in traditional medicine. To fully comprehend the methods by which Grangea maderaspatana exerts its effects, however, more research is required.

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CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation.

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