

Neuroprotective Effects of *Valeriana wallichii* on Scopolamine Induced Learning and Memory Impairment in Rats

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ABSTRACT

Objective: Alzheimer's disease (AD) is the most common cause of dementia in worldwide, treatment options is extremely limited and costly. The present study was conducted to investigate and validate the traditional claim of *Valeriana wallichii* on scopolamine treated rats as an AD model. **Methods:** The *Valeriana wallichii* rhizome ethanol extract (25 mg/kg/day) was administered daily along with scopolamine for a period of 14 days following which the elevated plus maze test were performed to assess learning and memory. Rats treated with scopolamine or vehicle only were also included in the experiment. **Result:** The study demonstrate that scopolamine treatment resulted in learning and memory deficits which were partially and significantly ameliorated by the *Valeriana wallichii* rhizome ethanol extract. **Conclusion:** The study demonstrates the ability of the *Valeriana wallichii* rhizome ethanol extract to reverse scopolamine-induced learning and memory deficits in rats.

Key words: Neuroprotective, *Valeriana wallichii*, Scopolamine, Elevated plus maze, Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disorder in elderly people and is the main cause of approximately two of three cases of dementia.¹ Extracellular amyloid b (A β) assemblies, which result in senile plaques, are considered to be the pathologic hallmark of AD.² Because the neuronal hyperactivity and aberrant network function occur at an early stage of pathologic alterations even before the formation of A β positive plaques, they are thought to be crucial events leading to mild cognitive impairment or AD.³⁻¹² As such, non-invasive methods aimed to restore both integrity and function of specific neural network are emerging as a useful new therapeutic tool to supplement or replace most drugs that were designed to clear A β deposits from brains of patients with AD, but failed in clinical trials because of toxicity and/or limited efficacy.¹³⁻¹⁴ Cognitive dysfunction is a major health problem in the 21st century, and many neuropsychiatric disorders and neurodegenerative disorders, such as schizophrenia, depression, Alzheimer's disease dementia, cerebrovascular impairment, seizure disorders, head injury and Parkinsonism, can be severely functionally debilitating in nature. In course of time, a number of neurotransmitters and signaling molecules have been identified which have been considered as therapeutic targets. Conventional as well newer molecules have been tried against these targets. Phytochemicals from medicinal plants play a vital role in maintaining the brain's chemical balance by influencing the function of receptors for the major inhibitory

neurotransmitters. In traditional practice of medicine, several plants have been reported to treat cognitive disorders. Some medicinal herbs focusing on their Neuroprotective active phytochemical substances like fatty acids, phenols, alkaloids, flavonoids, saponins, terpenes etc. The resistance of neurons to various stressors by activating specific signal transduction pathways and transcription factors are also discussed. It was observed in the review that a number of herbal medicines used in Ayurvedic practices as well Chinese medicines contain multiple compounds and phytochemicals that may have a neuroprotective effect which may prove beneficial in different neuropsychiatric and neurodegenerative disorders. Though the presence of receptors or transporters for polyphenols or other phytochemicals of the herbal preparations, in brain tissues remains to be ascertained, compounds with multiple targets appear as a potential and promising class of therapeutics for the treatment of diseases with a multifactorial etiology.¹⁵

MATERIALS AND METHODS

Animals

Male Wistar albino rats (10–15 week old, 150–180 g) were procured from the animal house of the institute. Six animals were housed per cage which contained sterile paddy husk as bedding and were allowed access to water and food *ad libitum*.

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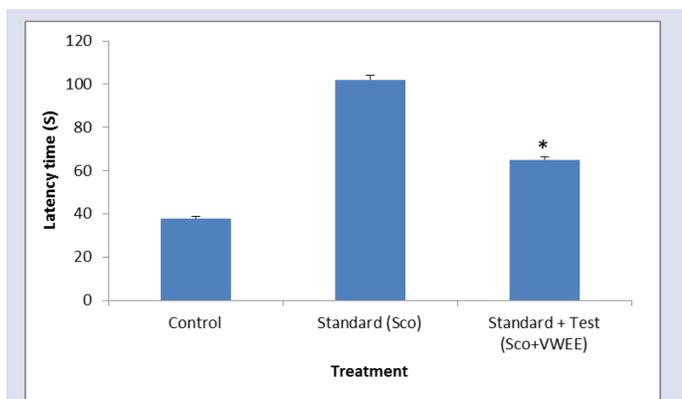


Figure 1: Effect of *Valeriana wallichii* ethanol extract (VWEE) on learning and memory in Scopolamine (standard) treated rats by using elevated plus maze model.

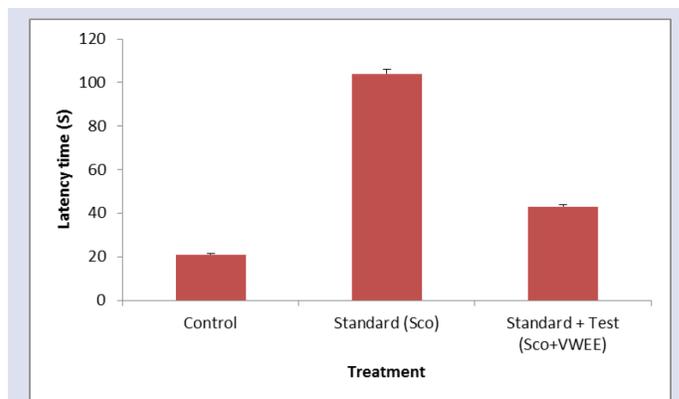


Figure 2: Effect of *Valeriana wallichii* ethanol extract (VWEE) on retention of memory in Scopolamine (standard) treated rats by using elevated plus maze model.

Constant temperature ($23 \pm 1^\circ\text{C}$) and humidity ($55 \pm 5\%$) under a 12 h light/dark cycle were maintained. All experiments were conducted according to standard guidelines for care and use of laboratory animals, with the approval of the Institutional animal ethical committee. The animals were acclimatized in laboratory conditions prior to the experiment.

Drugs and Chemicals

All the chemicals, reagents and solvents required for the study were procured from Himedia Private Ltd and were of analytical grade. All the solutions were freshly prepared prior to use. Scopolamine hydrobromide (henceforth referred to as scopolamine) was purchased from Sigma-Aldrich Chemical Co. India. A solution of scopolamine (2 mg/kg; dissolved in distilled water) was administered to the experimental animals through the intra-peritoneal (IP) route.

Experimental design

The Test extracts was administered daily along with scopolamine for a period of 14 days following which the elevated plus maze, passive avoidance, and Morris water maze tests were performed to assess learning and memory. Rats treated with scopolamine or vehicle only were also included in the experiment. Test drug contains the *Valeriana wallichii* rhizome ethanolic extracts (VWEE) 25 mg/kg. CMC and was administered to the animals orally (PO). Three groups, each consisting of 6 animals, were included in the study. The first group (control) was treated with vehicle daily (0.3% CMC; PO). The second group (standard) was treated with scopolamine (2 mg/kg/day; IP). The third group (test) was treated with 25 mg/kg/day VWEE and scopolamine (2 mg/kg/day; IP).

Elevated plus maze test

The elevated plus maze is designed to study behavioral patterns (such as sensitivity to external stimuli, anxiety, exploration, and learning and memory) of experimental animals. The maze consisted of four arms (two open and two closed), each 49 cm \times 10 cm. The closed arms consisted of 40 cm high walls with an open roof. The whole structure was elevated 50 cm above the ground. On the 14th day, 60 min after treatment, each rat was placed at the end of an open arm, facing away from the central platform. The time taken by the rat to enter any of the closed arms was recorded and considered as the transfer latency, and served as a parameter for learning and acquisition. If the rat did not enter into any one of the closed arms within 180 s, it was gently pushed into one of the two closed arms and the transfer latency was assigned as 180 s. For the next 15 s the rat was allowed to explore the maze before returning it to its

home cage. On the next day (24 h later), i.e. 15th day, the transfer latency was recorded again and served as a parameter for retention of memory. Between each session, the maze was carefully cleaned with 30% ethanol to remove any olfactory cues.¹⁶⁻¹⁸

Statistical analysis

All results are expressed as Mean \pm SEM (standard error of the mean). Statistical analyses were performed using one way analysis of variance (ANOVA). Statistical significance was set at $P < 0.05$. All statistical analyses of the data were performed by using Graph Prism Pad software version 5.0.

RESULTS

Elevated Plus Maze

Significantly higher transfer latencies were observed in the scopolamine treated rats compared to the controls during both the acquisition (day 14) and retention (day 15) sessions (Figure 1). Additionally, unlike the controls, no significant differences between the transfer latencies measured in the acquisition and retention sessions were observed in the scopolamine treated rats. Administration of the test extracts in scopolamine treated rats significantly lowered the transfer latencies during both the acquisition and retention trial sessions whilst also lowering transfer latencies in the retention session when compared to the acquisition session.

DISCUSSION

Neurodegenerative diseases such as AD are associated with a decline in cognitive abilities. The disease is highly prevalent in the aging population and progressive and debilitating in nature.¹⁹ Scopolamine, a muscarinic receptor antagonist, disrupts the cholinergic system and induces amnesia in animal models. Behavioral tests were employed to assess learning and memory in this study: the elevated plus maze test (anxiety based learning and spatial memory). Co-administration of the test extract (VWEE) in scopolamine treated rats ameliorated the learning and memory deficiencies induced by scopolamine in test [Table 1 and Figure 1] thereby corroborating the positive effects of the test extract (VWEE) on cognitive deficits in AD patients.²⁰⁻²² Additionally, unlike the controls, no significant differences between the transfer latencies measured in the acquisition and retention sessions were observed in the scopolamine treated rats [Table 2 and Figure 2]. Administration of the test extract (VWEE) in scopolamine treated rats significantly lowered the transfer latencies during both the acquisition and retention trial sessions whilst also lowering transfer latencies in the retention session when compared to the acquisition session.

Table 1: Effect of *Valeriana wallichii* ethanol extract (VWEE) on learning and memory in Scopolamine (standard) treated rats by using elevated plus maze model.

Groups	Treatment	Acquisition (time in S)
Control	0.3% CMC; PO	38
Standard	Scopolamine (2 mg/kg/day; IP)	102
Test	VWEE 25 mg/kg/day + Scopolamine (2 mg/kg/day)	65

As mentioned above scopolamine induced amnesia is mediated by the disruption of cholinergic signaling due to its muscarinic receptor antagonist activity. Additionally, several studies have also reported an increase in AChE activity in rodent brains following scopolamine administration and AChEI can reverse the amnesic effects of scopolamine.²³⁻²⁶

CONCLUSION

This study concluded that the test extract (*Valeriana wallichii* ethanol extract) ameliorated scopolamine induced learning and memory. Future studies into the anti-inflammatory and anti-amyloid properties of the test formulation will provide valuable insights on the mode and mechanisms of action of this novel drug product.

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CONFLICT OF INTEREST

All authors declare that there are no known conflicts of interest associated with this publication.

ABBREVIATIONS

AD: Alzheimer's disease; **A β :** Amyloid beta; **IP:** Intraperitoneally; **PO:** Orally; **VWEE:** *Valeriana wallichii* rhizome ethanolic extracts; **CMC:** Carboxy methyl cellulose; **SEM:** Standard error of the mean; **ANOVA:** Analysis of variance.

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Table 2: Effect of *Valeriana wallichii* ethanol extract (VWEE) on retention of memory in Scopolamine (standard) treated rats by using elevated plus maze model.

Groups	Treatment	Retention (time in S)
Control	0.3% CMC; PO	21
Standard	Scopolamine (2 mg/kg/day; IP)	104
Test	VWEE 25 mg/kg/day + Scopolamine (2 mg/kg/day)	43

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GRAPHICAL ABSTRACT



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Dr. Aslam Pathan is working at Department of Pharmacology & Therapeutics, College of Medicine, Shaqra University, Kingdom of Saudi Arabia. His field of research is neuroscience. He has more than 30 research publication in internationally indexed journals. He has author of two academic books published by international publishers. He has recipients of National Fellowship Award, Government of India, New Delhi, India.

SUMMARY

- **Systematic Review:** Alzheimer's disease (AD) is the most common cause of dementia in worldwide, treatment options is extremely limited and costly. The present study was conducted to investigate and validate the traditional claim of *Valeriana wallichii* on scopolamine treated rats as an AD model.
- **Interpretation:** The study demonstrates that scopolamine treatment resulted in learning and memory deficits which were partially and significantly ameliorated by the *Valeriana wallichii* rhizome ethanol extract.
- **Future Direction:** Future studies into the anti-inflammatory and anti-amyloid properties of the test formulation will provide valuable insights on the mode and mechanisms of action of this test extract.