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Research Article

Evaluation of the Neuroprotective Effects of Curcumin (Turmeric) Against Scopolamine Induced Cognitive Impairment in Mice.

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ABSTRACT

Objectives: To evaluate the neuroprotective effect of curcumin (turmeric) aqueous extract in scopolamine induced cognitive impairment in mice. To compare the neuroprotective action of curcumin (turmeric) against standard drug (Donepezil 50µg/kg). **Methods:** After obtaining Institutional Ethical Committee approval, Swiss albino mice (18-25g) of either sex were randomly divided into 5 groups of 6 animals each. Except the control group, other groups received scopolamine (0.05mg/kg) for 14 days. On 14th day, each animal were checked for cognitive impairment by using elevated plus maze (EPM). Dried powder of curcumin (turmeric) was boiled with distilled water, cooled, filtered, placed on hotplate for complete evaporation, finally weighed and stored. The control group, scopolamine control, test group and standard drug groups received saline, scopolamine (0.05mg/kg), curcumin (turmeric) extract (150 & 300 mg/kg), Donepezil (50 µg/kg) respectively by oral feeding. The neuroprotective effect was assessed by elevated plus maze (EPM) in mice. **Results:** In elevated plus maze (EPM) models, It implies that curcumin (turmeric) 150mg/kg and 300mg/kg significantly ($p<0.001$) decreases the duration of first retention transfer latency and second retention transfer latency. **Conclusion:** The current study demonstrates statistically significant neuroprotective activity of curcumin (turmeric) in dose independent manner.

Keywords: Curcumin (turmeric), neuroprotection, scopolamine, elevated plus maze, cognitive impairment

INTRODUCTION

Cognitive impairment is a progressive neurodegenerative disorder and causes significant dementia in elderly. The neuropathological hallmarks of cognitive impairment include, deposits of amyloid fibrils in senile plaques and presence of abnormal tau protein filaments in the form of neurofibrillary tangles[1]. Hippocampus, limbic system, and cortex are the primary areas involved in the pathophysiology of Alzeimer's disease[2].

The etiopathogenesis of this disorder is multifactorial and oxidative stress has been reported to play a significant role in the onset and progression of cognitive impairment[2]. Considering the mechanistic aspects, it has been recognized that amyloid aggregates and iron accumulation together cause oxidative damage by virtue of free radical generation[3,4]. Scopolamine-induced cognitive dysfunction is a well-known model that represents sporadic dementia of Alzheimer's type (SDAT)[5]. Scopolamine, a microtubule disrupting agent causes cytoskeletal alterations and axonal transport dysfunction[6] leading to the death of cerebellar granule cells, olfactory bulb neurons, cells of subventricular zone, dentate gyrus cells, and basal forebrain cholinergic neurons[7], thus causing cognitive impairment. It induces neurofibrillary degeneration by binding to tubulin, a principal structural protein of microtubules[8], thereby inhibiting axoplasmic transport and mitosis[9]. In addition, administration of scopolamine causes excessive free radical generation and oxidative damage, that can be positively correlated with the extent of cognitive impairment[10].

Curcumin (Curcuma longa - Haldi) is the source of the spice Turmeric and is used in the curries and other spicy dishes from India, Asia and the Middle East. Similar to many other herbal remedies, people first used curcumin as a food and later discovered that it also had impressive medicinal qualities. It has been used extensively in Ayurveda (Indian system of Medicine) for centuries as a

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Table 1: It shows the effect of Curcumin (CU) on Elevated Plus Maze (EPM) in mice.

Sl. No	Group & Dose (mg/kg oral) n = 6	Initial transfer latency in seconds (1st day) Mean ± SEM	1st retention transfer latency in seconds (14th day) Mean ± SEM	2nd retention transfer in seconds (21st day) Mean ± SEM
1	Control (Normal saline; 0.5 ml)	41.83 ±0.31	39.83 ±0.31	39.33 ±0.21
2	Scopolamine Control (0.05mg/kg)	46.83 ±0.48	56.83 ±0.40***	63.5 ±0.76***
3.	Curcumin (150mg/kg) + Scopolamine	40.17 ±0.31	34.0 ±0.45***	32.5 ±0.85***
4	Curcumin (300mg/kg) + Scopolamine	38.17 ±0.54	29.83 ±0.48***	27.33 ±0.42***
5.	Donepezil (50µg/kg)	36.17 ±0.79	27.17 ±0.75***	25.33 ±0.49***

****P<0.001 Compared to Controls*

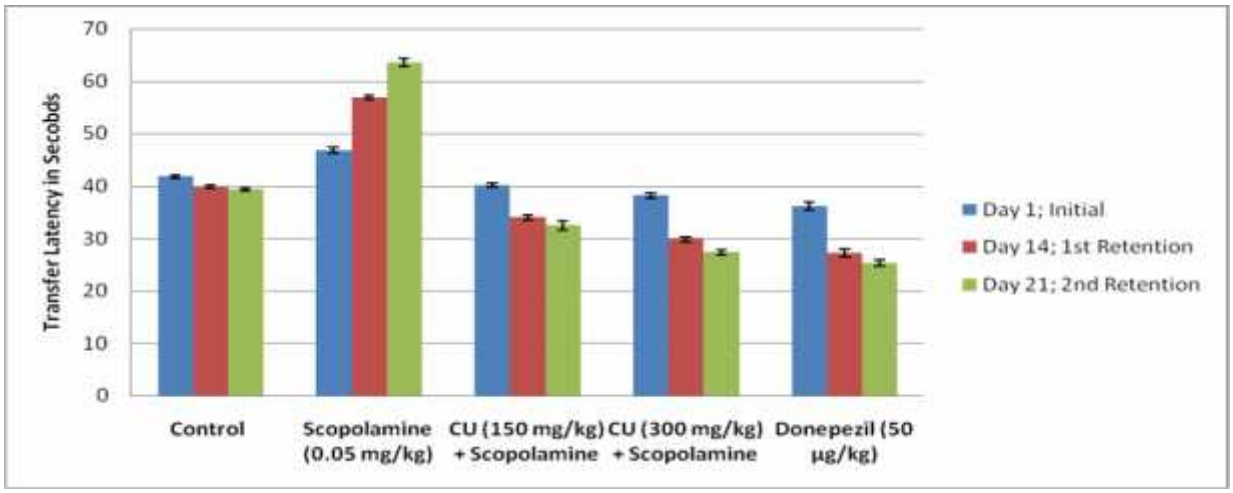

Fig. 1: It shows the effect of Curcumin (CU) on elevated plus maze [EPM] in cognitive impaired mice.

pain relieving, anti-inflammatory agent to relieve pain and inflammation in the skin and muscles. It has also proven to have anti-cancer properties[11, 12]. Curcumin holds a high place in Ayurvedic medicine as a "cleanser of the body," and today, science is finding a growing list of diseased conditions that can be healed by the active ingredients of turmeric[13].

Curcumin shows action as an anti inflammatory agent in alzheimer's disease[14-15], an anti-oxidant[15], on haem-oxygenase Pathway[16], on beta-amyloid Plaques [17], on metal Chelation[18] and possesses cholesterol lowering effect[19].

MATERIALS AND METHODS

Preparation of Aqueous Extract**:** Roots of curcumin (CU) were collected from local garden in Coimbatore, dried in shadow, and subsequently grounded. The plant

was authenticated for their correct botanical identity by the chief botanist. The aqueous extract of curcumin was prepared by refluxing curcumin (turmeric) (120g) with water (1.5L) for 2hr, filtered to remove plant debris and freeze-drying to yield a residue (11.5g)[11]. The mixture was subsequently filtered and concentrated at 35ºc. The extract was preserved in deep freezer in air tight container.

Animals: Swiss albino mice (18-25g) of either sex were procured from the central animal house of the Institute. They were housed in standard polypropylene cages and were kept under controlled room temperature at 25±2^{0}C in a 12h light /dark cycle. Animals were given dry pellets and water ad libitum. The animals were accustomed during the day time to new environment for at least 2 days prior to the experiment. Institutional Animal Ethics Committee approval was taken prior to the start of study. The ethical guidelines laid down by CPCSEA for the investigation of animals used in experiments were followed strictly in all tests.

Elevated Plus Maze (EPM): Mice were divided into 5 groups. Each group consisting of 6 mice. The elevated plus maze consist of two opposite black open arms (50 x10cm), crossed with two closed arms ofthe same dimensions with 40cm height walls. The arms were connected with a central square of dimensions 10cm. The entire maze was elevated to a height of 50cm from the floor.

Acquisition of memory was tested on day one. Animal was placed individually at one end of the open arm facing away from the central square. The time taken by the animal to move from the open arm to the closed arm was recorded as the initial transfer latency (ITL).

Animal was allowed to explore the maze for 20 seconds after recording the ITL and then returned to the home cage.

If the animal did not enter the enclosed arm within 90 seconds, it was guided on the back into one of the enclosed arm and the ITL was given as 90 seconds. Retention of memory was assessed by placing the rat in an open arm and the retention latency was noted on day 14 and day 21 and was termed as the first retention transfer latency (1st RTL) and second retention transfer latency (2nd RTL), respectively[13,14].

STATISTICAL ANALYSIS

Data were expressed by Mean ± SEM. For comparison among the groups we used ANOVA with multiple comparison Posthoc Tukey HSD method. Statistical analysis done by using SPSS for windows (V: 17.0).Statistical significance was considered $p<0.05$ level.

RESULTS

The mean duration of initial transfer latency, 1st retention transfer latency and 2nd retention transfer latency from open arms to closed arms in the Control, Scopolamine control, CU (150 mg/kg) + scopolamine, CU (300 mg/kg) + scopolamine and standard drug, Donepezil were recorded. The duration in 1st retention transfer latency and 2nd retention transfer latency was decreased with CU (150 mg/kg) and CU (300 mg/kg) when compared to scopolamine control group significantly ($p<0.001$). But, the effect was low when compared to the standard drug donepezil. It implies that CU (150mg/kg) & CU (300mg/kg) significantly ($p<0.001$) decreased the duration of 1st and 2nd retention transfer latency in scopolamine induced cognitive impaired mice in a dose independent manner. The percentage decrease in duration, compared to control also statistically significant ($p<0.001$).

The results were shown in the Table-1 & Figure-1.

DISCUSSION

The present study was aimed for evaluating the neuroprotective properties of Curcumin (CU) in comparison with standard drug, Donepezil using animal models. Curcumin (CU) is an indigenous ingredient of ayurvedic medicine[11-13]. It is mainly used in curries and other spicy dishes[11-13]. It acts as a memory enhancer, anticonvulsant, antianxiety, anti -depressant and to treat insomnia[14-19].

Curcumin (CU) proved to improve cognition, decreased malondialdehyde and nitrite levels, restored decrease in GSH, increased activities of glutathione-S-transferase, catalase, and SOD[20,21]. Scopolamine administration is characterized by progressive deterioration of learning and memory, oxidative stress, and decrease in acetylcholine turnover [20, 21].

Colchicine resulted in significant memory impairment in elevated plus maze tasks which were attenuated by chronic curcumin (CU) treatment[22, 23, 24]. Also, the chronic administration of curcumin (CU) was able to improve the cognitive deficit and attenuated oxidative stress, suggesting that curcumin (CU) improves cognitive task and has antioxidant-like effect[22, 23, 24]. Additionally, Curcumin (CU) root extract has been reported to improve spatial learning performance and enhance memory retention in neonatal rats during growth spurt period and also found efficient in enhancing hippocampal CA3 neuronaldendritic arborization in mice[22,23,24].

Administration of scopolamine produces marked destruction of hippocampal granule cells and septo hippocampal pathways resulting in loss of cholinergic neurons and decreased activities of acetylcholinesterase and choline acetyltransferase[25]. Scopolamine caused a significant increase in the acetylcholinesterase activity thereby leading to learning and memory deficits[25]. Curcumin (CU) normalizes the decreased AChE levels induced by scopolamine[25]. In contrast, turmeric showed no significant differences in changing MMSE score or plasma Aβ40 levels between 0 and 6 months[26].

In our present study, curcumin (CU) was used in a dose of 150 mg/kg and 300 mg/kg in scopolamine induced cognitive impairment in mice. Curcumin (CU) decreases the duration of transfer latency compared to scoplolamine control in a dose independent manner. Scopolamine induced cognitive impairment in mice and EPM is a best suitable test for evaluating neuroprotective properties of drugs, since it is the best-validated preclinical test, which predicts the effectiveness of the drug against cognitive impairment in mice.

In our study, there is reduction in 1st retention transfer latency and 2nd retention transfer latency in both curcumin (CU) 150 mg/kg and 300 mg/kg groups. It shows significant ($p<0.001$) neuroprotective activity with both 150 mg/kg and 300 mg/kg groups, compared to the control group. But, it has less activity when compared to that of standard drug donepezil.

CONCLUSION

The present study suggests that chronic administration of Curcumin (CU) prevents scopolamine--induced cognitive impairment and associated oxidative stress in a dose independent manner. Thus, the use of Curcumin (CU) is promising for the treatment of cognitive impairment and other neurodegenerative disorders. However, further studies and validation were required to establish the efficacy of the Curcumin in treatment of the cognitive impairment and other neurodegenerative disorders.

CONFLICT OF INTERESTS: NONE

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