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EFFECT OF *ACETOSELLA CORNICULATA L.* (*OXALIDACEAE*) ON CORTICOSTERONE INDUCED MILD COGNITIVE IMPAIRMENT ON ALBINO MICE

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ABSTRACT

Dementia is a syndrome (a group of related symptoms) that is associated with an ongoing decline of the brain and its abilities. These include Thinking, Language, Memory, Understanding, Judgement. People with dementia may also have problems controlling their emotions or behaving appropriately in social situations. Most cases of dementia are caused by damage to the structure of the brain. Here the aim of the present research work on memory-enhancing effects of the Methanolic Extract of *Acetosella corniculata* L (MEAC) on Corticosterone (5mg/kg) induced mild cognitive impairment on albino mice were assessed by Morris water maze (MWM) and step-down passive avoidance tests. In MWM tests, the impaired spatial memory of the mice was partly reversed by MEAC (200 and 400 mg/kg; $P < 0.05$) as compared with the control mice. In step-down tests, the nonspatial memory of the mice was improved by MEAC (200 and 400 mg/kg; $P < 0.05$). Additionally, MEAC could increase superoxide dismutase (SOD) and catalase (CAT) activities, inhibit monoamine oxidase (MAO) and acetyl cholinesterase (AChE) activities, and decrease the levels of malondialdehyde (MDA) in the brain tissue of the mice. The results showed that MEAC improved memory functions of the mice probably via its antioxidant properties and via decreasing the activities of MAO and AChE.

KEYWORDS: Dementia, Corticosterone, Morris water maze, passive avoidance, antioxidant etc.

INTRODUCTION

Medicinal plants play a vital role for the development of new drugs. The bioactive extract should be standardized on the basis of active compound. The bioactive extract should undergo safety studies. Almost, 70% modern medicines in India are derived from natural products. India has a very small share (1.6%) of this ever-growing global market.[1] To compete with the growing market, there is urgency to expeditiously utilize and scientifically validate more medicinally useful plants.[2,3] Natural pharmaceuticals, nutraceuticals and cosmeceuticals are of great importance as a reservoir of chemical diversity aimed at new drug discovery and can be explored as potential antimicrobial, cardiovascular, immunosuppressive, and anticancer drugs. Around 80% of all such products are of plant origin; their sales exceeded $ 65 billion in 2003. Examples of plant products and derivatives used by the pharmaceutical industry include Paclitaxel, Vincristine, and Vinblastine, Artemisinin, Camptothecin, Podophyllotoxin.[4,5]

Mild cognitive impairment (MCI) is the stage between the expected cognitive decline of normal aging and the more serious decline of dementia. It's characterized by problems with memory, language, thinking or judgment.[6] Mild cognitive impairment may increase your risk of later developing dementia caused by Alzheimer's disease or other neurological conditions. But some people with mild cognitive impairment never get worse, and a few eventually get better.[7]

The plant *Acetosella corniculata* L. (Creeping wood sorrel) also called procumbent yellow sorrel belongs to family *Oxalidaceae.* It is very popular perennial herb that is distributed throughout the world. It is a somewhat delicate appearing, low growing. It is common in damp shade places, road sides, pastures, plantations, lawns. In the literature survey the plant *Acetosella corniculata* L. is used traditionally by the tribal people and native local healers for the treatments of wounds, fractured bones, body pains, diarrhea, dysentery, convulsions, dementia, and used as hypoglycemic agent, diuretic.[8,9,10] It is used for the convulsions in children and healing for fractured bones. Crushed leaves are used to treat mouth infections in children. Leaves infusion is used to treat induration of breasts and warty vaginal discharges.[11] The plant studies have reported, that the *Acetosella corniculata* L. showed wound healing, Abortifacient[12] and

Antiimplantation, Relaxant activity[13], Anti diarrhoeal and Anti bacterial.[14]

MATERIALS AND METHODS

Animals used

Male albino mice (30-40mg) were obtained from the animal house in Sree Vidyanikethan College of Pharmacy, Tirupati, Andhra Pradesh. The animals were maintained in a well-ventilated room with 12:12 hour light/dark cycle in polypropylene cages. The animals were fed with standard pellet fed (Hindustan Level Limited, Bangalore) and water was given *ad libitum*. Ethical committee clearance was obtained from IAE (Institutional Animal Ethics Committee) of CPCSEA (Ref. No./AEC/XIII/05/SVCP/2008-09).

Treatments

Animals were devided into four groups, each consisting of six male albino mice. The methanol extract of *Acetosella corniculata* L. was blackish oily extract divided into two doses MEAC-200mg/kg, MEAC-400mg/kg given orally daily for 21 days, 30 min before Cortecosterone injection. Corticosterone (VHB lifesciences, 5mg/kg) was dissolved in absolute ethanol and subsequently diluted in water to the final concentration of 10% ethanol and injected subcutaneously in a volume 1ml/kg.

Group – I: Normal control mice administered normal saline (0.9% w/v),

Group – II: Disease control administered Cortecosterone inj subcutaneously (5mg/kg).

Group – III: Cortecosterone + MEAC 200mg/kg,

Group – IV: Cortecosterone + MEAC 400mg/kg given orally for 21 days, 30min before Cortecosterone administration.

Morris Water Maze Test

The Morris water maze is a circular pool (90cm in diameter and 45cm in height) with featureless inner surface. The circular pool was filled to a height of 30cm with water (18 ± 1°C), in which 500ml of milk was mixed. A white platform (6cm in diameter and 29cm I height) was centered in one of four quadrants of the pool (Southest area) and submerged 1cm below the water surface so that it was invisible at water level. In the water maze experiments the first week of the experiment was dedicated to swimming training for 60s. All animals were four groups we investigated the 3 weeks for treatment. In these days the mice were given one session of two trails each day for 21 days. During each trial, the mouse's escape latency, measured with a stop watch, were recorded. The parameter was averaged for each session of trials and for each mouse. One the mouse located the platform; it was permitted to remain on it for 10s. If the mouse did not locate the platform within 120s, it was placed on the platform for 10s. During this period, the platform was located in a fixed position. In the last day of training, mice were given a probe trial which considered of removing the plat form from the pool and allowing the mice to swim for 60's in search of it. A record was kept of the swimming time in the pool quadrant where the platform had previously been placed. Solutions of MEAC were given orally 30min prior to the consective training.[15,16]

Passive Shock Avoidance Paradigm

Passive Avoidance behavior based on negative reinforcement was used to examine the long term memory. The apparatus consisted of a box (27x27x27cm) having three walls of wood and one wall of plexi glass featuring a grid floor (3mm stainless steel rods set 8mm apart), with a wooden platform (10x7x1.7cm) in the center of a grid floor. The box was illuminated with a 15W bulb during the experimental period; electric shock (20VAC) was delivered to the grid floor. Training was carried out in two similar sessions. Each mouse was gently placed in the wooden platform set in the center of the grid floor. When the mouse stepped down and placed on the wooden platform set in the center of the grid floor.

When the mouse stepped down and placed all its paws on the grid floor, shocks were delivered for 15 sec and the step down latency (SDL) was recorded. SDL was define as the time taken by the mouse to step down from wooden platform to grid floor with its entire paw on the grid floor, animals showing SDL in the range (2-15 sec) during the first test were used for the second session and the retention test. The second-session was carried out 90min after the first test. When the animals stepped down before 60sec, electric shocks were delivered for 15sec. During the second test, animals were removed from the shock free zone if they did not step down for a period of 60sec. Retention was tested after 24h in similar manner, except that the electric shocks were not applied to the grid floor. Each mouse was again placed on the platform, and the SDL was recorded, with an upper cut-off time of 300sec.

In this passive avoidance shock test we devided four groups of animals. Group-I: Normal control group for mice (n=6), normal saline (0.9% w/v) was administered P.O. for 8 days. After 90 min of administration on 8th day, SDL was recorded retention was examined after 24h, Group-II and Group-III (n=6 each); MEAC (200 and 400mg/kg) respectively orally for 8 days. SDL was recorded after 90 min of administration on 8th day and after 24h. In this 30 min before corticosterone inj administration subcutaneously. Group-IV: corticosterone (5mg/kg) was administered subcutaneously in the negative control mice for upto 8 days continuously and 8th day SDL was recorded, retention was examined after 24h.[17]

Statistical analysis The statistical significance of the results of Morris water maze as well as passive shock avoidance tasks were analysed using ANOVA, followed by Tukey-Krammer multiple comparison test, the P values <0.05 were considered as significance.

RESULTS

Morris water maze test

In the Morris water maze ANOVA followed by Tukey-Krammer multiple comparison test. All the latencies to reach the location of the platform significantly (P<0.05) Table: 11. The methanol extract of *Acetosella corniculata* L. (MEAC) showed the significant activity in 21 days study. Saline treated control mice rapidly learned the location of the submerged platform at 21st day compared 0thday, Cortecosterone inj (5mg/kg) group memory impairment was rapidly increased significantly (P<0.001) from 0 to 21st day compare to saline treated control. MEAC treated mice (200 and 400mg/kg) found the platform significantly (P<0.001) earlier than Cortecosterone injected mice and also significantly (P<0.001) than saline treated control from 6th day to 21st day.

Table 11: Effect of *Acetosella corniculata* L. transfer latencies of mice on morris water maze test.

Groups	Treatment	Transfer Latency							
		0	3	6	9	12	15	18	21
I	Normal control	10.7± 0.9	10.2± 0.95	10.8± 0.95***	9.83± 0.83***	7.8± 0.70***	7.7± 0.71***	8.8± 1.2***	8.2± 0.8***
II	MEAC 200mg/kg	7.5± 0.43	8.8± 0.7	10.3± 1.0***	14.3± 0.84***	11.3± 1.02***	9.4± 1.04***	7.3± 0.6***	7.2± 0.4***
III	MEAC 400mg/kg	6.7± 0.7	9.8± 0.95	11.5± 0.05***	10.5± 0.95***	9.83± 0.8***	8± 0.58***	7.67± 0.42***	7.3± 0.61***
IV	Corticosterone	7.3± 0.42	10.5± 0.62	22± 1.7	35± 1.6	49.7± 1.38	58.3± 1.67	67.3± 1.86	70.5± 2.1

Values are expressed as mean±SEM, ANOVA followed by Tukey-Krammer multiple comparision test, 6 male albino mice in each group.

*** P<0.001, as compared to corticosterone injected group.

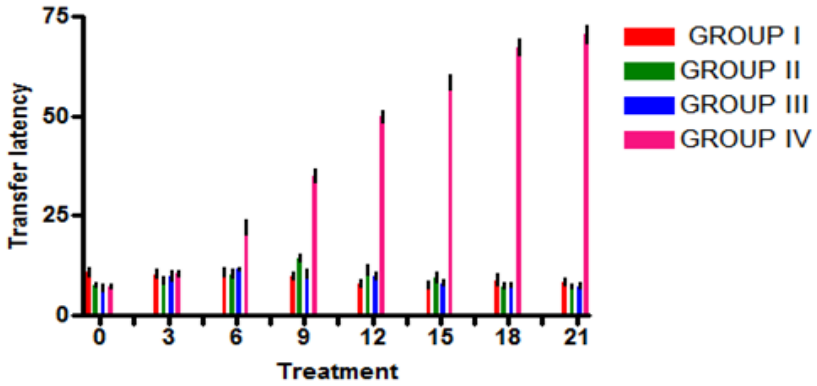

Fig. 1: Effect of *Acetosella corniculata* L. transfer latencies of mice on morris water maze test.

Passive Shock Avoidance Paradigm

In this passive Avoidance model the higher dose of MEAC-400mg/kg pretreatment for 8 days successively protected mice (P<0.001) against Cortecosterone induced memory impairment. The step down latency (SDL) of Cortecosterone injected mice was significantly (P<0.001) poor when compared to that of saline treated mice (Table-12). MEAC (400mg/kg P.O) profoundly increased step-down latency (SDL) significantly (P<0.001) compared to saline treated mice, indicating improvement in memory. MEAC (200mg/kg P.O) increased SDL significantly (P<0.001) compared to saline treated mice and lesser than MEAC (400mg/kg P.O) treated group.

Table 12: Effect of *Acetosella corniculata* L. on step down latency (SDL) using passive avoidance apparatus.

Group	Treatment	Dose (mg/kg)	SDL after 24h (score/sec±SEM)
I	Normal saline	---	104.5±4.42
II	MEAC	200	184±4.34***
III	MEAC	400	265±3.51***
IV	Cortecosterone	5	18.3±1.52***

Values are expressed as Mean ± SEM, ANOVA followed by Tukey-Krammer multiple, 6 male albino mice is comparison test each group.

***P<0.001, as compared to control.

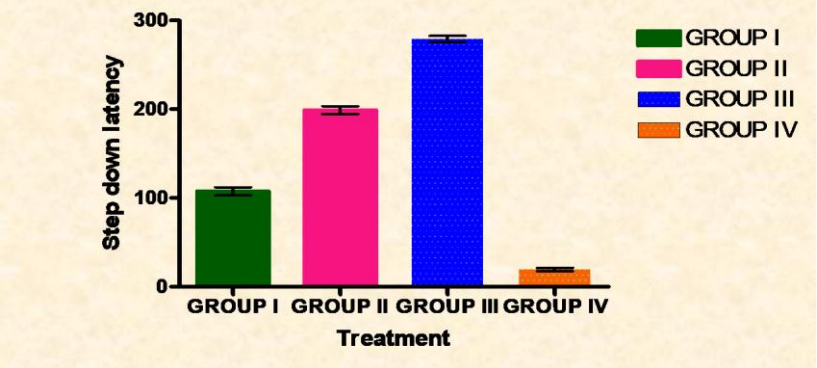

Fig. 2: Effect of *Acetosella corniculata* L. on step down latency (SDL) using Passive Avoidance paradigm.

DISCUSSION AND CONCLUSION

In this study, memory was assessed using Morris water maze and the Step-down Avoidance test. The effect of *Acetosella corniculata* L. on memory impairment induced by Cortecosterone in male albino mice was performed by using methanol extract, Cortecosterone significantly impaired other forms of hippocampus-dependent memory such as object recognition and retrieval of the passive avoidance behavior.[18] Corticosterone, the predominant glucocorticoid in rodents, chronic administration of cortecosterone it damages hippocampal subregion CA_3 that leads to impair spatial memory.[19] Also chronically elevated levels of cortecosterone inj administration is mice for 21 days can produce neuronal atrophy and cell death in the hippocampus while leaving other brain regions, the elevated levels of cortecosterone changes in various neurotransmitters such as catecholamines, serotonin and γ-aminobutyric acid (GABA) in several brain structures.[20] In the hippocampus corticosterone impairs GABA-mediated inhibitory neurotransmission[21] and causes neurodegeneration via diminished expression of $GABA_A$ receptors.[22] High amounts of corticosterone enhance action of norepinephrine (NE) via β-adreno receptors and increased dopamine (DA) turnover in prefrontal cortex is accompanied by the decreased spatial memory performance.[23,24]

In this study we investigated the two memory assessment behavioral model, Morris water maze test and passive avoidance paradigm in both models the methanol extract of *Acetosella corniculata* L. showed significant activity on memory impairment induced by chronic administration of Cortecosterone 5mg/kg subcutaneously into the male albino mice. In this morris maze test chronically elevated levels of Cortecosterone administered for 21 days that leads to memory impairment occurs in the hippocampal subregion. This can be overcome by the MEAC treated (200 and 400mg/kg) two groups showed significant action compared to saline treated mice and only Cortecosterone treated mice, Cortecosterone treated mice showed increasing latency period due to memory impairment. In the treatment 0^{th} day to 1^{st} day there is no action on the mice.

In the passive avoidance paradigm Cortecosterone injected mice showed decreased step down latency compared to saline treated mice after 24 hours later. In this continuously 8 days cortecosterore occurs. The MEAC treated (200 and 400mg/kg) showed significant activity and increasing the SDL after 24 hours compared to normal as well as Cortecosterone treated mice the higher dose of MEAC (400mg/kg P.O) pretreatment for 8 days successively protected mice against Cortecosterone induced memory impairment. The higher dose of MEAC (400mg/kg P.O) increased the SDL after 24 hours then the MEAC treated (200mg/kg P.O) group.

The plant *Acetosella corniculata* L. *(Oxalidaceae)* contain three C-glycosylflavones, rich in vitamin-C, the vitamins C, and E can effects the neurotransmitters and acetylcholinesterase activity in the brains of rodents treated with scopolamine inducing dementia. This is supported to our research work may be rich in the vitamin-C supplementation increases the Acetylcholinestrase activity in brain. Oxygen-free radicals and other products of oxidative metabolism have been shown to be neurotoxic. The protective effect of *Acetosella corniculata* L. extract may be attributed to antioxidant property due to rich in vitamin-C by virtue of which susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function thereby enhancing the memory.[25] There conditions were showed the neuroprotective role of methanol extract of *Acetosella corniculata* L. Cortecosterone induced memory deficits.

CONCLUSION

It is concluded from the current study, that the methanol extract of *Acetosella corniculata* L. possess significant Memory enhancing activity and may prove to be effective for the treatment of memory impairement and other cognitive disorders. The results showed that MEAC improved memory functions of the mice probably via its antioxidant properties and via decreasing the activities of MAO and AChE. However further studies required to elucidate the exact mechanism of action for develop its as potent memory enhancing drug. These natural memory enhancing drugs will help to develop new drug candidates for dementia therapy.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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