

The effect of *Oxalis corniculata* extract against the behavioral changes induced by 1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the development of rigidity, resting tremors and postural instability. Recently, the focus of PD's treatment has shifted towards herbal medicines. The aim of the study was to evaluate neuroprotective effect of alcoholic extract of *Oxalis corniculata* (Oxalidaceae), via the analysis of behavioral features in MPTP (1-methyl,4- phenyl-1,2,3,6-tetra hydro pyridine) mouse model. Behavioral studies were performed by the actophotometer, elevated plus maze, rotarod, hole board, step down and step through tests. Treatment with *O. corniculata* reversed the alterations in locomotor and muscle coordination in MPTP induced Parkinsonic mouse. The results achieved in this study reveal that different doses of *O. corniculata* increased memory retention and retrieval significantly. Memory retention and retrieval enhancement by *O. corniculata* extract could be due to the presence of antioxidants such as flavonoids, coumarins, tocopherols and phenolic acids and their power in scavenge reactive oxygen species.

INTRODUCTION

Parkinson's disease (PD) is an age-related progressive neurodegenerative disease, which is characterized by resting tremors, rigidity, postural abnormalities, particularly stooped posture, and difficulty or failure to execute willed movements, i.e. bradykinesia, akinesia and festinating gait (Tillerson *et al.*, 2003; Oida *et al.*, 2006). Parkinson's disease was recorded in ancient India. It was called as *Kampavatha*. Many traditional medicinal plants were used for the healing of many diseases including stress, insomnia, anxiety, arthritis and other disorders related to the central nervous system (CNS) such as PD and Alzheimer's disease. The extracts of herbal medicine have been reported for its defensive effects against neurotoxicity *in vitro* and *in vivo* models of Parkinson's disease (Sankar *et al.*, 2007;

Babita *et al.*, 2014; Rajasankar *et al.*, 2009; Srinivasagam Raja Sankar *et al.*, 2007). MPTP (1-methyl -4 -phenyl-1, 2, 3, 6-tetrahydropyridine) is a potent neurotoxin which results in selective degeneration of dopaminergic neurons projecting from substantia nigra pars compacta (SNpc) into striatum and mimics PD-like symptoms in experimental models (Smeyne and Jackson-Lewis, 2005). *Oxalis corniculata* is a medicinally important plant indigenous to tropical and subtropical regions of the world. *Oxalis corniculata* exhibits wound healing activity (Taranalli *et al.*, 2004), cardio relaxant activity (Achola *et al.*, 1995), nematocidal activity (Silamar and Leandro, 2005), anticancer activity (Kathiriya *et al.*, 2010), antimicrobial activity (Raghvendra *et al.*, 2006), antifungal activity (Iqbal *et al.*, 2001), antiamebic activity (Manna *et al.*, 2010), antiimplantation and abortifacient (Sharangouda and Patil, 2007), allelopathic activity (Itani *et al.*, 1999), antioxidant activity (Reddy *et al.*, 2010) and steroidogenic activity (Seraphim and Sinha, 2010). Recently, *O. corniculata* was also reported to exhibit potent anxiolytic potential, nephroprotective, anti-stress and memory enhancing properties (Sai Sampath *et al.*, 2011).

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But so far their protective effect in neurodegenerative disorders such as PD has not been studied. In the present study, the protective effect of *O. corniculata* against MPTP-induced behavioral deficits in mouse model of PD was investigated.

EXPERIMENTAL

Chemicals and reagents

MPTP hydrochloride was purchased from Sigma Chemical Co. Analytical grade chemicals were used for the experimental analysis. Stock solutions of all chemicals were prepared in double distilled water and the dilutions were made fresh on the day of the experiment.

Plant extract

The medicinal plant *Oxalis corniculata* was collected from Tirunelveli District, Tamil Nadu, India. Mature and healthy plants were collected naturally from different locations after the rainy season (February, March and April). The collected specimens were identified referring to the Flora of Presidency of Madras (Gamble, 1915-1921) and Flora of Tamil Nadu Carnatic (Mathew, 1983 -1988). The collected plant materials were shade-dried at room temperature (20-25°C) for a period of 3 weeks to 8 weeks. For extraction, the completely dried materials were made into coarse powder by mechanical grinder. The powder was passed through a 40-mesh sieve, to get a uniform particle size. A weighed quantity of powder was subjected to continuous hot percolation in soxhlet apparatus with ethanol at 65-70°C. All the solvent had been removed by evaporating under reduced pressure using rotaflash evaporator. The concentration of the extract was 12% w/w. when compared to the dried starting material. It was then stored at -20°C until required.

Animals

C57 Black male mice, weighing 25-30 gm were used. All animals were obtained from the Animal house, KMCH College of Pharmacy, Coimbatore, Tamil Nadu. They were allowed food and water *ad libitum* upto the experimentation period. Prior to use, the mice were housed in polypropylene cages in group of six to eight animals under natural light-dark cycle. Each animal was used only once under standard laboratory conditions. All the observations were made at room temperature in a noiseless diffusely illuminated room and were made between 9.00 to 17.00 h in the experimental room. All the experimental protocols were approved by Institutional Animals Ethics Committee (IAEC) as per provisions of Committee for the Purpose of Control and Supervision of Experimental Animals (CPCSEA) (KMCRET/PhD/ /2014-15), New Delhi, India.

Experimental protocol

The following experimental procedure was followed to evaluate the locomotor behavioral effect of *O. carniculata* (OC) on MPTP induced mice. 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP): 15 mg/kg of MPTP as a neurotoxin

i.p. twice, 4 h apart *in vivo* and 20 µM *in vitro*. MPTP was purchased from Sigma, India. MPTP was dissolved in 0.9 % saline and administered i.p. Intraperitoneal injection of MPTP was given to Groups II,III, IV and V. Oral dosage of Carbidopa + Levodopa (Standard drug for Parkinson's disease treatment) was given to Groups III.

The animals were divided into six groups, each consisting of six mice.

1. Group I served as vehicle control (Distilled water)
2. Group II received MPTP (20 mg/kg, i.p) (Sigma-Aldrich, Bangalore, India) four consecutive days,
3. Group III received MPTP + carbidopa + levodopa (100 mg/kg, p.o)
4. Group IV received MPTP + crude extract (250 mg/kg, p.o)
5. Group V received MPTP + crude extract (500 mg/kg, p.o)
6. Group VI received only crude extract (500 mg/kg, p.o)

Experimental analysis

The actions of plant extract on spontaneous locomotor activity were measured automatically using Actophotometer (Medicraft photoactometer, model No: 600-40, S. No: PA-0149, India) (Rabbani *et al.*, 1995). Motor Co-ordination test was conducted using a Rota Rod apparatus (Inco Ambala, India) (Kulkarni, 1987). The elevated plus maze was carried out as described by Pellow *et al.* (1985). Hole board test was done by the standard procedure (Nade and Yadav, 2008). Step down inhibitory avoidance was measured by the procedure given by Dhingra *et al.* 2006. Passive avoidance task (Step Through Latency - STL) was studied by the Tamburella's procedure (Tamburella *et al.*, 2012).

Statistical analysis

Values are expressed as the mean ± S.D. Statistical implication (p) calculated by one way ANOVA followed by Dunnett's. ns- not significant * $P < 0.001$ ** $P < 0.01$ *** $P < 0.05$ calculated by comparing treated group with control group.

RESULTS

Actophotometer

The animals induced with MPTP shows sluggish movement in the Actophotometer. But, when the animals are treated with MPTP and 500 mg of *Oxalis* extract the movements are increased. When the animals are treated only with the alcoholic extract of *Oxalis* show significant increase in movement ($p < 0.001$) when compared to MPTP + standard treated group as shown in Table 1. MPTP + 500 mg/kg *Oxalis* extract shows improvement in movement of the animal when compared with the movement of MPTP induced groups. This may be due to the CNS stimulant property of the drug.

Table 1: Effects of *O. corniculata* ethanol extract in the Actophotometer test and Elevated plus maze test.

Group	Actophotometer (A.F)	Elevated plus maze (A.F) open entries	Elevated plus maze (A.F) Dark entries
Control	79.60 ±12.012	12.00 ±10.040	157.00 ±20.861
Only MPTP	48.80 ±29.201	2.17 ±1.169	140.67 ±15.175
MPTP + Standard	63.00 ±9.772	8.17 ±7.167	156.50 ±12.046
MPTP + Oxalis 250mg/kg	56.20 ±14.516	5.33 ±5.279	142.83 ±13.393
MPTP + Oxalis 500mg/kg	57.80 ±20.813	4.83 ±8.035	146.00 ±14.642
Only Oxalis 500mg/kg	67.33 ±14.306	5.80 ±3.033	158.50 ± 8.871

Table 2: Effects of *O. corniculata* ethanol extract in the Hole Board test and Rota rod test.

Group	Hole board (A.F)	Rota rod apparatus (A.F)
Control	16.43 ±24.186	133.67 ±30.898
Only MPTP	7.29 ±10.935	40.17 ±12.090
MPTP + Standard	12.14 ±16.466	33.00 ±10.119
MPTP + Oxalis 250mg/kg	8.71 ±3.251	43.00 ±13.100
MPTP + Oxalis 500mg/kg	13.50 ±4.416	35.33 ±16.525
Only Oxalis 500mg/kg	14.57 ±18.564	36.50 ±11.502

Table 3: Effects of *O. corniculata* ethanol extract in the Step down test and step through test

Group	Step down (A.F)	Step through (A.F)
Control	1.50 ±0.548	1.67 ±0.516
Only MPTP	1.17 ±0.408	1.17 ±0.408
MPTP + Standard	1.33 ±0.516	1.33 ±0.516
MPTP + Oxalis 250mg/kg	1.17 ±0.408	1.17 ±0.408
MPTP + Oxalis 500mg/kg	1.33 ±0.516	1.33 ±0.516
Only Oxalis 500mg/kg	1.17 ±0.408	1.50 ±0.548

Elevated plus maze

The entries of C57 mice into dark are the normal character. The control group of mice shows more number of dark entries. The MPTP induced mice shows reduction of number of dark entries. But the group treated with MPTP and 500 mg of *Oxalis* extract shows increase in dark entries (146.00 ±14.642). This proves that the nature of normal activity (i.e. entering into the dark area) of the animals is induced when the extract of *Oxalis* is administered. The effects of group and maze experience on plus-maze behavior in male mice are summarized in Table 1.

Hole Board

In the hole board test, the normal, control group of animals show more number of dips into the hole board as an escaping mechanism. The group induced by MPTP shows less number of dips compared to control group. But, when the animals are treated with *Oxalis* 500 mg extract, show great improvement and exhibit more number of dips more than that of MPTP + standard groups. The number of head poking after administration of MPTP + *Oxalis* 500 mg/kg was comparable with the standard drug carbidopa + levodopa (100 mg/kg) and the values are significantly higher compared to the control group (Table: 2). Selected plant extract exhibits significant activity as compared to MPTP + standard.

Rota rod apparatus

A formal test related to beam walking is balancing on a rotating rod, the "rotorod" test. The test consisted of a rotating rod upon which the animal balances. As the animals learn to balance, the rod is turned increasingly faster. The measure of motor skill is

the time the animal spends on the rotorod as a function of speed with which the rod rotates (Le Marec *et al.*, 1997).

The capacity of withstanding in the rotarod apparatus is more in the control group. But, when the animals are induced with MPTP, they fall very easily from the rotarod and the time taken for each fall becomes very minimal. The group treated with MPTP and 250 mg of *Oxalis* extract shows slight improvement. The result from the Rotarod test showed that the extract significantly increased the motor coordination of the tested animals. The data shows that an average the mice treated with 250 and 500 mg/kg of the ethanolic extract of *Oxalis corniculata* were able to maintain equilibrium on the rotating rod and stayed on longer without falling (Table: 2) as compare with MPTP + standard.

Step down

Effect of ethanol extract of *Oxalis corniculata* on memory was observed using step down model in mice. Almost all the groups show similar results only. There is no much difference between the control group or induced group or treated group with *Oxalis*. The results obtained for the MPTP + 500 mg/kg *Oxalis* treated group can improve the long-term retention of a step-down inhibitory avoidance task in mice (Table: 3). MPTP + 500 mg/kg *Oxalis* treated and MPTP + Standard drug exhibits similar activity.

Step through

Step through is a passive avoidance test. It is a simple and rapid test method for memory assessment (Das *et al.*, 2000). In the test-performed animals treated with MPTP exhibited a sharp decline in memory retention and treatment with *O. corniculata* improved the condition and was comparable to control animals.

On the 7th day MPTP administered mice showed significant difference and remarkable decrease in step through transfer latency (1.17 ± 0.408), when compared to control (1.67 ± 0.516) and *O. corniculata* (500 mg/kg) ethanol extract treated mice (1.50 ± 0.548) (Table: 3). Group V and Group VI animals were treated with alcoholic extracts of *O. corniculata* shows restoration of locomotion compared to control group at the significant level.

DISCUSSION

Alcoholic extract of *O. corniculata* was assessed for the neuropharmacological evaluation in MPTP treated mice. Spontaneous motor activity, exploratory behaviour and motor synchronization were decreased in MPTP treated group, it could be due to motor mutilation and muscle relaxant effect. On treatment with alcoholic extract of *O. corniculata* reversed the behavior alterations induced by MPTP on 3rd day, but maximum effect of extract was seen on 6th day of treatment. It might be due to presence of phytoconstituents like L-dopa, polyphenols and flavonoids (Mohanasundari *et al.*, 2006).

Elevated plus maze (EPM) is one of the most important animal behavioral experiments used in evaluation of anxiolytic effect of drugs (Pellow *et al.*, 1985; Pellow and File, 1986). Moreover, it is known that anxiolytic agents increase the frequency of entries and the time spent in open arms of the EPM (Pellow *et al.*, 1985). Administration of *O. corniculata* extract significantly increased ($p < 0.05$) the percentage of entries and permanence time into open arms, compared with control group. The results of experiment confirmed that on first exposure to the plus maze, male mice exhibit a clear preference for the closed/protected parts of the apparatus. The transfer latency measured and the *Oxalis* treated mice was drastically shorter than on the first day, indicating the ability of the rats to recall the learned aspect in a lesser period of time. The effects of *O. corniculata* seem to be more potent than MPTP group in comparison to experimental groups. The fear due to height induces anxiety in the animals when placed on the EPM. The ultimate manifestation of anxiety and fear in the animals is exhibited by decrease in the motor activity and preference to remain at safer places. Antianxiety agents are expected to increase the motor activity, which is measured by the time spent by the animal in the open arms. The spontaneous decrease in basal activity score implicates the reduced anxiety recorded using Actophotometer. The antianxiety and antidepressant effects may be due to the flavonoid (Vikas *et al.*, 2012) content present in the alcoholic extract of *Oxalis corniculata*. Hole board test indicates that head dipping behaviour is sensitive to changes in the emotional state of the animal and suggested that the expression of an anxiolytic state in animals may be reflected by an increase in head poking behaviour (Takeda *et al.*, 1998). *O. corniculata* extract increased head-dip counts without changing locomotion in the hole-board test. Additionally, *O. corniculata* increased visits numbers to board compared with control group. These results imply that *O. corniculata* has a considerable anxiolytic effect in this paradigm.

The ethanolic extract of *O. corniculata* contains flavanoids, phenolic content as well as terpenoid compounds like β – sitosterol, caemphesterol, etc, which are probably responsible for the actions (Bajracharya, 1979).

The hole board test is useful for modeling anxiety in animals, in this test an anxiolytic-like state may be reflected by an increase in head –dipping behaviors (Takeda *et al.*, 1998). In the present study, results showed that ethanolic extract (500 mg/kg) of *Oxalis corniculata* increased the head dipping corroborating the anxiolytic-like effect previously shown in the light- dark test. The anxiolytic effect of alkaloids (Martinez-Vazquez *et al.*, 2012), flavonoids (Li *et al.*, 2011) and saponins (Wei *et al.*, 2007) has been previously reported and, therefore, suggest that these anxiolytic effects may be due to the above constituents. Most of the anxiolytic agents exert their action by opening of activated GABAchloride channel. It is also reported that many flavonoids were found to be ligands for the GABA-A receptors in the central nervous system (Mohammed, 2014). The above results reveals that the ethanolic extract of *Oxalis corniculata* have satisfactory anxiolytic effect.

Rota rod test a classical animal behaviour test used to evaluate peripheral neuromuscular blockade and the motor coordination (Amos *et al.*, 2001), a deficit in motor coordination would very likely affect performance in the behavioral tests. Rota rod test, the difference in the fall of time from the rotating rod between the vehicle and extract treated groups were taken as an index of muscle relaxation. Plant extract showed significant increase in the locomotory score and fall of time of the mice from the rotating rod.

The investigation of the pharmacology of memory between the 1960s and 1980s involved the analysis of the modulation of memory, namely the drugs, hormones, neurotransmitters and neuromodulators that affect memory consolidation. The studies showed that modulatory substances could influence the basic mechanisms of memory processing (Bär *et al.*, 1982). Memory improving drugs generally work by altering the neurotransmitters in the brain that are involved in the initial learning of a memory or its subsequent reinforcement (Ingole *et al.*, 2008). The present study investigated the effect of *Oxalis corniculata* on memory retention and retrieval using the passive avoidance step down model. The results achieved in this study reveals that different doses of *O. corniculata* improved memory retention and retrieval significantly ($p < 0.05$). Previous studies on memory retention and retrieval indicated that plants contain large amounts of antioxidants which improve memory, for example, various species of *Ocimum* (Dokania *et al.*, 2011; Sarahroodi *et al.*, 2012), Saffron (Abe and Saito, 2000), *Ginkgo biloba* (Rigney *et al.*, 1999), green tea (Wu *et al.*, 2012), *Magnolia officinalis* (Lee *et al.*, 2012), Curcumin (Bishnoi *et al.*, 2008) and *Anacyclus pyrethrn* (Sujith *et al.*, 2012). Memory retention and retrieval enhancement by *O. corniculata* extract could be due to the presence of antioxidants such as flavonoids, cinnamic acid derivatives, coumarins, tocopherols and phenolic acids and their power in scavenge reactive oxygen species.

In view of the above results, it concludes the *O. corniculata* extract in different experimental series enhanced learning and memory performance in mice, probably a result of reduces of oxidative stress by antioxidant defense mechanisms. This effect of *O. corniculata* concerned modulation of cholinergic neurotransmission, and that it may be utilize as a potential agent in treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinsonism and other type of dementia and memory deterioration. There were some significant improvements in motor performance, coordination and spontaneous activity with no significant change in stride length or grooming tendencies. It can be interpreted that these parameters are correlated with dopaminergic markers in the striatum (Tillerson *et al.*, 2002; Tillerson and Miller, 2003).

CONCLUSION

The findings of this study indicate that OC extract attenuates MPTP-induced cognitive and behavioural impairments in mouse model of PD. Regulation of antioxidant defense mechanisms by OC may partly be responsible for its neuroprotective effect in MPTP-induced PD mice.

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