Effect of ethanolic extract of *Coriandrum sativum* L. on tacrine induced orofacial dyskinesia

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The effect of ethanolic extract of *Coriandrum sativum* L. seeds (100, 200 mg/kg) was studied on tacrine induced orofacial dyskinesia. Tacrine (2.5 mg/kg, i.p.) treated animals were observed for vacuous chewing movements (VCM), tongue protrusions (TP) and orofacial bursts (OB) for 1 h followed by observations for locomotor changes and cognitive dysfunction. Sub-chronic administration of *Coriandrum sativum* L. seed extract (E-CS) (100, 200 mg/kg, p.o., for 15 days significantly ($P<0.05$) decreased the tacrine induced VCM, TP and OB; and also significantly ($P<0.05$), increased locomotion and cognition compared to the tacrine treated group. Biochemical analysis revealed that tacrine administration significantly ($P<0.05$) decreased the levels of superoxide dismutase (SOD), Catalase (CAT), glutathione reductase (GSH) levels and also significantly ($P<0.05$) increased lipid peroxidation (LPO) as an index of oxidative stress, whereas sub-chronic administration of E-CS significantly ($P<0.05$) improved the antioxidant enzyme (i.e. SOD, CAT, and GSH) levels and also significantly ($P<0.05$) decreased lipid peroxidation (LPO). The results have demonstrated the protective role of ethanolic extract of *Coriandrum sativum*. L against tacrine induced orofacial dyskinesia.

**Keywords**: Alzheimer’s disease, Anticholinesterase inhibitor, Bradykinesia, Cognitive dysfunction, Coriander, Parkinson disease, Oxidative stress, Vacuous chewing movements.

The anticholinesterase inhibitor, tacrine is used therapeutically to improve memory function in patients with early and late onset Alzheimer’s disease. The drug is associated with extrapyramydal motor side effects in humans. These effects include various parkinsonian symptoms such as bradykinesia, cogwheel rigidity, and tremor. In rats, central muscarinic receptor stimulation produce different orofacial movements, the most common being vacuous jaw movement and purposeless chewing. These are characterized as rapid, vertical deflections of the lower jaw that resemble chewing but are not directed at any stimulus. They share some characteristics with human parkinsonian symptoms.

Muscarinic receptor stimulation in ventrolateral striatum results in excitotoxicity and oxidative stress. Rats with vacuous chewing movements have higher thiobarbituric acid reactive species (TBRS) in striatum, suggesting increased lipid peroxidation and free radical production in these animals. Acute tacrine administration has also been reported to cause decreased activity of antioxidant defense enzymes, superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSH). This data supports the free radical hypothesis of orofacial dyskinesia.

*Coriandrum sativum* L., family Umbelliferae (Apiaceae), is a glabrous, aromatic, herbaceous annual plant. Coriander seeds and/or its fine powder are a popular spice. *C. sativum* L. has been reported to possess potent antioxidant activity has apart from anti-diabetic, anti-mutagenic, sedative-hypnotic, anticonvulsant, diuretic, cholesterol lowering, protective role against lead toxicity, antifungal, anti-feeding, anticancer, anxiolytic, hepatoprotective, anti protozoal, anti-ulcer, post-coital anti-fertility, neuroprotective, heavy metal detoxification, and antihelmenthic activities. Phytochemical studies have revealed the presence of flavonoids (quercetin 3-glucoronide), linalool, camphor, geranylacetate, geraniol, isocoumarins, coumarins and coriandrones. Caffeic acid, protocatechic acid, and glycitin were characterized as major polyphenolics of coriander. The flavonoid content of the seeds was reported to be 12.6 quercetin equivalents/g and the polyphenolic content was reported to be 12.2 gallic acid equivalents/g.

In view of its rich antioxidant properties, the seed extract of *C. sativum* can be used as a prophylactic to

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overcome the oxidative stress damage leading to parkinsonian symptoms. There is no major investigative report available pertaining to the antiparkinsonian effect of *C. sativum*. Therefore, in the present study, we explored the effect of *Coriandrum sativum* in tacrine induced orofacial dyskinesia.

**Materials and Methods**

**Animals**—Male Wistar rats weighing 200 ± 20 g were purchased from Mahaveer Enterprises, Hyderabad, India and housed in colony cages and maintained at 25 °C ± 1.2 °C, 12:12 L:D cycle and 50% RH with free access to food and water *ad libitum*. Animals were acclimatized to laboratory conditions before test. All the experiments were carried out during the light period (9:00-17:00 h). The Institutional Ethical Committee approved the protocol of the study.

**Chemicals**—Tacrine was obtained from Sigma, Aldrich, Mumbai. All other chemicals and reagents used were of analytical grade and purchased from standard manufacturers.

**Plant material and extraction**—Dry seeds of *Coriandrum sativum* were purchased locally and got authenticated by the Department of Pharmacognosy, Priyadarshini College of Pharmaceutical Sciences (PDCPS), Hyderabad. The collected material was defatted with petroleum ether (60-80 °C). The marc was dried and extracted with ethanol using hot percolation method by Soxhlet’s extractor. The extract was filtered and dried. The yield of ethanolic extract was found to be 4.8% w/w. The ethanolic extract of *C. sativum* seeds (E-CS) was subjected to phytochemical analysis following Evans (2005)32.

**Treatment**—Twenty male Wistar rats were randomly divided into 4 groups of 5 animals each. Group I received vehicle (Distilled Water: PEG in 1:1 ratio) and served as control group. Group II received Tacrine (2.5 mg/kg, i.p.). Group III received E-CS (100 mg/kg, p.o.) for 15 days and Tacrine (2.5 mg/kg, i.p.) on day-15 after one hour of administration of the extract. Group IV received E-CS (200 mg/kg, p.o.) for 15 days and Tacrine (2.5 mg/kg, i.p.) on day 15 after one hour of administration of the extract33.

**Behavioral assessments**—Immediately after tacrine administration the rats were placed in a plexiglass observation cage (22×22×22 cm³). After 10 min of habituation period the animal was observed for 1 h and the number of vacuous chewing movements (VCM), tongue protrusions (TP), and orofacial bursts (OB) were carefully recorded. VCMs and tongue protrusions were defined as a single mouth opening in the vertical direction not directed towards any physical material and visible extension of tongue outside of mouth respectively. The observations during grooming period were not taken into account. The effect on locomotion was evaluated using the open field apparatus and actophotometer34. The total no. of squares traversed and number of rearing in the open field apparatus were counted for 5 min. The actophotometer counts were recorded for 5 min.

Cognitive behavior was assessed using the elevated plus maze learning task. Transfer latency, the time taken by the animal to move from the open arm to the centre was utilized as an index of learning memory process. Animals were placed individually at open arm and the transfer latency was noted35.

**Biochemical assessments**—The animals were sacrificed after behavioral assessments, the brain was isolated, and the fore brain was dissected out and rinsed with ice cold isotonic saline and weighed. A 10% (w/v) tissue homogenate was prepared in phosphate buffer (pH-7.4). The homogenate was centrifuged at 10000 rpm for 20 min and supernatant was used for estimation of antioxidant enzyme levels. The supernatant was used for determination of SOD36, CAT37, GSH38 levels and the extent of LPO39. UV-Vis Spectrophotometer (ELICO, SL-159) was used for the assessment of SOD, CAT, GSH and LPO.

**Statistical analysis**—The mean ± SEM values were calculated for each group. One-way ANOVA followed by Dunnett’s multiple comparison tests were used for statistical analysis. Values of *P* <0.05 were considered statistically significant.

**Results**

**Phytochemical analysis**—The phytochemical analysis of ethanolic extract of *Coriandrum sativum* showed the presence of flavonoids, alkaloids, tannins, saponins, steroids and glycosides (Data not shown).

**Behavioural assessments**—Administration of Tacrine (2.5 mg/kg, i.p.) significantly (*P* <0.05) induced vacuous chewing movements (VCM), tongue protrusions (TP) and orofacial bursts (OB) in rats. Prophylactic treatment with E-CS (100, 200 mg/kg) for a period of 15 days significantly (*P* <0.05) and dose dependently decreased the tacrine induced VCMs, TPs and OBs (Fig. 1). Tacrine administration significantly (*P* <0.05) decreased the locomotor
activity, E-CS (100, 200 mg/kg) attenuated the tacrine induced hypolocomotion and restored the locomotor activity significantly (P <0.05) (Fig. 2a and 2b). Tacrine significantly (P <0.05) increased the transfer latency on elevated plus maze. The E-CS (100, 200 mg/kg) decreased transfer latency significantly (P <0.05) in tacrine treated animals (Fig. 2c).

**Biochemical assessments**—The tacrine treated animals showed a significant (P <0.05) increase in the levels of lipid peroxidation (LPO), and a significant (P <0.05) decrease in the levels of antioxidant enzymes such as SOD, CAT & GSH suggesting exaggerated free radicals generation. Treatment with E-CS (100, 200 mg/kg) dose dependently and significantly (P <0.05) raised the levels of GSH, SOD & CAT, and significantly (P <0.05) decreased the levels of LPO suggesting its antioxidant potential (Fig. 3).

**Discussion**

It has been suggested that vacuous jaw movements could represent a rat model of parkinsonian tremor. Cholinomimetics (Tacrine) induces orofacial movements in rats. The predicted mechanisms involved are excitotoxicity and oxidative stress. Tacrine results in increased levels of ACh in the ventrolateral striatum leading to increased muscarinic receptor stimulation. This results in manipulation of GABA and glutamate transmission which may lead to excitotoxicity. It has also been reported that increased turnover of monoamines results in its

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**Fig. 1**—Effect of ethanolic extract of *C. sativum* L. (100, 200 mg/kg, p.o.) on tacrine induced orofacial movements. [n=5. Data represented as mean±SEM. (one way ANOVA followed by Dunnett’s test) *P <0.05 compared to vehicle treated group. #P <0.05 compared to tacrine group. VCM, Vacuous chewing movement; TP, tongue protrusion; OB, orofacial bursts; E-CS, ethanolic extract of *C. sativum* L. 1= Vehicle, 2= Tacrine (2.5), 3= E-CS (100) and 4= E-CS (200)]

**Fig. 2**—Effect of ethanolic extract of *C. sativum* L. (100, 200 mg/kg, p.o.) (a) on tacrine induced locomotor dysfunction assessed using actophotometer; (b) assessed using open field apparatus; (c) on cognitive dysfunction assessed using transfer latency on the elevated plus maze. [n=5. Data represented as mean±SEM. (one way ANOVA followed by Dunnett’s test) *P <0.05 compared to vehicle treated group. #P <0.05 compared to tacrine group. E-CS, ethanolic extract of *C. sativum* L.; SOD, superoxide dismutase; CAT-catalase; GSH, glutathione reductase; LPO, lipid peroxidation. 1= Vehicle, 2= Tacrine (2.5), 3= E-CS (100) and 4= E-CS (200)]

**Fig. 3**—Effect of ethanolic extract of *C. sativum* L. (100, 200 mg/kg, po) on biochemical alterations in tacrine treated rats. [n=5. Data represented as mean±SEM. (one way ANOVA followed by Dunnett’s test) *P <0.05 compared to vehicle treated group. #P <0.05 compared to tacrine group. E-CS, ethanolic extract of *C. sativum* L.; SOD, superoxide dismutase; CAT-catalase; GSH, glutathione reductase; LPO, lipid peroxidation. 1= Vehicle, 2= Tacrine (2.5), 3= E-CS (100) and 4= E-CS (200)]
oxidative metabolism during this hyper activation implying excessive free radical generation and, thus oxidative stress leading to neurochemical alterations manifested as orofacial dyskinesia and other parkinsonian symptoms. The neurons in the substantia nigra are hyperactive during tremulous jaw movements and that GABA-induced inhibition of substantia nigra reverses both the neuronal hyperactivity and jaw movements.\(^\text{41,42}\) In the present study, the E-CS (100, 200 mg/kg) has protected mice from PTZ induced convulsions in a dose dependent manner (data not shown) which is in corroboration with the above statement. Tacrine significantly (\(P < 0.05\)) induced orofacial dyskinesia, locomotor and cognitive dysfunction in rats. The E-CS (100, 200 mg/kg) significantly inhibited these changes. Tacrine treated animals showed increased levels of lipid peroxidation and also exhibited low levels of detoxifying enzymes such as SOD, CAT and GSH supporting the free radical hypothesis. The E-CS (100, 200 mg/kg) attenuated this increased levels of lipid peroxidation and decreased levels of antioxidant defensive enzymes.

Earlier reports on neuroprotective effect\(^\text{25}\) of Coriandrum sativum seeds in an oxidative stress model of ischemic reperfusion insult in brain have corroborated with our findings on changes in the antioxidant status, enabling to overcome the oxidative stress. The antioxidant properties of the extract were attributed to its polyphenolic constituents. The observed beneficial effects of the E-CS (100, 200 mg/kg) in tacrine induced behavioral and biochemical changes may be attributed to its diversified chemical constituents. The other possible mechanism of neuroprotection could be attributed to modulation of neurotransmitters.

The E-CS significantly (\(P < 0.05\)) attenuated tacrine induced orofacial dyskinesia, locomotor, cognitive dysfunctions. The seed extract (100, 200 mg/kg) dose dependently protected the tacrine treated rats against the increase in LPO, decrease in GSH, CAT and SOD levels. These results support the oxidative stress hypothesis of orofacial dyskinesia and proved the beneficial role of the E-CS in the treatment of drug induced parkinsonian symptoms and cognitive dysfunction.

References


