MEMORY-ENHANCING ACTIVITY
OF CORIANDRUM SATIVUM IN RATS

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Summary

Coriandrum sativum L., commonly known as coriander belonging to the family Apiaceae (Umbelliferae) is cultivated throughout India for its nutritional value. The fresh leaves of Coriandrum sativum (CSL) are routinely added for the delicious taste and flavor, they import to various vegetarian dishes in India. The pharmacological studies have been proved that the presence of hypolipidemic, antioxidant and anti-inflammatory activity in Coriandrum sativum leaves. In light of the above, the current study was undertaken to investigate the effects of Coriandrum sativum fresh leaves on cognitive functions in rats. Coriandrum sativum leaves (5, 10 & 15 % w/w) were fed orally along with a specially prepared diet for 45 days consecutively to male Wistar rats. Elevated plus-maze and Hebb-Williams maze served as the exteroceptive behavioral models for testing memory. Diazepam-, scopolamine-, and ageing-induced amnesia served as the interoceptive behavioral models. CSL (5, 10 & 15 % W/W of diet) produced a dose-dependent improvement in memory scores of young as well as aged rats. CSL also reversed successfully the memory deficits induced by scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.). Cholesterol-lowering, anti-inflammatory and antioxidant properties of CSL may favorably contribute to its memory-enhancement effect. Therefore, Coriandrum sativum leaves appears to be a promising candidate for improving memory, and it would be worthwhile to explore the potential of this plant in the management of Alzheimer patients.

Keywords: Coriandrum sativum, amnesia, elevated plus-maze, Hebb-Williams maze, memory.

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Introduction

Dementia is characterized by a progressive decline in cognitive function depending on neurodegeneration, which particularly affects elder population in their daily activities such as memory, speaking and population dissolving. The most well known type of dementia is Alzheimer’s disease (AD), which proceeds at stages from mild and moderate to severe and gradually destroys the brain (1). A community based study showed that the prevalence of AD is 3% for persons 65-74 years old, 18.7% for those 75-84 years old, and 47.2% for those over 85 years old. It is the fourth or fifth leading cause of death in developed countries. With the aging of society, it has been estimated that approximately 9 million individuals could develop AD by the year 2040 (2). AD is a genetically heterogeneous, crippling neurodegenerative disorder, which is slow in onset but relentless in progress (3). The major symptoms of AD include dementia, aphasia, apraxia,agnosia, dyslexia and agraphia. Excessive deposits of extra cellular β-amyloid (Aβ) plaques, intraneuronal fibrillary tangles and neuronal loss in certain brain areas constitute the three major hallmarks of Alzheimer’s disease (4). Furthermore, brain aging is know to be related to excessive neuronal loss, decrease in acetylcholine level, increase in neuronal inflammation and oxidative stress (5). Since the allopathic system of medicine is yet to provide a radical cure for AD, it is worthwhile to look for new directions, which would minimize the memory loss of patients with neuropsychiatric disorders. The utility of traditional medicines may be explored for treating patients with dementia.

Coriandrum sativum L., commonly known as coriander belonging to the family Apiaceae (Umbelliferae) is cultivated throughout India for its nutritional value. The fresh leaves of Coriandrum sativum are routinely added for the delicious taste and flavor, they import to various vegetarian dishes in India. The leaves contain proteins, traces of fats, minerals (like calcium, phosphorus, and iron), carotene, fiber and carbohydrates. The coriander leaves stimulate the appetite and the fresh juice is recommended for patients suffering from Vitamin A, B and C deficiencies and also for the relief of anxiety and insomnia (6,7). Coriander fruit is also reputed as refrigerant, tonic, diuretic and aphrodisiac, while the oil is considered useful in flatulent colic, rheumatism, neuralgia, etc. (8). Coriander is also used as antiedemic, anti-inflammatory, antiseptic, emmenagogue, antidiabetic, antihypertensive, lipolytic and myorelaxant, and possess nerve-soothing property (9). Pharmacological studies have demonstrated the hypoglycemic (10), hypolipidemic (11-13), antimutagenic (14), antihypertensive (15), antioxidant (16-18), anxiolytic (19), antimicrobial (20,21), and post-coital antifertility (22) activity of Coriandrum sativum. It has also been used in heavy metal detoxification (23). In the light of this, the present study was undertaken to investigate the influence of fresh leaves of Coriandrum sativum on memory of rats.
Materials and Methods

Plant Material
The fresh leaves of *Coriandrum sativum* were obtained from local market of Hisar, Haryana (India), and taxonomically identified by Dr. H.B. Singh, The Head, Raw Materials, Herbarium and Museum division, National Institute of Science Communication and Information Resources (NISCAIR), New Delhi, India. A voucher specimen (GJU/PHARM/10) has been preserved at Pharmacology Division of Department of Pharmaceutical Sciences, G.J. University of Science and Technology, Hisar, India for ready reference. These fresh leaves were cut into fine pieces with the help of a sharp knife and were mixed in varying concentrations (5, 10 and 15 % w/w) in normal animal diet. This special diet containing CSL was fed to rats for 45 days.

Animals
Young (3 - 4 months old) rats weighing around 150 g and aged (12 – 15 months old) rats weighing around 250 g were used in the present study. All animals were procured from the disease-free small animal house of CCS Haryana Agricultural University, Hisar (Haryana), India, were maintained under standard environmental conditions. The normal diet given to rat consisted of wheat flour kneaded with water and mixed with a small amount of refined vegetable oil. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and the care of laboratory animals was taken as per the guidance of CPCSEA, Ministry of Forests and Environment, Government of India (registration number 0436).

Chemicals
The drugs used in this study were obtained from following drug houses. Scopolamine hydrobromide (Sigma-Aldrich, USA), diazepam injection (Calmpose®, Ranbaxy, India) and piracetam (UCB India Ltd., India).

Drug treatment
In the present investigation, the rats were divided into different groups (n = 6) for investigations using various interoceptive as well as exteroceptive memory models. The daily diet doses (5, 10 & 15 % w/w) of CSL were fed to young and aged rats of different groups for 45 days. These rats were exposed to the training session using elevated plus maze or Hebb-Williams maze on the 45th day 90 min after the last feed. Retention (memory) of the learned task was recorded after 24 h i.e. on 46th day. Amnesia was induced in separate groups (interoceptive model) of young rats by scopolamine (0.4 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) on 45th day after 90 min of the last feed. The animals were exposed to the training session (on 45th day) after 45 min of scopolamine or diazepam injection. The retention (memory) was measured after 24 h (on 46th day). Piracetam (400 mg/kg, i.p.), an established nootropic agent was injected for seven days to
positive control groups of animals. The control group animals were fed with normal diet of wheat flour (3 g/animal/day) for 45 days.

**Elevated plus-maze**

Elevated plus-maze served as the exteroceptive behavioral model to evaluate memory in rats. The procedure, technique and end point for testing memory was followed as per the parameters described by the investigators working in the area of psychopharmacology (24-26). The elevated plus maze apparatus for rats consisted of a central platform (10 cm²) connected to two open arms (50 cm × 10 cm) and two covered (enclosed) arms (50 cm × 40 cm × 10 cm) and the maze was elevated to a height of 50 cm from the floor (27). On the first day (i.e. 45th day of drug treatment), each rat was placed at the end of an open arm, facing away from the central platform. Transfer latency (TL) was defined as the time (in s) taken by the animal to move from the open arm into any one of the covered arms with all its four legs. TL was recorded on the first day (training session) for each animal. The rat was allowed to explore the maze for another 2 min and then returned to its home cage. Retention of this learned-task (memory) was examined 24 h after the first day trial (i.e. 46th day, 24 h after last dose). Significant reduction in TL value of retention indicated improvement in memory.

**Hebb-Williams maze**

Hebb-Williams maze is an incentive based exteroceptive behavioural model useful for measuring spatial working memory of rats (27). It consists of mainly three components. Animal chamber (or start box), which is attached to the middle chamber (or exploratory area) and a reward chamber at the other end of the maze in which the reward (food) is kept. All the three components are provided with guillotine removable doors. On the first day (i.e. 45th day of drug treatment), the rat was placed in the animal chamber or start box and the door was opened to facilitate the entry of the animal into the next chamber. The door of start box was closed immediately after the animal moved into the next chamber so as to prevent back entry. Time taken by the animal to reach reward chamber (TRC) from start box was recorded on first day (training session) for each animal. Each animal was allowed to explore the maze for 3 min with all the doors opened before returning to its home cage. Retention of this learned task (memory) was examined 24 h after the first day trial (i.e. 46th day, 24 h after last dose) (26).

**Statistical analysis**

All the results were expressed as Mean ± Standard Error (S.E.M.). Data was analyzed using one-way ANOVA followed by Dunnett’s t-test and student’s unpaired t-test. P-values < 0.05 were considered as statistically significant.
Results

Effect on transfer latency using elevated plus-maze

The young ($P<0.05$) and aged ($P<0.001$) rats fed with CSL (5, 10 & 15 % w/w of diet) showed dose-dependent reduction in TL of 46th day, indicating significant improvement of memory (Fig.1). Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) injected before training significantly increased ($P<0.001$) TL indicating impairment in memory (Fig.2). The CSL (5, 10 & 15% w/w of diet) successfully reversed memory deficits induced by scopolamine and diazepam. Piracetam (used as the positive control) at a dose of 400 mg/kg, i.p. also improved memory ($P<0.001$) in both young and aged rats and reversed the amnesia induced by scopolamine and diazepam.

Fig.1: Effect of various concentrations of Coriandrum sativum leaves (CSL 5, 10 & 15% w/w of diet) on transfer latency of young (3-4 months) and aged (12-15 months) rats using elevated plus maze. Piracetam (400 mg/kg, i.p.) was used as a positive control. Values are in mean ± SEM. (n=6); ***$P<0.05$ as compared to control group of young rats. ****$P<0.001$ as compared to control group of young rats. (One-way ANOVA followed by Dunnett’s t-test and student’s unpaired t-test)
Fig. 2: Reversal of scopolamine (0.4 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) induced amnesia by Coriandrum sativum leaves (CSL 5, 10 & 15% w/w of diet) in young rats using elevated plus maze. Piracetam (Pira) 400 mg/kg, i.p. was used as a positive control. Values are in mean ± SEM. (n=6); ** ** ** P<0.001 as compared to control group of young rats. �� P<0.01 as compared to scopolamine (Sco) alone. ��� P<0.001 as compared to scopolamine (Sco) alone. ��� P<0.01 as compared to diazepam (Dia) alone. ��� P<0.001 as compared to diazepam (Dia) alone. (One-way ANOVA followed by Dunnett’s t-test and student’s unpaired t-test)

Effect on time taken to reach reward chamber (TRC) using Hebb-Williams maze

CSL (5, 10 & 15% w/w of diet) administered orally in young and aged rats for 45 days markedly reduced (P<0.01) TRC as compared to the respective control groups (Fig.3). Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) significantly increased (P<0.001) TRC as compared to control group of young rats, indicating impairment of memory (amnesia). CSL administered for seven days reversed the amnesia induced by both scopolamine and diazepam (Fig.4). The groups of rats, which were treated with piracetam (400 mg/kg, i.p.) for seven successive days showed improvement (P<0.001) in memory of young as well as aged rats. Piracetam also reversed amnesia induced by scopolamine and diazepam.
**Fig.3:** Effect of various concentrations of *Coriandrum sativum* leaves (CSL 5, 10 & 15% w/w of diet) on transfer latency of young (3-4 months) and aged (12-15 months) rats using Hebb-Williams maze. Piracetam (400 mg/kg, *i.p.*) was used as a positive control. Values are in mean ± SEM. (n=6)

- **★★** *P*<0.01 as compared to control group of young rats.
- **★★★★** *P*<0.001 as compared to control group of young rats.
- **★★** *P*<0.01 as compared to control group of aged rats.
- **★★★★** denotes *P*<0.001 as compared to control group of aged rats.

(One-way ANOVA followed by Dunnett’s t-test and student’s unpaired t-test)
Fig. 4: Reversal of scopolamine (0.4 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) induced amnesia by Coriandrum sativum leaves (CSL 5, 10 & 15% w/w of diet) in young rats using Hebb-Williams maze. Piracetam (Pira) 400 mg/kg, i.p. was used as a positive control.

Values are in mean ± SEM. (n=6)

★★★★ P<0.001 as compared to control group of young rats.

● P<0.05 as compared to scopolamine (Sco) alone.

★★★ P<0.001 as compared to scopolamine (Sco) alone.

■ ■ P<0.01 as compared to diazepam (Dia) alone.

★★★★ P<0.001 as compared to diazepam (Dia) alone.

(One-way ANOVA followed by Dunnett’s t-test and student’s unpaired t-test)

Discussion

Memory is the ability of an individual to record sensory stimuli, events, information, etc., retain them over short or long periods of time and recall the same at a later date when needed. Poor memory, lower retention and slow recall are common problems in today’s stressful and competitive world.
Age, stress, emotions are conditions that may lead to memory loss, amnesia, anxiety, high blood pressure, dementia, to more ominous threats like schizophrenia and Alzheimer’s disease (28-30). Alzheimer’s disease (AD) is a progressive, neurodegenerative, debilitating disorder manifested by loss of memory, impaired judgment, irritability, agnosia, restlessness, aphasia and apraxia (31). There are around 35 million patients suffering from Alzheimer’s disease all over the world, out of which United States of America alone has around 4.5 million patients (32). Presently, the Allopathic system of medicine principally relies on nootropic agents such as piracetam, aniracetam, fosracetam, nefiracetam etc., and anticholinesterases such as tacarine, donepezil, metrifonate and rivastigmine (33-37). Despite the severity and high prevalence of this disease, Allopathic system of medicine is yet to provide a satisfactory remedy. Therefore, neurobiologists all over the world are looking for new directions and alternative strategies for managing this disease of senior citizens. In India AD patients are estimated to be less than 3.5 million (38), a figure that is considerably smaller than that of USA. There is the idea that certain nutrients of the Indian dishes may be responsible for the protection of the population against AD. In the present study, the potential of Coriandrum sativum leaves fed along with normal diets for 45 days on improving the memory of the rats was investigated.

Rats readily accepted the specially prepared diet containing CSL. The results showed a dose-dependent (5-15% w/w) diminished TL and enhanced TRC values similar to piracetam (400 mg/kg). Furthermore, pre-treatment with CSL for 45 days, similar to piracetam, protected the animals from memory deficits produced by scopolamine and diazepam. These findings suggest possible neuroprotective role for Coriandrum sativum. It seems likely that Coriandrum sativum may prove to be a useful anti-Alzheimer agent, in view of its presently demonstrated memory enhancing property.

Oxygen free-radicals are implicated in the process of age-related decline in cognitive performance and may be responsible for the development of Alzheimer’s disease in elderly persons (39-43). Oxygen-free radicals and other byproducts of oxidative metabolism have been shown to be neurotoxic and antioxidant rich diets improved cerebellar physiology and motor learning in aged-rats (44-46). Antioxidant compounds have been reported present in CSL and their volatile oils may be favorably contributing to the memory enhancing effect seen in the present study (47-48). Thus, the protective effect of CSL may be attributed to its antioxidant property by virtue of which susceptible brain cells get exposed to less oxidative stress resulting in reduced brain damage and improved neuronal function.

Immunohistochemical studies suggested that existence of chronic inflammation in certain regions of the brain in Alzheimer’s disease patients. Since inflammation can be damaging to host tissue, it was hypothesized that anti-inflammatory drugs might be inhibiting both the onset and the progression of Alzheimer’s disease.
This hypothesis is supported by the observation that indomethacin (NSAID) halted the progressive memory loss seen in Alzheimer’s disease patients. Moreover, it has also been observed that elderly patients suffering from Alzheimer’s disease showed reduction in symptoms of Alzheimer’s disease upon chronic use of anti-inflammatory drugs (49). Indomethacin, a non-steroidal anti-inflammatory drug exhibited a memory protective effect against electroconvulsive shock-induced retrograde amnesia and also against amyloid deposits in the brain (50,51). Anti-inflammatory action of compounds like ascorbic acid, cineole, berneol, alpha-pinene and beta-pinene are present in Coriandrum sativum leaves (9) might also be contributing to the observed memory-enhancing activity of CSL in the present study.

Recently, several reports are pouring in showing a strong link between high cholesterol levels and high incidence of Alzheimer’s disease (52). Therefore, a new therapeutic strategy aimed at reducing blood cholesterol levels is gathering momentum for the management of Alzheimer’s disease. The main histological features of AD include extracellular protein deposits termed as β-amyloid (Aβ) plaques, Aβ deposits in blood vessels and intraneuronal neurofibrillary tangles. Abnormal accumulation of cholesterol levels increase Aβ in cellular and most animal models of AD; and drugs that inhibit cholesterol synthesis lower Aβ in these models (52,53). Clinical studies suggested that the net brain cholesterol concentration is regulated by serum cholesterol level and that there is a cross-talk between the CNS and peripheral cholesterol pools (54). Therefore, it is plausible that peripheral cholesterol levels modulate CNS cholesterol levels and vice versa. Epidemiological studies revealed that individuals with high peripheral cholesterol levels show more susceptibility to AD, and that the incidence of AD is higher in countries with high-fat and high-calorie diets (55). Coriandrum sativum leaves have been reported to possess hypolipidemic activity in animals (11-13). Therefore, a combination of cholesterol-lowering, anti-inflammatory, antioxidant and neuroprotective role could all be leading to the net memory-enhancing effect of CSL.

References