

## *Coriandrum sativum*: evaluation of its anxiolytic effect in the elevated plus-maze

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### Abstract

The clinical applications of benzodiazepines as anxiolytics are limited by their unwanted side effects. Therefore, the development of new pharmacological agents is well justified. Among medicinal plants, *Coriandrum sativum* L. has been recommended for relief of anxiety and insomnia in Iranian folk medicine. Nevertheless, no pharmacological studies have thus far evaluated its effects on central nervous system. Therefore, the aim of this study was to examine if the aqueous extract of *Coriandrum sativum* seed has anxiolytic effect in mice. Additionally, its effect on spontaneous activity and neuromuscular coordination were evaluated. The anxiolytic effect of aqueous extract (10, 25, 50, 100 mg/kg, i.p.) was examined in male albino mice using elevated plus-maze as an animal model of anxiety. The effects of the extract on spontaneous activity and neuromuscular coordination were assessed using Animex Activity Meter and rotarod, respectively. In the elevated plus-maze, aqueous extract at 100 mg/kg showed an anxiolytic effect by increasing the time spent on open arms and the percentage of open arm entries, compared to control group. Aqueous extract at 50, 100 and 500 mg/kg significantly reduced spontaneous activity and neuromuscular coordination, compared to control group. These results suggest that the aqueous extract of *Coriandrum sativum* seed has anxiolytic effect and may have potential sedative and muscle relaxant effects.

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**Keywords:** *Coriandrum sativum*; Anxiolytic; Elevated plus-maze; Spontaneous activity; Neuromuscular coordination

### 1. Introduction

Anxiety disorders in a modern society have a relatively high prevalence and command considerable financial resources. Currently, the most widely prescribed medications for anxiety disorders are the benzodiazepines. However, the clinical uses of benzodiazepines are limited by their side effects such as psychomotor impairment, potentiation of other central depressant drugs and dependence liability. Therefore, the development of new medications possessing anxiolytic effect without the complications of benzodiazepines would be of great importance in the treatment of anxiety-related disorders. Medicinal plants are a good source to find new remedies for these disorders.

In Iranian traditional medicine, *Coriandrum sativum* L. (Umbelliferae) has been indicated for a number of medical problems such as dyspeptic complaints, loss of appetite, convulsion, insomnia and anxiety (Zargari, 1991; Mir Heidar, 1992). For the medical purposes, coriander seed is empirically used in different dosage forms, including powdered seeds or dry extract (2–5 g/day), tea (4–8 g/100 ml; up to 30 g), tincture (1:8 g/ml) (10–20 drops), decoction or infusion (Zargari, 1991; Mir Heidar, 1992). The juice of fresh leaves (30 g) and tea, or powdered seeds of coriander have been recommended for the relief of anxiety and insomnia (Mir Heidar, 1992), taken usually as a single dose before sleeping. Similar uses of coriander seed (i.e. for relief of nervousness and insomnia) have been indicated in other folk medicines as well (Duke, 1983, 2002). However, no pharmacological or medical studies have evaluated the effects of *Coriandrum sativum* L. (coriander) on central nervous system. Therefore, the present study was undertaken to see if the

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aqueous extract of coriander seed has any anxiolytic effect in mice. Additionally, the possible effects of the coriander extract on spontaneous activity and motor coordination were evaluated.

## 2. Materials and methods

### 2.1. Animals

Male albino mice weighting 25–35 g were purchased from the Animals House, Shiraz University of Medical Sciences. Mice were housed in cages of 5 at  $22 \pm 1^\circ\text{C}$  in a 12-h light/dark cycle. Tap water and food pellets were available as libitum. Groups of 6–11 mice were randomly assigned to different treatment groups and tested in a counterbalancing order. Animals were naive to experiment conditions. All experiments were carried out in a quiet room under dim red light between 9:00 a.m. and 2:00 p.m.

### 2.2. Plant material

Dried seeds of coriander were purchased from a commercial source in Shiraz, Iran. The identity of the seeds was confirmed by the Department of Pharmacognosy, Tehran University of Medical Sciences, Pharmacy School, Tehran, Iran. A voucher specimen (C-100) was kept in our laboratory for future reference.

### 2.3. Preparation of aqueous extract

Dried coriander seeds were homogenized to a fine powder. Hundred grams of powdered coriander was infused in 500 ml cold distilled water for 24 h, brought to the boil, then removed from the heat source and allowed to infuse for 15 min. The extract was filtered, then concentrated over the water bath and brought to dryness under vacuum. The yield of the extract was 7.9% (w/w).

### 2.4. Drugs

Diazepam hydrochloride (10 mg/2 ml; Darou Pakhsh, Tehran, Iran) was used as a reference drug. It was diluted to 0.3 and 3 mg/10 ml with saline before use. Different concentrations of the coriander extract were prepared by serial dilution from a stock solution of 50mg/ml of the extract in saline. All solutions were prepared freshly on test days and administered intraperitoneally (i.p.) in a volume of 0.1ml/10 g body weight of mice.

### 2.5. Elevated plus-maze model of anxiety

Anxiolytic activity was measured using the elevated plus-maze test (Lister, 1987). The maze consisted of two open ( $30\text{ cm} \times 5\text{ cm} \times 0.2\text{ cm}$ ) and two closed ( $30\text{ cm} \times 5\text{ cm}$

$\times 15\text{ cm}$ ) arms, extending from a central platform ( $5\text{ cm} \times 5\text{ cm}$ ) and elevated to a height of 45 cm above the floor. The entire maze was made of clear Plexiglas. Mice were individually placed on the center of the maze facing an open arm, and the number of entries and the time spent in closed and open arms were recorded during a 5-min observation period. Arm entries were defined as entry of all four paws into an arm. The percentage of open arm entries ( $100 \times \text{open}/\text{total entries}$ ) was calculated for each animal. The experimental animals were intraperitoneally treated with diazepam (0.3 mg/kg,  $n = 10$ ) or the aqueous extract (10, 25, 50 or 100 mg/kg,  $n = 6$ –10), 30 min and 45 min, respectively, before evaluation in the maze. The coriander extract at doses higher than 100 mg/kg caused a marked decrease in motor activity that interfered with an accurate evaluation of anxiolytic effect. Therefore, higher doses of the extract were not included in the plus-maze test.

### 2.6. Spontaneous activity

Activity of individual mice was recorded using Animex Activity Meter (AB FARAD model, Sweden). Activity counts were cumulated 20 min after administration of saline (i.p.,  $n = 11$ ), diazepam (3 mg/kg, i.p.;  $n = 7$ ) or the coriander extract (10, 50, 100 or 500 mg/kg, i.p.;  $n = 7$ ) at 5-min intervals for 30 min.

### 2.7. Neuromuscular coordination – Rotarod

The effect of the coriander extract on coordinated motor movements was assessed using the rotarod test. A day before the test, mice were trained to stay on the rotating wheel (3 cm in diameter, 20 rpm) for more than 1 min. On the test day, mice were tested on the rotarod (model 7600, UGO Basile, Italy) before and 50 min after the administration of saline, diazepam or the aqueous extract of coriander seed (i.e. immediately after the activity test). The number of seconds each mouse remained on the rotating wheel was recorded for a maximum of 300 s.

### 2.8. Statistics

Data from evaluation of the coriander extract in the elevated plus-maze test were statistically analyzed using one-way ANOVA. Independent *t*-test was used for the comparison of means between saline-treated group and diazepam in the elevated plus-maze. Spontaneous activities were evaluated using an analysis of variance for repeated measures (between-subject factor: treatment; within-subject factor: postdosing time). Data from the rotarod were evaluated using univariate analysis of variance with time spent on the rotarod before injection as covariate. Post hoc comparisons between individual groups were performed using Dunnett *t* test. Statistical analyses were performed using SPSS 10.0 software.  $P < 0.05$  was considered as a significant level.

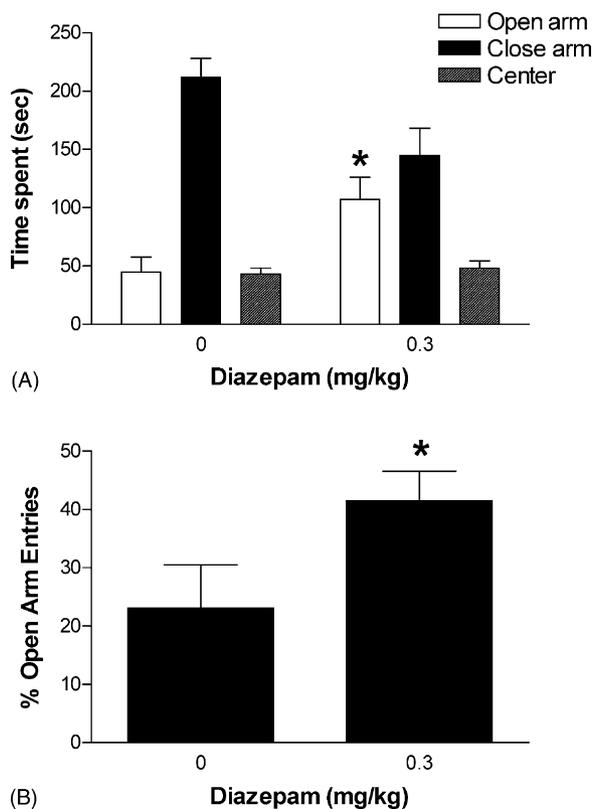


Fig. 1. The effect of diazepam (0, 0.3 mg/kg; i.p.;  $n = 10$ ) on the time spent on the open and close arms (A) and on the percentage of open arm entries (B) during a 5-min test on the elevated plus-maze in mice. Bars represents mean  $\pm$  S.E.M. \* $P < 0.05$  compared to control group.

### 3. Results

#### 3.1. Elevated plus-maze

Independent *t*-test revealed that administration of diazepam (0.3 mg/kg) significantly increased the amount of time spent in the open arms and the percentage of open arm entries ( $P < 0.05$ ), compared to saline-treated group (Fig. 1). The aqueous extract of coriander seed at 100 mg/kg significantly increased both the time spent in the open arms ( $F_{(4,39)} = 3.5$ ,  $P < 0.05$ ) and the percentage of open arm entries ( $F_{(4,39)} = 2.7$ ,  $P < 0.05$ ), compared to saline-treated group (Fig. 2). There were no significant differences between the coriander extract and saline-treated groups for the number of close arm entries ( $F_{(4,39)} = 1.8$ ,  $P > 0.05$ ) and total entries ( $F_{(4,39)} = 0.9$ ,  $P > 0.05$ ).

#### 3.2. Spontaneous activity

Repeated measures ANOVA showed a significant effect of treatment ( $F_{(5,38)} = 7.7$ ,  $P < 0.001$ ) and postdosing time ( $F_{(5,34)} = 15.7$ ,  $P < 0.001$ ), but no significant interaction of time by treatment ( $F_{(25,190)} = 0.9$ ,  $P > 0.05$ ) (Fig. 3). Dunnett *t* post hoc comparison revealed that diazepam at 3 mg/kg and the aqueous extract of coriander seed at 50, 100 and

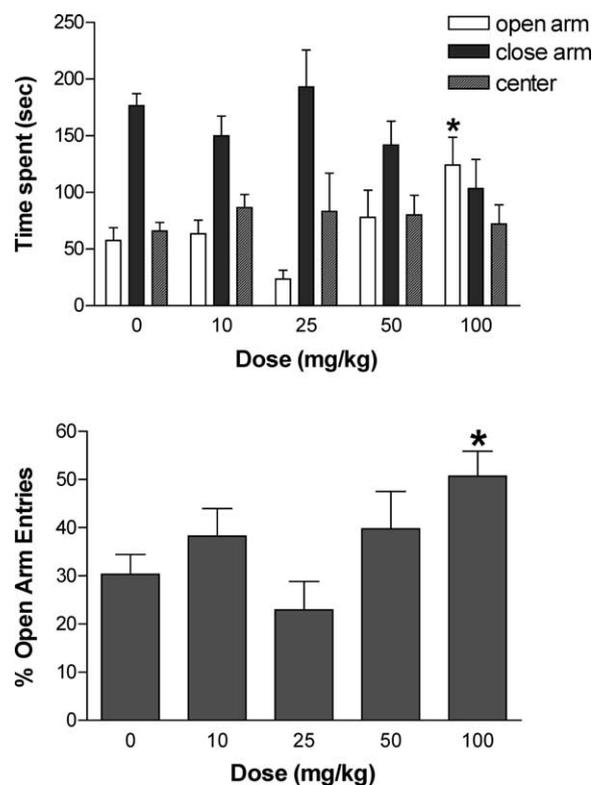


Fig. 2. The effect of the aqueous extract of coriander seeds (0, 10, 25, 50 and 100 mg/kg; i.p.;  $n = 6-10$ ) on the time spent on the open and close arms (A) and on the percentage of open arm entries (B) during a 5-min test on the elevated plus-maze in mice. Bars represents mean  $\pm$  S.E.M. \* $P < 0.05$  compared to control group.

500 mg/kg caused a significant reduction in spontaneous activities, compared to control group ( $P < 0.01$ , Fig. 3-insert). Linear regression analysis showed that the effect of the coriander extract on spontaneous activity was dose-dependent (slope =  $-0.41$ ,  $P = 0.001$ ), i.e. increasing the dose of the coriander extract caused an increased effect on spontaneous activity (Fig. 3-insert). In addition, one-way ANOVA followed by Tukey post hoc comparison showed a significantly higher reduction of spontaneous activity by coriander extract at doses of 100 and 500 mg/kg, compared to the coriander extract at dose of 10 mg/kg ( $F_{(4,35)} = 14.4$ ,  $P < 0.001$ ) (Fig. 3-insert).

The differences between doses of 10 and 50 mg/kg of the coriander extract did not reach statistical significance ( $P = 0.06$ ).

#### 3.3. Neuromuscular coordination – Rotarod

Diazepam at 3 mg/kg and the aqueous extract of coriander seed at doses of 50, 100 and 500 mg/kg caused significant reduction in the number of seconds spent on the rotarod, compared to control group ( $F_{(5,38)} = 8.4$ ,  $P < 0.001$ ) (Fig. 4). Linear regression analysis showed that the effect of the coriander extract on motor coordination was dose-dependent (slope =  $-0.28$ ,  $P = 0.003$ ), i.e. increasing the dose of the

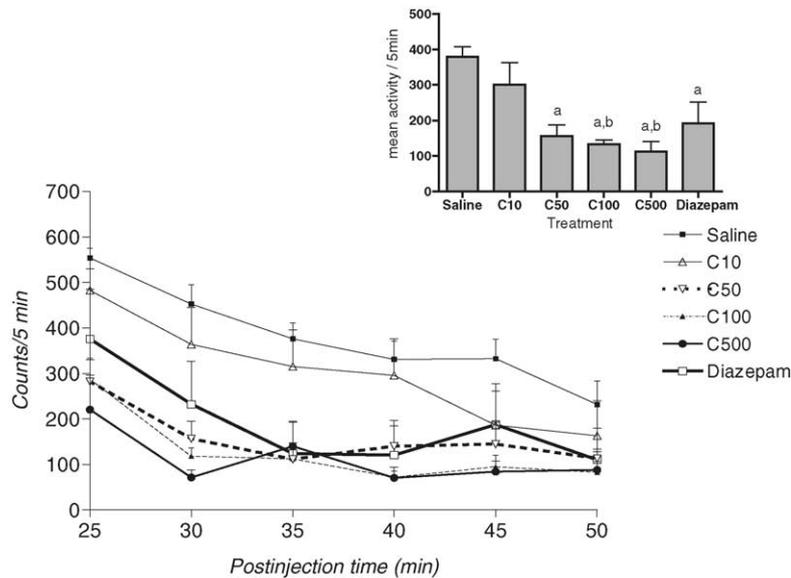


Fig. 3. Mean ( $\pm$ S.E.M.) spontaneous activity counts in mice accumulated at 5-min intervals for 30 min, 20 min following administration of saline (i.p.,  $n = 11$ ), diazepam (3 mg/kg, i.p.;  $n = 7$ ) and the aqueous extract of coriander seeds (10, 50, 100, and 500 mg/kg, i.p.;  $n = 7$ ). Diazepam (from 30 to 40 min postdosing) and the aqueous extract at 50, 100 and 500 mg/kg (from 25 to 45 min postdosing) significantly reduced activity compared to saline group ( $P < 0.01$ ). Insert: Bars represents mean  $\pm$  S.E.M. of mean activity counts/5 min during 30-min test period. (a)  $P < 0.01$  compared to saline group, (b)  $P < 0.05$  compared to the aqueous extract at dose of 10 mg/kg.

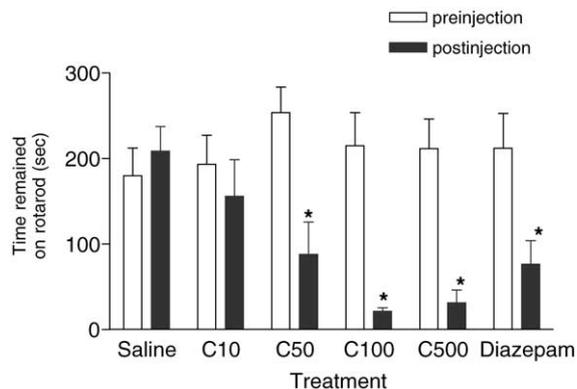


Fig. 4. The effect of the aqueous extract of coriander seeds (10, 50, 100 and 500 mg/kg, i.p.;  $n = 7$ ), diazepam (3 mg/kg, i.p.;  $n = 7$ ) and saline (i.p.,  $n = 11$ ) on neuromuscular coordination as evaluated on the rotarod in mice. Bars represent the mean  $\pm$  S.E.M. number of seconds mice remained on the rotarod. \* $P < 0.01$  compared to saline group.

coriander extract enhanced its effect on motor coordination (Fig. 4). One-way ANOVA followed by Tukey post hoc comparisons of means showed that the coriander extract at a dose of 100 mg/kg significantly reduced motor coordination, compared to the dose of 10 mg/kg ( $F_{(4,35)} = 7.9$ ,  $P < 0.001$ ). The differences between doses of 500 and 10 mg/kg of the coriander extract did not reach statistical significance ( $P = 0.07$ ).

#### 4. Discussion and conclusion

The elevated plus-maze is currently one of the most widely used models of animal anxiety (Hoggs, 1996; Rodgers, 1997),

and has been validated for use with both rats and mice (Pellow et al., 1985; Lister, 1987). Therefore, we chose this test to investigate the anxiolytic potential of the aqueous extract of coriander seed. The indices of anxiety in this test, percent of open arm entries and time spent in the open arm are sensitive to agents thought to act via the GABA<sub>A</sub> receptor complex, justifying the use of diazepam as a positive control in this study. In agreement with previously published reports, diazepam increased the percentage of open arm entries and the time spent in the open arms (Moser, 1989; Helton et al., 1996; Eguchi et al., 2001), confirming its anxiolytic effects. The aqueous extract of coriander seed had similar effects on these parameters. The effect of 100 mg/kg coriander on the elevated plus-maze test was almost equivalent to that of 0.3 mg/kg diazepam. These observations clearly indicate that coriander seed exerts an anxiolytic activity.

In the present study, the anxiolytic activity of the coriander extract occurred at a dose of 100 mg/kg in mice. Although we should be cautious in extrapolating the dose obtained from animal studies to human subjects, it may be suggested that the effective dose for a 75 kg adult man would be 7.5 g dry extract of coriander seed. This corresponds to an infusion of approximately 20 g of coriander seed in 100 ml water, considering the yield of the extract (see Section 2.3). This is in the range of the coriander doses empirically used in traditional medicine. However, the optimum therapeutic dose for human would require further studies, evaluating the effect of the extract in a clinical situation.

It is well known that benzodiazepines have sedative and ataxic side effects (Woods and Winger, 1995; Helton et al., 1996; Charney et al., 2001). In this study, diazepam at 3 mg/kg produced a reduction in spontaneous activity and neuromus-

cular coordination. The aqueous extract of coriander seed also caused a general reduction of the spontaneous activity of the animals in a dose-dependent manner, suggesting that it may possess a sedative effect. However, it is noteworthy that a reduction in spontaneous activity can be due to a variety of causes other than sedation, such as motor impairment or muscle relaxation. Therefore, other behavioral measures such as prolongation of pentobarbital-induced sleep is needed to confirm the sedative effect of the coriander extract and to determine the doses at which the extract causes sedation. In addition to anxiolytic activity and a depressant effect on locomotor activity, administration of the coriander extract had a profound influence on motor coordination in a dose-dependent manner, suggestive of a possible muscle-relaxant effect.

The effects of the extract on spontaneous activity and motor coordination occurred at identical range of doses (i.e. 50, 100 and 500 mg/kg) and in a dose-dependent manner. Therefore, the observed reduction of the spontaneous activity may be related to the muscle-relaxant effect of the extract or vice versa. On the other hand, the anxiolytic effect of the extract reached statistical significance only at the dose of 100 mg/kg. These findings raised the possibility that the anxiolytic and other central depressant effects of the extract may be exerted by different phytoconstituents possibly acting through different receptor subtypes or having different affinity for the relevant receptors. Future studies using different fractions of coriander seed can address these possibilities.

The results of this study indicated that the aqueous extract of coriander seed had central depressant effects. The phytoconstituent(s) responsible for the observed central effects has to be isolated and identified in future studies. However, the flavonoids identified in coriander seed, including quercetin and isoquercitrin (Kunzemann and Hermann, 1977), may be attributed to the observed effects. The flavonoids occur both in the free state and as glycosides; the glycosides are generally soluble in water. Flavonoids with anxiolytic activity have been described in many plant species used in folk medicine such as *Passiflora coerulea* (Wolfman et al., 1994). This effect has been attributed to the affinity of flavonoids for the central benzodiazepine receptors (Medina et al., 1997; Griebel et al., 1999; Paladini et al., 1999). Furthermore, a sedative effect on central nervous system has been shown for quercitrin (Picq et al., 1991), and quercetin and isoquercitrin glycosides in mice (Kang et al., 2000).

Besides flavonoids, coriander seed contains an essential oil composed of monoterpenoids and fatty acids (Blumenthal et al., 2000). Linalool, the major monoterpenoid compound of essential oil in coriander seed (Blumenthal et al., 2000), may have contributed to the observed central effects as well. Psychopharmacological in vivo evaluation have showed that linalool has dose-dependent marked effects at the central nervous system, including hypnotic and anticonvulsant properties (Elisabetsky et al., 1995). In addition, linalool has been shown to exert anxiolytic and sedative effects in human subjects (Sugawara et al., 1998). Interestingly, glucosides of

(3S)-linalool derivatives have been recently isolated from the polar fractions of coriander seed, confirming the ingredient relationship between the essential oil and the water-soluble constituents of coriander (Ishikawa et al., 2003). In addition to linalool, other monoterpenoids such as limonene and myrcene are present in the essential oil of the coriander seed, and may be considered as candidates for the observed central effects of coriander seed. These monoterpenoids have shown to possess sedative and motor relaxant, but no anxiolytic, effects in mice (do Vale et al., 2002). Clearly, future studies are needed to investigate the likelihood of these possibilities.

In summary, the aqueous extract of coriander seed has an anxiolytic activity, and may possess sedative and muscle-relaxant effects. Therefore, its usefulness in clinical practice may be similar to that of diazepam. Further studies are needed to identify the anxiolytic mechanism(s) and the phytoconstituents responsible for the observed central effects of the aqueous extract of coriander seed.

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