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Original Article

Antidepressant-like effect of *Cuminum cyminum* essential oil on the forced swim and tail suspension tests in male mice

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Abstract

Background and aims: Several pharmacological and biological activities have been attributed to *Cuminum cyminum* L. (CC), including analgesic, antioxidant, anti-inflammatory, and anti-epileptic effects. In this regard, the present study evaluated the antidepressant-like effects of the CC essential oil (EO) on the forced swim test (FST) and tail suspension test (TST) in male mice.

Materials and Methods: The gas chromatography-mass spectrometry (GC-MS) apparatus was used for detecting the chemical compounds of CC EO. In the present study, 72 male NMRI mice were randomly allocated to 12 groups (each containing 6 animals) including control or vehicle (10 mL/kg, i.p.), fluoxetine (20 mg/kg, i.p.), imipramine (30 mg/kg, i.p), and the CC EO (100, 200, and 300 mg/kg, i.p.). Then, several parameters were measured and recorded, including immobility time, swimming time, and climbing time in FST, along with immobility time in TST, respectively.

Results: Cuminaldehyde followed by cymene, γ-terpinene, phenylglycol, 2-caren-10-al, 2-β-pinene, acoradiene, and cuminic acid were the major components of the CC EO. Based on the results, all doses of the CC, fluoxetine, and imipramine reduced immobility time in both FST ($P<0.001$) and TST ($P<0.001$). On the other hand, all doses of the CC and fluoxetine increased swimming time ($P<0.001$) although climbing time was only increased by 200 and 300 mg/kg of the EO ($P<0.01$ and $P<0.001$, respectively) and imipramine ($P<0.001$).

Conclusion: Based on the findings of the present study, the components of the CC induced antidepressant-like activity similar to that of fluoxetine and imipramine in both tests. However, further studies are required to confirm the role of different active components and the exact mechanism of action.

Keywords: *Cuminum cyminum,* Depression, Animal models, Monoaminergic system, Mice

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Introduction

Depression is one of the most important and chronic mental disorders so that it affects nearly 25% and 12% of women and men, respectively (1). It has been shown that commonly applied antidepressants for treating depression act through increasing the activity of the monoaminergic system, especially through the involvement of serotonergic and noradrenergic systems. In this respect, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants are effective in treating most episodes of depression although only approximately one-third of people respond or partially respond to these medications. Therefore, it is essential to use medications with fewer side effects or herbal remedies (2). In this regard, our previous and other studies (3-12) identified the antidepressant properties of different extracts or essential oils (EOs).

Cumin or *Cuminum cyminum* L. (CC) is an aromatic herb that belongs to the Apiaceae family and is a delicate, glabrous reaching a height of up to 50 cm. Further, its stems are cylindrical and branched, its leaves are cordate, and its flowers are pink or white. Furthermore, this spice is cultivated in many countries including Iran. The most important component of the CC EO is cuminaldehyde or cuminol whose amount varies in different variants of cumin. Moreover, cuminic alcohol, carvone, and phellandrene are other main compounds of the EO. The CC seed also contains fixed oil, tannin, and resin. Previous research reported numerous properties of cumin (CC) such as anti-inflammatory, antioxidant, and antispasmodic effects (13). Other studies reported anticonvulsant, analgesic, and suppressing effects on morphine tolerance and dependence as well (14,15). However, no study has so far investigated the antidepressant-like effect of CC EO. Accordingly, the present study aimed to evaluate the antidepressant-like effect of CC EO on the forced swim test (FST) and tail suspension test (TST) in male mice.

Materials and Methods

Preparation of essential Oil

The cumin or *Cuminum cyminum* EO was obtained from

Giah Essence Phytopharm Company (Gorgan, Iran) under Bath No. 007.

The gas chromatography-mass spectrometry analysis (GC-MS)

The Agilent 6890 GC apparatus equipped with an HP-5MS with an FID and a DB-5 capillary column (30 m × 0.25 mm i.d., 0.25 µm) and an Agilent 5973 mass detector were utilized for separating and detecting chemical compounds (16). The related data are presented in Table 1. The components of the EO were identified by their retention time, retention indices, relative to C_5-C_{28} n-alkanes, computer matching with the WILEY275.L library, and by the comparison of their mass spectra with data already available in the literature.

Drugs

The applied drugs were imipramine (Sobhan Darou Company, Iran) and fluoxetine (Abidi Pharmaceutical Company, Iran) HCL. In the present study, the drugs and CC EO were dissolved in the normal saline and *dimethyl sulfoxide* (5%), respectively, and administrated intraperitoneally (i.p.) at a constant volume of 10 mL/kg. The FST and TST were performed 60 minutes after a single administration of the drugs or the EO.

Table 1. The Chemical Compounds of *Cuminum cyminum* Essential Oil

Name	RT (min)	Area%
α-Thujene	6.532	0.26
α -Pinene	6.766	0.63
Sabinene	8.208	0.24
2-β-Pinene	8.343	6.70
β -Myrcene	8.903	0.39
l-Phellandrene	9.422	0.37
Cymene	10.361	12.99
Limonene	10.475	0.61
γ-Terpinene	11.85	11.60
β-Pinene oxide	16.671	0.58
4-Terpineol	17.169	0.38
α-Terpineol	17.854	0.32
Cuminaldehyde	20.671	36.00
2-Caren-10-al	22.606	8.22
Phenyl glycol	22.985	10.25
Carvacrol	23.795	0.36
Methyl 12-tridecynoate	23.992	0.31
1,2,4-trimethylcyclohexane (1r,2t,4t)	24.241	0.32
4-Isopropylphenylacetic acid	24.957	0.28
Cuminic acid	29.346	2.77
(6E)-7,11-Dimethyl-3-methylene-1,6,10-dodecatriene	29.507	0.43
Acoradiene	30.099	4.49
Caryophyllene oxide	33.627	0.59
Carotol	34.099	0.84

Note. RT: Retention time.

Animals

Male NMRI mice (20-30 g) were prepared from the Urmia University of Medical Sciences (Urmia, Iran) and studied in cages (n=6) with standard conditions including a 12-hour light/dark cycle, the temperature of 23-25°C, and the humidity of 50±10%. The animals had free access to standard commercial pellet food and water *ad libitum*.

Forced swim test

In this test, mice were forced to swim in an open cylindrical container (10 cm diameter × 25 cm height) filled with 15 cm of water at 23-27 °C. In addition, the total duration of immobility time, swimming time, and climbing time were registered for the last four minutes by a six-minute test using a chronometer (Citizen, Japan). A decrease in immobility time and an increase in swimming or climbing behaviors are considered as behavioral profiles consistent with an antidepressant-like activity (17).

Tail suspension test

In the TST, mice were isolated from exposure to sound and vision and suspended 50 cm above the floor by an adhesive tape placed about 2 cm from the tip of their tail. Furthermore, immobility time was recorded for the last 4 minutes within a 6-minute test. Finally, the immobility time was recorded using a chronometer (Citizen, Japan) in the opposite of the apparatus (18).

Animal grouping and treatment protocols

In both FST and TST, a total of 72 male NMRI mice were randomly divided into 12 groups (each containing 6 animals) as follows:

- Groups I and II: Control or vehicle (the normal saline plus 5 % *dimethyl sulfoxide*, 10 mL/kg) for FST and TST;
- Groups III and VI: Fluoxetine (20 mg/kg) or imipramine (30 mg/kg) as reference drugs for FST and TST;
- Groups VII-XII: Three doses (100, 200, and 300 mg/kg) of the CC EO for FST and TST.

In the present study, the groups of both tests were different from each other and each animal was used only once. Moreover, the administration schedule and drugs and EO administration were chosen based on our recent studies and previous literature (6,7,19).

Statistical analysis

The data were normally distributed, presented as mean ± SD (n=6), and analyzed by one-way ANOVA, followed by Tukey's comparison test, and $P < 0.05$ was considered statistically significant. All statistical analyses were

performed using GraphPad Prism 7 (San Diego, CA, USA).

Results

GC-MS analysis data

Based on the GC-MS analysis, CC EO was made up of 24 compounds (representing 99.94%). Cuminaldehyde (36%) was the main component, followed by cymene (12.99%), γ-terpinene (11.60%), phenylglycol (10.25%), 2-caren-10-al (8.22%), 2-β-pinene (6.70%), acoradiene (4.49%), and cuminic acid (2.77%). Additionally, these components (8) accounted for 93.02% of the yield while the other detected components represented <2% (Table 1).

Effects of the CC EO on immobility, swimming, and climbing behaviors in FST

As shown in Figure 1, all doses of the CC EO significantly decreased immobility time ($P=0.002$, $P<0.0001$ and $P<0.0001$,respectively) while increasing the swimming time ($P=0.002$, $P<0.0001$ and $P<0.0001$,respectively) compared to the control group in FST. Furthermore, only 200 and 350 mg/kg of the EO significantly increased the climbing time ($P=0.0027$ and $P=0.001$,respectively)

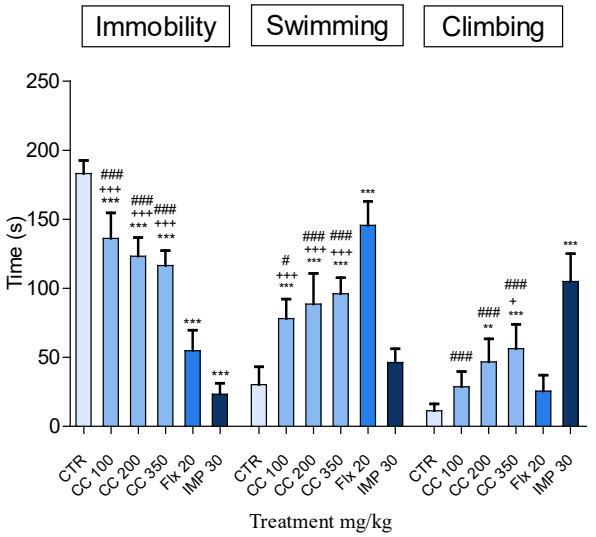

Figure 1. The Effects of CC Essential Oil, Fluoxetine, and Imipramine on the Mean Immobility, Swimming, and Climbing Times in FST.
Note. Values are presented as mean ± SD. Significant differences between the groups were assessed using the one-way ANOVA, followed by Tukey's test. *, **, and *** show significant differences between the vehicle (control) group at $P<0.05$, $P<0.01$, and $P<0.001$ in immobility time, swimming time, and climbing time, respectively. In addition, +, ++, and +++ indicate significant differences between the CC group and fluoxetine at $P<0.05$, $P<0.01$, and $P<0.001$ in immobility time, swimming time, and climbing time, respectively. Further, #, ##, and ### demonstrate significant differences between the CC group and imipramine at $P<0.05$, $P<0.01$, and $P<0.001$ in immobility time, swimming time, and climbing time, respectively. CTR: Control; CC: *Cuminum cyminum*; Flx :Fluoxetine; IMP: Imipramine; SD: Standard deviation TST: Tail suspension test; ANOVA: Analysis of variance.

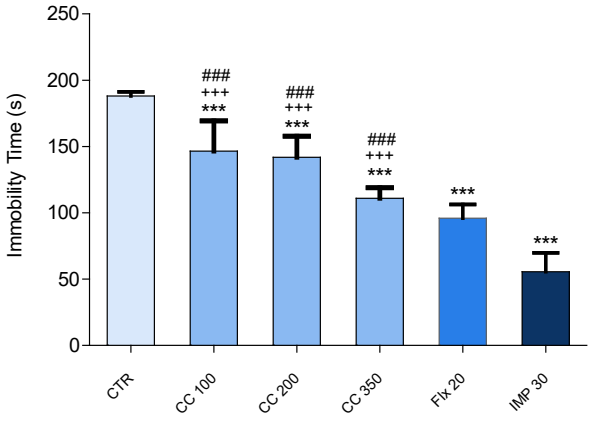

Figure 2. The Effects of the Intraperitoneal Administration of the CC Essential Oil, Fluoxetine, and Imipramine on the Mean Immobility Time in the TST.
Note. Values are presented as mean ± SD. Significant differences between the groups were assessed using the one-way ANOVA, followed by Tukey's test. *** shows significant differences between the vehicle (control) group at $P<0.001$ in immobility time. Further, +++ shows significant differences between the CC group and fluoxetine at $P<0.001$ in immobility time. ### represents significant differences between the CC group and imipramine at $P<0.001$ in immobility time. CTR: Control; CC: *Cuminum cyminum*; Flx: Fluoxetine; IMP: Imipramine; SD: Standard deviation TST: Tail suspension test; ANOVA: Analysis of variance.

compared to the control group. In addition, fluoxetine significantly decreased immobility time ($P<0.001$) whereas it increased swimming time ($P<0.001$) without any significant change in the climbing time ($P=0.9990$). Contrarily, imipramine significantly decreased immobility time ($P<0.001$) while increasing climbing time ($P<0.001$) without any significant change in the swimming time ($P=0.195$). Moreover, both fluoxetine ($P<0.001$) and imipramine ($P<0.001$) higher than all doses of the CC EO reduced immobility time. On the other hand, the results demonstrated that fluoxetine higher than all doses of the EO ($P=0.013$, $P=00004$ and $P<0.0001$) increased the swimming time. Based on the results, all doses of the CC EO ($P<0.05$ and $P<0.001$, respectively) higher than imipramine increased swimming time. The results further revealed that imipramine ($P<0.001$) higher than all doses of the EO increased climbing time. Similarly, the highest dose (350 mg/kg) of the EO better increased climbing time compared to fluoxetine ($P=0.0114$).

Effects of the CC EO on immobility time in TST

As displayed in Figure 2, all doses of the CC EO decreased immobility time in TST ($P<0.001$). Further, fluoxetine ($P<0.001$) and imipramine ($P<0.001$) significantly decreased immobility time in TST. Similar to FST, both fluoxetine ($P<0.001$) and imipramine ($P<0.001$) higher than all doses of CC EO decreased immobility time in TST.

Discussion

This study aimed to investigate the antidepressant effect of CC EO on the animal models of depression (FST and TST), namely male mice. The results of this study showed that all doses of CC EO reduced immobility time in both FST and TST in comparison with the control group. On the other hand, all doses of the CC increased swimming time while climbing time increased only 200 and 300 mg/kg of the EO. The results also showed that fluoxetine, as a positive control drug, decreased immobility time, increased swimming time, and insignificantly increased climbing time. Nonetheless, imipramine resulted in decreased immobility time, increased climbing time, and a nonsignificant increase in swimming time, which is in line with the findings of (20). Based on the finding of the above-mentioned study, selective noradrenaline reuptake inhibitors (e.g., imipramine) decreased the immobility time while increasing the climbing time, which is consistent with the findings of the present study. Conversely, SSRIs (e.g., fluoxetine) reduced the immobility time whereas significantly increased swimming time without increasing the climbing time (21). According to other studies, some synthetic agents or herbs, which reduce immobility time and substantially increase swimming and climbing behaviors in FST, are believed to act through a monoaminergic mechanism (22-24). Different compounds were identified based on the GC-MS and phytochemical evaluation of CC. In other words, our results showed that the CC EO contains cuminaldehyde, followed by cymene, γ-terpinene, phenyl glycol, 2-caren-10-al, 2-β-pinene, acoradiene, and cuminic acid, which perfectly corroborates with the results of (25).

According to Ebada (26), the pharmacological and biological activities of the CC (e.g., anti-inflammatory, anti-tumor, anti-diabetic, neuroprotective, antibacterial, and antifungal activities) are attributed to cuminaldehyde (26). However, no study has so far focused on the antidepressant effects or possible antidepressant mechanism of the CC or its active ingredient (cuminaldehyde). Therefore, one of the strengths of the present study was to investigate the effects of the acute doses of the CC EO on the animal models of depression (FST and TST). However, the weakness of this study is the lack of the study of interference in the monoaminergic system (i.e., the role of serotonergic, dopaminergic, and noradrenergic systems) in the CC exact mechanism of action.

Some studies demonstrated that oxidative stress may play a role in the pathogenesis of depression. In other words, an imbalance or decrease in antioxidant activity was in people with depression (27,28). Therefore, the use of antioxidants is another optimal approach to treat depression. In this regard, previous research reported the antioxidant effect of cuminaldehyde (29). In addition, it was indicated the antidepressant-like effects of antioxidants and argued that antioxidants block serotonin (5-HT) reuptake (30). Therefore, some of the effects of the CC EO can be related to its antioxidant effects. Despite the role of cuminaldehyde in the serotonergic system, another study revealed that CC blocks 5-HT reuptake by increasing the amount of 5-HT in the synaptic cleft and thus leads to weight loss (31).

According to the above-mentioned results, it seems that the dopaminergic system is also involved in the antidepressant-like effects of the CC. Similarly, Bina et al observed that the CC EO potentiates the effects of bromocriptine (as a dopamine agonist) on ovaries in female rats. They argued that the CC EO produced these effects through dopaminergic mechanisms (32). Moreover, another study reported that cuminaldehyde in CC reduces the oxidative stress induced by the rotenone. It was observed that that the CC and its active compounds (e.g., cuminaldehyde) produced these effects through dopaminergic mechanisms and could, therefore, be effective in neurodegenerative diseases such as Parkinson's disease (33).

Previous studies also represented the role of the noradrenergic system in CC activities. In this regard, it was observed that CC, similar to sibutramine, as an appetite suppressant, suppresses appetite and thus leads to weight loss although sibutramine acts by blocking the reuptake of 5-HT and noradrenaline (34,35).

Generally, a decrease in immobility time and increases in swimming and climbing times after the treatment with CC EO was related to the components present in CC) especially cuminaldehyde (, which are likely to produce antidepressant effects through the monoaminergic mechanism.

Conclusion

Based on the findings of the present study, the components of the CC induced antidepressant-like activity similar to that of fluoxetine and imipramine in both tests. However, further studies are needed to approve the role of different active components and the exact mechanism of action.

Conflict of Interests

The authors have no conflict of interests.

Ethical Approval

All the ethical principles were in agreement with guidelines of Urmia Branch, Islamic Azad University for the care and use of laboratory animals (IR.IAUrmia.REC.1397.08).

Authors Contribution

KA done all testes and collect the data. SAM and GSH designed the study and analyses the data. SAM wrote and revised the manuscript. All the authors approved the final version of the manuscript.

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