The Fruit Essential oil of *Cuminum cyminum* L. Reduced the Acquisition but not Expression of Ineffective dose of Morphine-Induced Conditioned Place Preference in Morphine- Sensitized Mice

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Abstract

Background: ***Cuminum cyminum*** **fruit essential oil (FEO) dose-dependently can attenuate the expression of morphine tolerance and dependence in morphine-dependent mice.**

Objective: In this study, the effects of *Cuminum cyminum* FEO on acquisition and expression of morphine-induced conditioned place preference (CPP) in morphine-sensitized mice were studied.

Methods: Repeated subcutaneous (s.c.) administration of morphine (5 mg/kg), once daily for three and 5 days free of the opioid (sensitization period), increased conditioning response induced by ineffective doses of morphine (0.25, 0.5 and 0.75 mg/kg).

Results: The results showed that intra-peritoneal (i.p.) injection of Cumin FEO (0.001, 0.01, 0.1, 0.5, 1 and 2%; 5 ml/kg) or Tween-80 (0.5%; 5 ml/kg), 60 min before administration of morphine or saline during sensitization period (acquisition), decreased the conditioning response induced by ineffective dose of morphine (0.5 mg/kg; s.c.) at the doses of 1% ($P<0.05$) and 2% ($P<0.001$) while Cumin FEO (0.001-2%; i.p.), just 60 min before the test on post-conditioning phase (expression experiments), did not alter the conditioning scores in morphine- and non-sensitized mice.

Conclusion: Our findings showed that the *Cuminum cyminum* fruit essential oil reduces the acquisition but not expression of morphine-induced conditioned place preference in morphine-sensitized mice.

Keywords: ***Cuminum cyminum*****, Morphine, Conditioned place preference, Sensitization, Mice**

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Introduction

Drug craving and behavioral sensitization to opioid rewarding effects are of the most important problems against treatment of drug abuse and addiction. There is a close relation between psychopathology of addiction, drug craving and behavioral sensitization. It has been shown that pre-exposure to drug of abuse leads to increase in rewarding effects of them [1]. This phenomenon has an important role in drug craving and development of addiction to opiates [2]. As previous studies showed that pre-exposure to morphine can enhance its rewarding effects as measured with place preference paradigm in rats [3] and mice [1]. Now it is accepted that dopaminergic system has an important role in sensitization to rewarding effects of morphine [1, 4]. Following expression of behavioral sensitization, dopamine transmission is enhanced in the ventral tegmentum area and nucleus accumbens [2, 5, 6].

Cuminum cyminum L. (Apiaceae) is an annual herbaceous plant which is aborigine to in Iran. Originally from the Mediterranean area, it is a small annual herb about 50 cm (20 inches) high, with deep green, narrow feathery leaves and tiny white/pink flowers, followed by small oblong seeds. In Iranian folk medicine it is used for treatment of diarrhea, toothache and epilepsy [7]. Janahmadi et al. [8] previously showed that cumin fruit essential oil (FEO) can inhibit the seizure induced by Pentylenetetrazol (PTZ) in F1 neurons of sub-oesophageal ganglia in *Helix aspersa* (Iranian garden snail). In addition, Sayyah et al. [9] indicated the anticonvulsant effects of Cumin FEO against seizure induced by PTZ and maximal electroshock (MES). They showed that Cumin FEO can suppress the seizure and mortality induced by MES and PTZ. Recent studies in this laboratory showed that Cumin FEO significantly can attenuate the expression of morphine tolerance and dependence in a dose-dependent manner while this effect was lesser on the development of morphine tolerance and dependence [10] and Cumin FEO also reduces the acquisition and expression of morphine-induced conditioned place preference (CPP) in mice [11]. Therefore, in this study, we try to examine the possible effects of *Cumin* FEO on the acquisition and expression of morphine-induced conditioned place preference in morphine sensitized mice.

Materials and methods

Plant material and preparation of the FEO

Fruits of *Cuminum cyminum* were obtained from a local market. The plant was authenticated by M. Kamalinejad (Department of pharmacognosy, faculty of pharmacy, Shahid Beheshti University, M.C., Tehran, Iran). A voucher specimen (no. C-1456) was deposited in the herbarium of this department. The fruits were subjected to hydrodistillation for 4 h by using a Clevenger apparatus and produced 3% (v/w) yield.

Animals

384 adult male albino Wistar mice (Pasteur Institute, Tehran) weighing 18 - 30 g were used in these experiments. They were kept 8-10 per cage (45×30×15 cm) at a room controlled temperature (23±1^{oC}) and maintained on a 12-h light/dark cycle (light on 07:00 h) with free access to the standard rodent breeding diet and tap water. Each

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animal was used only once and killed immediately after the experiment. All Experiments were executed in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences.

Drugs

The following drugs were used: morphine sulfate (Temad Co., Iran) and Tween-80 (Gerbu, Germany). Tween-80 was dissolved in distilled water and prepared 0.5% (v/w). Morphine sulfate was dissolved in normal saline. Two control groups were selected, one received Tween-80 (0.5%) and other group received normal saline. The FEO and Tween-80 as a vehicle were given in a volume of 5 ml/kg, except morphine which was given 10 ml/kg, to decrease in volume injection and were prepared immediately before use.

Experimental procedure

Conditioned place preference paradigm

Conditioned place preference consisted of three phases: pre-conditioning, conditioning and post-conditioning that it has been described in our previous study [11] in details. A two-compartment CPP apparatus (15×30×15 cm) was used in these experiments. Place preference was conducted using an un-biased procedure. The mean spent time for each mice in both compartments during a 10-min period was recorded by a 3CCD camera and analyzed using the Ethovision software in order to calculate the conditioning score as the preference criteria; the time spent in the drug-paired place minus the time spent in saline-paired place. Total distance traveled for each animal was also recorded in order to evaluating the locomotor activity in all control and experimental groups.

Induction of morphine sensitization

Animals received a single subcutaneous (s.c.) injection of morphine (5 mg/kg) for three consecutive days in a room distinct from that in which conditioning occurred. Five days later, the place-conditioning paradigm was induced by ineffective doses of morphine (0.25, 0.5 and 0.75 mg/kg, s.c.). However, higher doses of morphine were not examined because they were able to induce CPP in non-sensitized animals.

Morphine dose-response on CPP in non-sensitized and sensitized mice

In these experiments, we established a dose-response relationship for morphine and Cumin FEO on place conditioning paradigm. Different doses of morphine (0.25, 0.5, 0.75, 1, 2.5, 5, 7.5 and 10 mg/kg; s.c.) were tested for producing place preference during three days of conditioning session in non-sensitized. In order to confirm that the injection and conditioning schedule did not affect the time spent in the compartments, a separate group of animals received saline (10 ml/kg; s.c.) in two compartments. This group was used as a saline-control group. On the other hand, the CPP induced by graded ineffective doses of morphine (0.25, 0.5 and 0.75 mg/kg; s.c.) in animals, which had previously received once daily morphine (5 mg/kg, s.c.) for three consecutive days (sensitization period). Place conditioning commenced 5 days later. Control

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animals received saline (10 ml/kg; s.c.) instead of morphine during sensitization period.

Effect of Cumin FEO on the acquisition of morphine-induced CPP in morphine-sensitized mice

A total of 128 mice were used in these experiments. Intraperitoneal (i.p.) administration of different doses of Cumin FEO (0.001, 0.01, 0.5, 0.1, 1 and 2%; 5 ml/kg) or Tween-80 (0.5%; 5 ml/kg) was done 60 min before injection of morphine (5 mg/kg; s.c.) or saline (10 ml/kg; s.c.) during the sensitization period in three days of induction of behavioral sensitization. Then, animals received ineffective dose of morphine in three days of conditioning schedule and tested on the test day for measurement of induced preference.

Effect of Cumin FEO on the expression of morphine-induced CPP in morphine-sensitized mice

In this set of experiments, different doses of Cumin FEO (0.001-2%; 5 ml/kg) or Tween-80 (0.5%; 5 ml/kg) were intraperitoneally injected 60 min before post-conditioning test to animals that received ineffective dose of morphine in three days of conditioning schedule in morphine- and non-sensitized mice which have received morphine (5 mg/kg; s.c.) or saline (10 ml/kg; s.c.) during the sensitization period, respectively.

Statistics

Conditioning score represents the differences between the time spent in drug-paired compartment and the time spent in the saline-paired compartment, and is expressed as mean ± SEM (standard error of mean). In order to compare the conditioning scores or locomotor activity obtained in all groups (saline-control, vehicle and experimental groups) one-way analysis of variance (ANOVA) and randomized blocks model followed by post hoc analysis (Dunnett's or Tukey's test) were used, as needed. *P*-values less than 0.05 were considered to be statistically significant.

Results

Morphine dose-response on conditioned place preference paradigm

Fig. 1A showed that injection of different doses of morphine (0.25-10 mg/kg, s.c.) results in significant increase in the time spent in conditioning (drug-paired) compartment compared to other (saline-paired) compartment [F (8,71)=6.706, p<0.0001] in a dose-dependent manner. Injection of saline to the animals in the conditioning compartments did not produce any preference or aversion for either place. Based on these data, the graded doses of morphine (0.25-0.75 mg/kg; s.c.) were selected as ineffective doses for the rest of experiments. However, this part of the experiments indicated that the apparatus and the paradigm are sufficient. One-way ANOVA indicated that all different doses of morphine (0.25-10 mg/kg; s.c.) did not affect the locomotor activity during 10-min test period in comparison with that of the saline control group [F (8, 71)=0.2116, P=0.9877; Fig. 1B]. Thus, the different doses of morphine used in this set of experiments did not impress the conditioning scores because of alteration to the locomotor activity. These results indicated that any observed effect in CPP paradigm is not due to change in locomotor activity.

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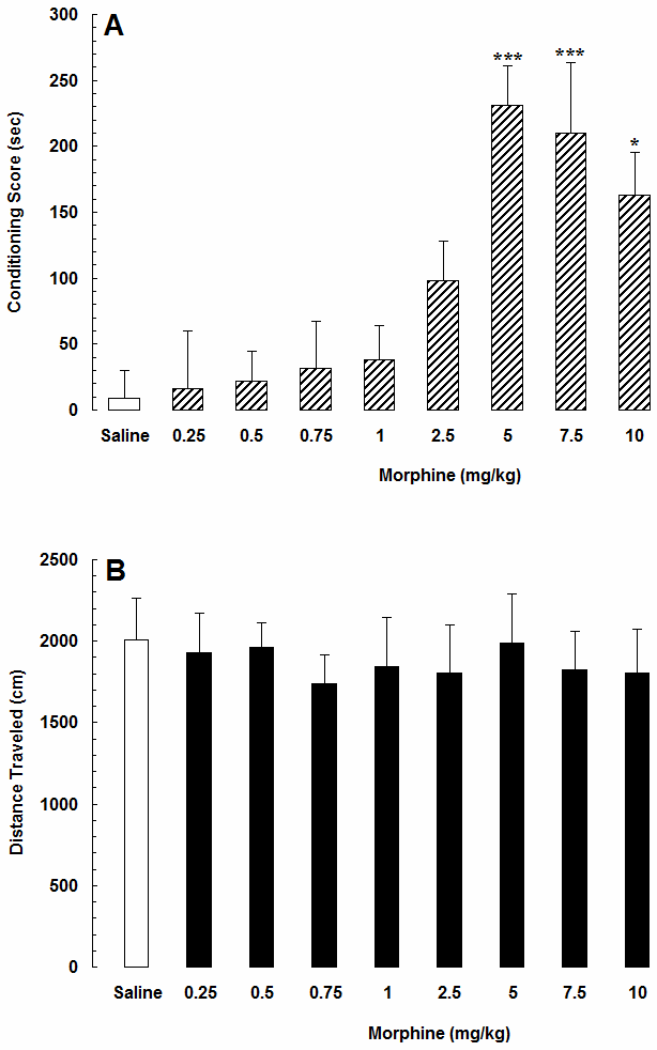


Figure 1 (Haghparast et al.)

Fig. 1- Effects of different doses of morphine on *(A)* place preference and *(B)* locomotor activity in mice. Each point shows the mean ± SEM for 8 mice.
***p*<0.05, ****p*<0.001 different from the saline control group**

Morphine dose-response on CPP in sensitized mice

Fig. 2 shows the conditioned place preference produced by graded doses of morphine (0.25-0.75 mg/kg) in animals, which had previously received once daily morphine (5 mg/kg, s.c.) for three consecutive days. Place conditioning commenced 5 days later. In animals with a prior history of morphine administration, an enhanced response to morphine was observed. The maximum response was observed at 0.5 mg/kg of morphine [F (6, 55) =8.978, p<0.0001]. Therefore, the dose of 0.5 mg/kg of morphine was selected as the dose for the rest of experiments in CPP paradigm in morphine-sensitized mice. Injection of saline

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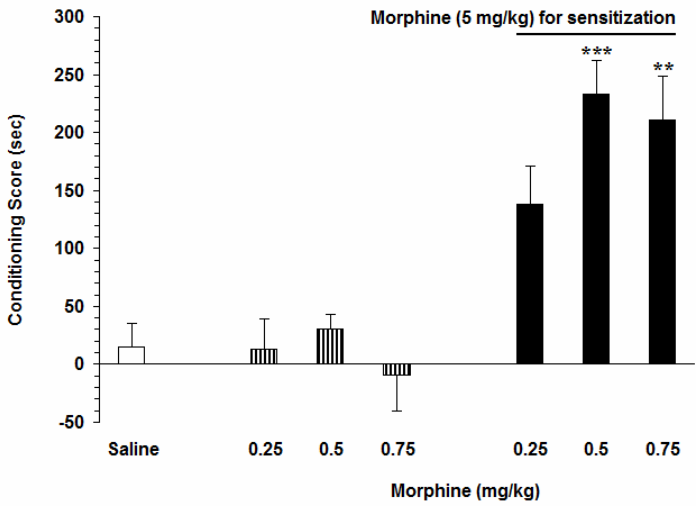


Figure 2 (Haghparast et al.)

Fig. 2- Effects of repeated concomitant morphine administration on the animal responsibility to low doses of morphine (i.e. sensitization). Animals received three morphine (5 mg/kg, s.c.) injections in three consecutive days following five days of resting. After this period, these animals were conditioned to ineffective doses of morphine (0.25, 0.5 and 0.75 mg/kg, s.c.). As indicated in the figure, animals that have previous history of morphine, showed prominent response to low doses of morphine than those that have no previous history of morphine. Each point shows the mean ± SEM for 8 mice.
****p*<0.01, *****p*<0.001 different from the saline control group**

(10 ml/kg, s.c.) instead of morphine (5 mg/kg, s.c.) during the sensitization days did not produce any sensitization in the animals.

Effects of Cumin FEO on the acquisition of morphine CPP in morphine-sensitized mice

To determine the effects of Cumin FEO on the acquisition of ineffective dose of morphine-induced CPP in morphine-sensitized mice, the *Cuminum cyminum* FEO (0.001-2%; 5 ml/kg; i.p.) was administered 60 min before each morphine (5 mg/kg, s.c.) in the sensitization period. The control groups received saline (10 ml/kg, s.c.) instead of morphine during 3-day sensitization period. One-way ANOVA indicated that administration of Cumin FEO at two doses (1 and 2%) significantly decreased the acquisition of morphine-induced CPP in sensitized animals compared to saline or vehicle group that received Tween-80 (0.5%; 5 ml/kg; i.p.) during the induction of sensitization [F (7, 63)=6.593, p<0.0001; Fig. 3A] in a dose-dependent manner. On the other hand, in non-sensitized animals, repeated administration of Cumin FEO (0.001-2%; 5 ml/kg; i.p.) for three consecutive days before saline (10 ml/kg; s.c.) instead of morphine (5 mg/kg; s.c.) during the sensitization period, did not caused the acquisition of morphine-induced CPP at the ineffective dose (0.5 mg/kg; s.c.) compared to saline and/or Tween-80 groups [F(7,63)=0.1164, P=0.997] as shown in Fig. 3B.

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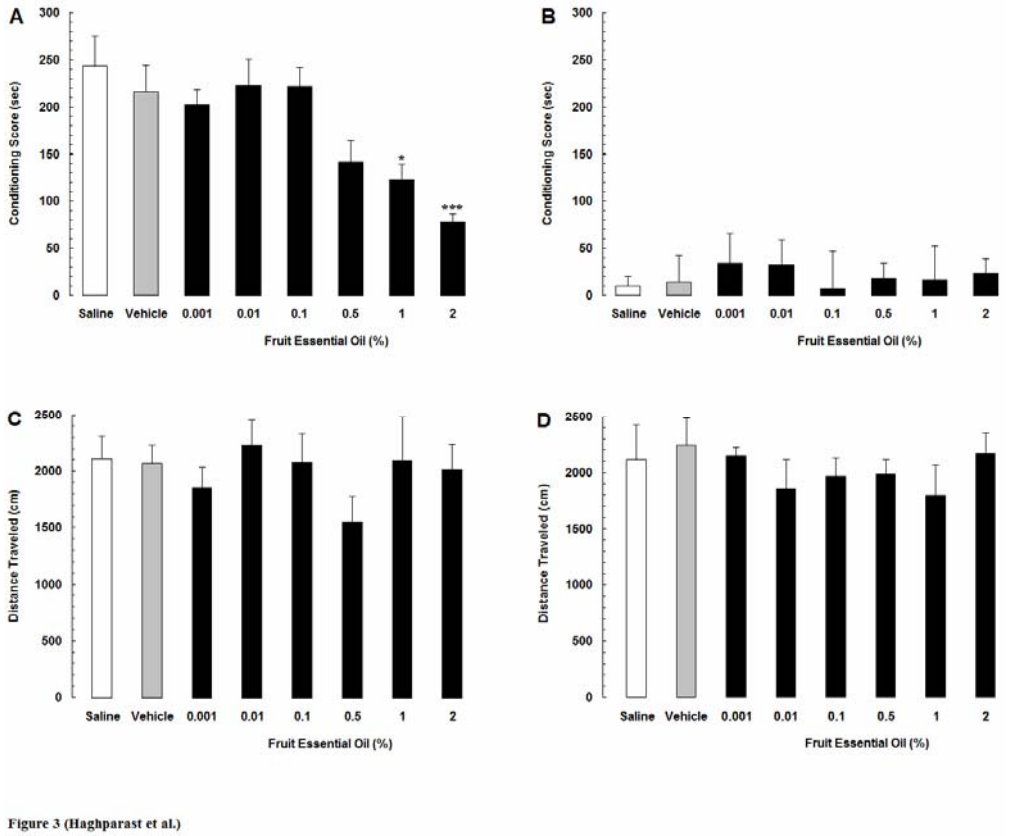


Figure 3 (Haghparast et al.)

Fig. 3- Effects of repeated administration of Cumin fruit essential oil (FEO) on the acquisition of ineffective dose (0.5 mg/kg; s.c.) of morphine-induced conditioned place preference in *(A)* morphine-sensitized and *(B)* non-sensitized (saline-treated) animals. Animals received Cumin FEO (0.001-2%; 5 ml/kg; i.p.) or Tween-80 (0.5%; 5 ml/kg; i.p.) as a vehicle 60 min before morphine (5 mg/kg; s.c.) or saline (1 ml/kg; s.c.) injection during the induction of sensitization. On the other hand, the repeated administration of Cumin FEO (0.001-2%) did not affect the locomotor activity (distance traveled) in *(C)* morphine-sensitized and *(D)* non-sensitized mice. Each point shows the mean ± SEM for 8 mice.
***p*<0.05, ****p*<0.001 different from the vehicle (Tween-80) group**

On the other hand, Tukey's multiple comparison test indicated that the repeated administration of different doses of *Cumin* FEO (0.001-2%), 60 min prior to morphine [$F(7,63)=0.7527$, $P=0.6288$; Fig. 3C] or saline [$F(7,63)=0.5241$, $P=0.8126$; Fig. 3D] injection during the induction of sensitization (acquisition experiments) can not affect the locomotor activity during 10-min test session on the test day compared to the vehicle (Tween-80) or saline groups. Therefore, the different doses of Cumin FEO used in acquisition experiments did not impress the conditioning scores because of change in the locomotor activity.

Effects of Cumin FEO on the expression of morphine CPP in morphine-sensitized mice

In this set of experiment, to determine the effects of *Cumin* FEO on the expression of morphine-induced CPP in morphine-sensitized mice, the Cumin FEO (0.001-2%; 5 ml/kg; i.p.) was administered on the test day 60 min before the test. The control groups received saline or vehicle (Tween-80; 0.5%; 5 ml/kg;

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i.p.). One-way ANOVA indicated that administration of Cumin FEO (0.001-2%) did not significantly alter the expression of ineffective dose of morphine-induced CPP in sensitized animals as compared to saline and/or vehicle groups on the test day [$F(7,63)=1.21$, $P=0.3127$; Fig. 4A]. In non-sensitized animals, the Cumin FEO (0.001-2%) also could not caused the expression of conditioning response induced by ineffective dose of morphine (0.5 mg/kg; s.c.) compared to saline and/or Tween-80 groups [$F(7,63)=0.1584$, $P=0.9921$; Fig. 4B]. On the other hand, one-way ANOVA followed by Tukey's multiple comparison test indicated that single administration of different doses of *Cumin* FEO (0.001-2%), before the post-conditioning phase can not affect the locomotor activity during 10-min test session on the test day compared to the vehicle (Tween-80) or saline groups in morphine-sensitized [$F(7,63)=0.6477$, $P=0.7146$; Fig. 4C] or non-sensitized [$F(7,63)=0.2418$, $P=0.9728$; Fig. 4D] animals. Therefore, the different doses of Cumin FEO used in expression experiments did not impress the conditioning scores because of change in the locomotor activity. These results indicated that any observed effect in CPP paradigm is not due to change in locomotor activity.

Discussion

The present study indicated that administration of morphine induced conditioned place preference in a dose-dependent manner. In addition, repeated administration of morphine (5 mg/kg; s.c.), once daily for three days (sensitization period) that followed by 5 days without any injection, increased conditioning response induced by ineffective doses of morphine. The major findings of this study were **(1)** i.p. administration of Cumin FEO dose-dependently reduced the acquisition but not expression of morphine-induced CPP in morphine-sensitized mice **(2)** in non-sensitized animals, administration of Cumin FEO for three consecutive days before saline instead of morphine during the sensitization period could not induce the acquisition and/or expression of conditioning response induced by ineffective dose of morphine in CPP paradigm. On the other hand, our result also showed that administration of different doses of neither morphine nor Cumin FEO can affect the locomotor activity in this study.

Our data indicate that morphine dose-dependently produces a significant CPP for the drug-associated place. This finding supported previous studies [12, 13] and demonstrated that morphine induces rewarding effects which, through a mechanism of associative learning, becomes connected to the environment in which these effects occurred [13, 14]. The behavioral sensitization to morphine resulting in this study was in agreement with previous studies showing that the animals, which have become sensitized to morphine, show an increase responsibility to low doses of morphine in place conditioning paradigm [5].

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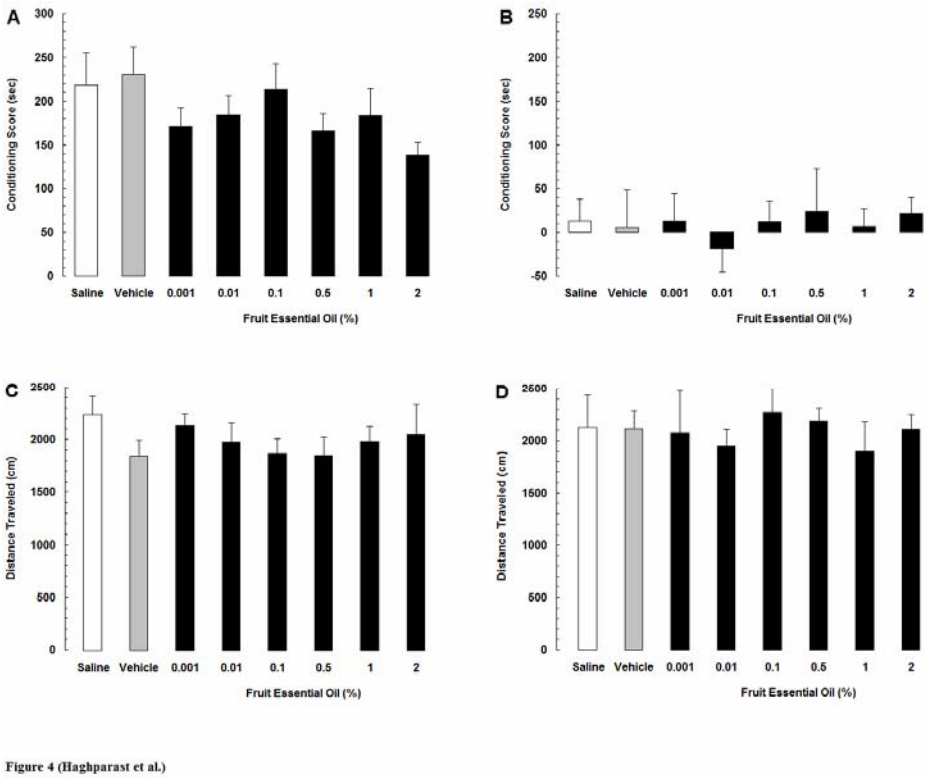


Fig. 4- Effects of single administration of Cumin fruit essential oil (FEO) on the expression of ineffective dose (0.5 mg/kg; s.c.) of morphine-induced conditioned place preference in *(A)* morphine-sensitized and *(B)* non-sensitized (saline-treated) animals. Animals received Cumin FEO (0.001-2%; 5 ml/kg; i.p.) or Tween-80 (0.5%; 5 ml/kg; i.p.) as a vehicle 60 min prior to post-conditioning test. On the other hand, the single injection of Cumin FEO (0.001-2%) before the post-conditioning phase can not affect the locomotor activity (distance traveled) during 10-min test session on the test day in *(C)* morphine-sensitized and *(D)* non-sensitized mice. Each point shows the mean ± SEM for 8 mice.

Several lines of evidences, from clinical to experimental, showed that encountering the to opioids such as morphine and cocaine can induce sensitization to rewarding properties of them while the lower doses can produce the rewarding properties of higher doses without sensitization [3, 5, 6]. Many studies considered the short-term and log-term changes in neurotransmitter system for rewarding properties of opioids such as morphine. Furthermore, there are many other drugs and components that can prevent or reverse the effects of morphine on central nervous system (CNS). Considering the literature of working on *Cuminum cyminum* FEO, two distinct mechanisms are discussed regarding its role in reversing the effects of morphine: Gamma Amino Butyric Acid (GABA) and Nitric Oxide (NO) system [10]. The GABA transmission system was in the focus of more investigations using Cumin FEO. In a previous study, Janahmadi et al. [8] showed that administration of Cumin FEO can inhibit the epileptic activity of F1 neurons of Helix aspersa (Iranian snail garden) induced by pentylentetrazol (PTZ). Also sayyaah et al. [9] previously indicated that the lethality and seizure induced by PTZ or maximal electroshock can be reduced by i.p. injection of Cumin FEO. They also showed that the

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seizure induced by PTZ can be prevented by administration of drug enhancing the $GABA_A$ receptor mediated inhibitory transmission. In addition, Bartoletti et al. [15] showed that administration of Baclofen as a $GABA_B$ agonist can block the behavioral sensitization to morphine. They proposed that the sensitization to morphine is associated with enhanced transmission of dopamine in CNS [16]. They showed that direct administration of Baclofen to ventral tegmentum area can decrease the somatodendritic dopamine release in this area [15]. Overall, considering the antiepileptic properties of Cumin FEO and also the anti-sensitization effects of anticonvulsant drugs that act through GABA transmission system (e.g. Baclofen) on rewarding properties of morphine it could be concluded that cumin FEO reverse the sensitization to rewarding effects of morphine through changes in GABAergic system, but it still need more investigations.

There are different proposition about role of NO in induction of rewarding properties of morphine [10]. In a recent study Sahraei and his collaborators [6] proposed that NO within the nucleus accumbens has important role in acquisition and expression of sensitization to morphine. They showed intra-accumbal injection of L-arginine (a NO precursor) results in significant reduction in acquisition and expression of morphine sensitization. Also they showed intra-accumbal administration of L-NAME as nitric oxide synthase (NOS) inhibitor also reduces the acquisition and expression of CPP in morphine-sensitized rats. On the other hand, previous studies showed that there are major constituents in *Cumin* seeds, such as gamma-terpinene, thujadien, *para*cymene, d-glucopyranosides and linolool [17], which have inhibitory effects on NOS in different cells and tissues. For example, in various studies β-d-glucopyranoside, which are found in *Cumin* seeds [17], represented an inhibitory action on NOS [18, 19]. Considering inhibitory effects of Cumin FEO constituents on NOS and also previously investigations on effect of NOS inhibition on morphine induced place preference in sensitized animals [6], it could be concluded that *Cumin* FEO takes action on morphine sensitization through NOS inhibition. Further investigation need to evaluate this claim as well.

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References

1. Manzanedo C, Aguilar MA, Rodriguez-Arias M, Minarro J. Sensitization to the rewarding e¡ects of morphine depends on dopamine. *Neuroreport*. 2004; 16 (2): 201 - 5.

2. Robinson TE, Berridge KC. Addiction. *Annu Rev Psychol.* 2003; 54: 25 - 53.

3. Shippenberg TS, Heidbreder C, Lefevour A. Sensitization to the conditioned rewarding effects of morphine: pharmacology and temporal characteristics. *Eur. J. Pharmacol*. 1996; 299: 33 - 9.

4. Jeziorski M, White FJ. Dopamine receptor

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[DOR: 20.1001.1.2717204.2009.8.31.8.3]

antagonists prevent expression, but not development, of morphine sensitization. *Eur. J. Pharmacol.* 1995; 275: 235 - 44.

5. Sahraei H, Aliabadi AA, Zarrindast M-R, Ghoshooni H, Nasiri A, Barzegari-Sorkheh AA, et al. Ascorbic acid antagonizes nicotine-induced place preference and behavioral sensitization in mice. *Eur. J. Pharmacol.* 2007; 560: 42 - 8.

6. Sahraei H, Zarei F, Eidi A, Oryan S, Shams J, Khoshbaten A, et al. The role of nitric oxide within the nucleus accumbens on the acquisition and expression of morphine-induced place preference in morphine sensitized rats. *Eur. J. Pharmacol.* 2007; 556: 99 - 106.

7. Zargari A. Medical Plants. Tehran: Tehran University 1994.

8. Janahmadi M, Niazi F, Danyali S, Kamalinejad M. Effects of the fruit essential oil of *Cuminum cyminum Linn.* (Apiaceae) on pentylenetetrazol-induced epileptiform activity in F1 neurones of Helix aspersa. *J. Ethnopharmacol.* 2006; 104: 278 - 82.

9. Sayyah M, Mahboubi A, Kamalinejad M. Anticonvulsant effect of the fruit essential oil of *Cuminum cyminum* in mice. *Pharmac. Biol.* 2002; 40 (6): 478 - 80.

10. Haghparast A, Shams J, Khatibi A, Alizadeh A-M, Kamalinejad M. Effects of the fruit essential oil of *Cuminum cyminum Linn.* (Apiaceae) on acquisition and expression of morphine tolerance and dependence in mice. *Neurosci. Lett.* 2008; 440 (2): 134 – 9.

11. Khatibi A, Haghparast A, Shams J, Dianati E, Komaki A, Kamalinejad M. Effects of the fruit essential oil of *Cuminum cyminum* L. on the acquisition and expression of morphine-induced conditioned place preference in mice. *Neurosci Lett.* 2008; 448: 94 - 8.

12. Gholami A, Haeri-Rohani A, Sahraie H, Zarrindast MR. Nitric oxide mediation of morphine-induced place preference in the nucleus accumbens of rat. *Eur. J. Pharmacol.* 2002; 449: 269 - 77.

13. Rezayof A, Nazari-Serenjeh F, Zarrindast MR, Sepehri H, Delphi L. Morphine-induced place preference: involvement of cholinergic receptors of the ventral tegmental area. *Eur. J. Pharmacol.* 2007; 562: 92 - 102.

14. Rodriguez De Fonseca F, Rubio P, Martin-Calderon JL, Caine SB, Koob GF, Navarro M. The dopamine receptor agonist 7-OH-DPAT modulates the acquisition and expression of morphine-induced place preference. *Eur. J. Pharmacol*. 1995; 274: 47 - 55.

15. Bartoletti M, Ricci F, Gaiardi M. A GABA (B) agonist reverses the behavioral sensitization to morphine in rats. *Psychopharmacol.* (*Berl*). 2007; 192 (1): 79 – 85.

16. Vanderschuren LJMJ, Kalivas PW. Alteration in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacol.* (*Berl*). 2000; 151: 99 - 120.

17. Kitajima J, Ishikawa T, Fujimatu E, Kondho K, Takayanagi T. Glycosides of 2-C-methyl-d-erythritol from the fruits of anise, coriander and cumin. *Phytochem.* 2003; 62: 115 - 20.

18. Tewtrakul S, Itharat A. Nitric oxide inhibitory substances from the rhizomes of *Dioscorea membranacea. J. Ethnopharmacol.* 2007; 109: 412 – 6.

19. Xu LL, Zou K, Wang JZ, Wu J, Zhou Y, Dan FJ, et al. New polyhydroxylated furostanol saponins with inhibitory action against NO production from Tupistra chinensis rhizomes. *Molecules* 2007; 12: 2029 – 37.

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