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Article

Artemisia dracunculus essential oil: phytochemical study, pre-treatment and co-treatment effects on morphine withdrawal syndrome

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Drug addiction is one of the most important global problems. Medicinal herbs have been traditionally used in the management and treatment of opioid withdrawal syndrome and pain. The aim of this study was to determine the effect of *A. dracunculus* essential oil in reducing the symptoms of morphine withdrawal in mice. Male mice (25-30 g) were randomly assigned into 4 groups (n=10). Morphine-dependent groups received morphine (50 and 75 mg/kg ip; three times/day, 3 days) and a single injection of morphine (50 mg/kg) and then naloxone on the fourth day via IP injection. The control group received saline. The post-treated group received morphine for 3 days; on the fourth day, ten minutes before receiving naloxone, *A. dracunculus* essential oil with a dose of 75 mg/kg was injected. All groups received naloxone 2 hours after receiving the last dose of morphine; then, the morphine withdrawal symptoms were measured for 30 minutes. In the post-treated and co-treated groups, the body stretching and shaking the claw were significantly less than morphine-dependent groups ($p<0/05$). Also, in the post-treated and co-treated groups, the blinking, itching, and the number of standing on two legs significantly decreased compared to the morphine group. Hence, it might be concluded that *A. dracunculus* essential oil can significantly reduce morphine withdrawal symptoms.

Keywords: Mice. *Artemisia dracunculus*. Morphine. Essential oil.

INTRODUCTION

Addiction is an acute or chronic toxicity due to a natural or industrial drug, in a way that one acquires resistance as a result of its use, and consumes more amounts of it over time without discomfort due to the gradual reduction of its effects (Thakur, 2015). Addiction to opioids, including morphine, is one of the most important issues facing the health system and has imposed heavy economic burdens on the community by afflicting many people (Meysamie, Faramarzi, Naieni, 2006). The frequent use of medications can lead to adverse effects, including tolerance, psychological dependence, and physical dependence (Health *et al.,* 2009). Tolerance refers to the decrease of efficacy of some drugs such as morphine after being used repeatedly at a constant dosage or the need to use a higher dosage of it to retain previously experienced effects. The increase in opioid use will increase certain side effects such as constipation, itching, weight loss, loss of libido, and respiratory problems (Zarrindast *et al.,* 2003). Some studies have been done with the aim of reducing the symptoms of addiction withdrawal (Fu *et al.,* 2010). One group of methods to treat addicted patients are those in which the patient tolerates the fewest possible problems during the withdrawal. Medicinal Plants contain natural active ingredients that might be effective in treating different phases of addiction with comparatively less cost and fewer side effects. For example, *A. dracunculus* has drawn special attention due to pain killing and anti-anxiety properties. This plant, which is from the Asteraceae family, may also be called as tarragon, estragon, and wild dragon in English. *A. dracunculus* can be found as cultivated and

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agricultural in Iran (Bown, 1995). *A. dracunculus* is an aromatic and perennial plant with straight, branched, and rhizomatous stems. The plant's aerial organs contain fatty essential oils (Kordali *et al.,* 2005). The most important compounds of the essential oil are estragole (belonging to anethole isomers), α-pinene, β-pinene, comfan, sabine, myrcene, phellandrene, limonene, linalool, delta-4-carene, alpha-phellandrene, cis-Ocimene, and trans-Ocimene. *A. dracunculus* has been demonstrated to exhibit several properties, such as mild sedative, and cardiovascular disease- and obesity-preventing. The plant also exerts antioxidant, antinociceptive, and anti-anxiety properties by affecting opioid receptors (Sayyah, Nadjafnia, Kamalinejad, 2004). The tincture extract of *A. dracunculus* has been shown to have a calming and anticonvulsant activity, as well as antidiabetic action and inhibition of blood platelet adhesion action (Duric *et al.,* 2015). Therefore, this study was conducted to investigate the effect of the *A. dracunculus* essential oil in reducing morphine withdrawal symptoms in mice.

MATERIAL AND METHODS

Preparation of medicinal plants and essential oils

The *A. dracunculus* plant used in this study was obtained from a research farm in Shahrekord. A herbarium specimen (No.1019) was deposited at the Medicinal Plant Research Center of the Shahrekord University of Medical Sciences after the sample was identified by an expert botanist. Plant aerial parts were collected at the flowering stage. The samples were then dried away from light and moisture and at room temperature. After shadow drying, the plant samples were pulverized. Finally, 50 g of the sample was weighed for the essential oil extraction. The extraction was done by a Clevenger Apparatus. Extraction was done over 4 hours. The collected essential oil was dehydrated with anhydrous sodium sulfate. The resulting essential oils were stored in a freezer at -20 °C (Sayyah, Nadjafnia, Kamalinejad, 2004; Kordali *et al.,* 2005).

Identification of essential oil's chemical compounds

The identification of essential oil compounds was performed using a gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). The instrument used was TRACE MS (ThermoQuest-Finnigan Co.). The type of column was DB-5, the length of the column was 30 m, the internal diameter was 0.25 mm, and the column's thermal protocol ranged from 60°C to 250 °C at a rate of 5 °C per minute. Carrier gas was helium 99.999%, type of injection Spilit, 0.2 µL, and the gas flow rate was adjusted to 1.1 ml/min.

Animal study

The animals used in this experimental study were purchased from the Pasteur Institute of Iran. All mice were kept at the appropriate standard temperature [(21 ± 2) °C] and 12-hour light/12-hour dark cycle and were given free access to water and food. All ethical considerations and the protocols of work with laboratory animals approved by the Laboratory Animal Rights Monitoring Committee of the University were observed in this study (ethics code: IR.SKUMS.1395.4).

Forty male mice weighing 25-30 g were divided into 4 groups of 10 each: Morphine group receiving morphine for 4 days; control group receiving normal saline (1 ml/kg) for 4 days. post-treatment group receiving 75 mg/kg of essential oil via IP injection 10 min before receiving naloxone after receiving morphine for 3 days; and the co-treatment group receiving 75 mg/kg of essential oil along with morphine for 4 days (Maham, Moslemzadeh, Jalilzadeh-Amin, 2014). To induce morphine dependence, morphine at doses of 50 and 75 mg/kg was administered intraperitoneally three times per day at 8, 11, and 14 o´clock for 3 days, and on the fourth day, a single injection of morphine (50 mg/kg) was conducted (Zarrindast *et al.,* 2003; Gholami *et al.,* 2015; Alipour *et al.,* 2018). For the induction of morphine withdrawal syndrome, 2 hours after receiving the last dose, naloxone (5 mg/kg)

was injected. Then, the frequency of the symptoms of morphine withdrawal including the number of standing on two legs, body stretching, jumping, shaking the claw, and falling eyelids after naloxone injection was determined (Miladi-Gorgi *et al.,* 2009).

Data analysis

The data are shown as the mean±SEM. All the results were analyzed by analysis of variance (ANOVA) test followed by Tukey's test. A p-value of less than 0.05 was considered to be significant.

RESULTS

GC-MS analysis of *A. dracunculus* essential oil

The results of GC-MS analysis of essential oil are shown in Table I. A total of 22 compounds were identified in the essential oil of *A. dracunculus*, accounting for 99.83% of all essential oil compounds. The main compounds of essential oil included p-allylanisole (75.83%), e-β-ocimene (72.5%), z-β-ocimene (62.5%), and limonene (1.94%) (Figure 1).

TABLE I - Chemical compounds identified in *Artemisia dracunculus* essential oil by GC-MS analysis

No	Compound	RI	Area% GCMS
1	Hexenal<2E->	816/18	0/05
2	α-Pinene	931/98	0/53
3	Camphene	947/09	0/06
4	Sabinene	970/93	0/07
5	β-Pinene	975/58	0/07
6	β-Myrcene	987/21	0/1
7	Limonene	1026/6	1/94
8	E-β-Ocimene	1033/3	5/72
9	Z-β-Ocimene	1044/1	5/62
10	α-Terpinene	1086/5	0/12
11	p-Allylanisole	1205/9	83.75
12	Bornyl acetate	1284/9	0/15
13	Methyleugenol	1404/3	0/37
14	trans-Caryophyllene	1418/8	0/14
15	Germacrene D	1480/8	0/27
16	Unknown	1492/2	0/16
17	Bicyclogermacrene	1496/3	0/32
18	E-E-Farnesene	1505/2	0/11
19	Sesquiphellandrene<beta->	1522/3	0/11
20	Spathulenol	1579/4	0/14
21	Hexadecane	1586/3	0/09
22	Heptadecane	1690/2	0/1

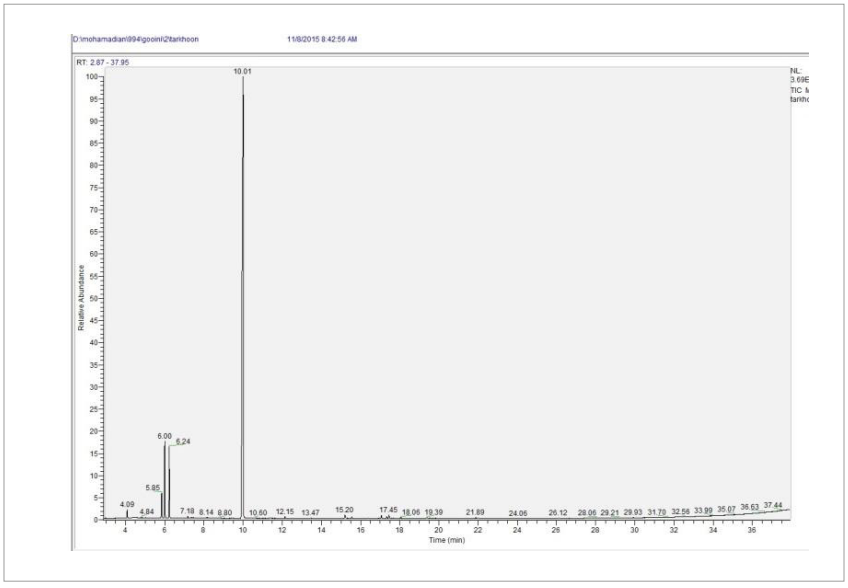

FIGURE 1 - The chromatography spectrum of *Artemisia dracunculus* essential oil.

The effect of *A. dracunculus* essential oil on the frequency of jumping

The effects of the *A. dracunculus* essential oil co-treatment and post-treatment on the frequency of jumping are illustrated in Figure 2. The frequency of jumping in the morphine-dependent group after naloxone administration and in the control group was not significantly different (P>0.05). Essential oil co-treatment and post-treatment did not significantly decrease the frequency of jumping (P>0.05). No significant difference was observed in the frequency of jumping between the co-treatment and post-treatment groups (P>0.05).

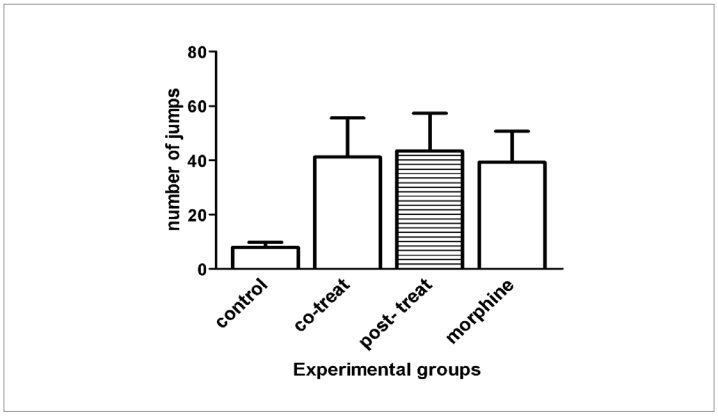

FIGURE 2 - The effects of *Artemisia dracunculus* essential oil co-treatment and post-treatment on the frequency of jumping after naloxone administration in morphine-dependent mice. Post-treatment group received morphine for 4 days and then naloxone on the fourth day; one the group received 75 mg/kg of essential oil before naloxone administration; co-treatment group received morphine along with essential oil at 75 mg/kg; and the control group received normal saline for 4 days.

The effect of *A. dracunculus* essential oil on the frequency of blinking

As Figure 3 illustrates, the frequency of blinking was significantly higher in the morphine-dependent group after naloxone administration than in the control group (P<0.01).

Essential oil co-treatment significantly decreased the frequency of blinking compared to the morphine-dependent group (P<0.01). However, no significant decrease in the frequency of blinking was observed in the post-treatment group compared to the morphine-dependent group (P>0.05). Furthermore, no significant difference in this variable was seen between the post-treatment and co-treatment groups (P>0.05).

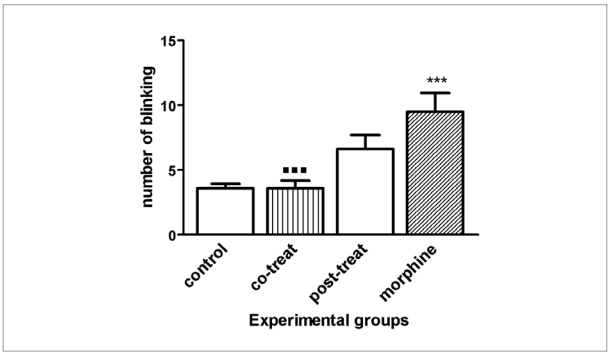

FIGURE 3 - The effects of *Artemisia dracunculus* essential oil co-treatment and post-treatment on the frequency of blinking after naloxone administration in morphine-dependent mice. The post-treatment group received morphine for 4 days and then naloxone on the fourth day; one group received 75 mg/kg of essential oil before naloxone administration; the co-treatment group received morphine along with essential oil at 75 mg/kg; and the control group received normal saline for 4 days; *** $P<0.001$ (morphine-dependent vs. control); ■■■ $P<0.001$ (morphine-dependent vs. co-treatment).

The effect of *A. dracunculus* essential oil on the frequency of falling eyelids

The frequency of falling eyelids was significantly higher in the morphine-dependent group after naloxone administration than in the control group (P<0.01). Essential oil co-treatment and post-treatment did not significantly decrease the frequency of falling eyelids compared to the morphine-dependent group (P>0.05). No significant difference was observed in the frequency of falling eyelids between the co-treatment and post-treatment groups (P>0.05) (Figure 4).

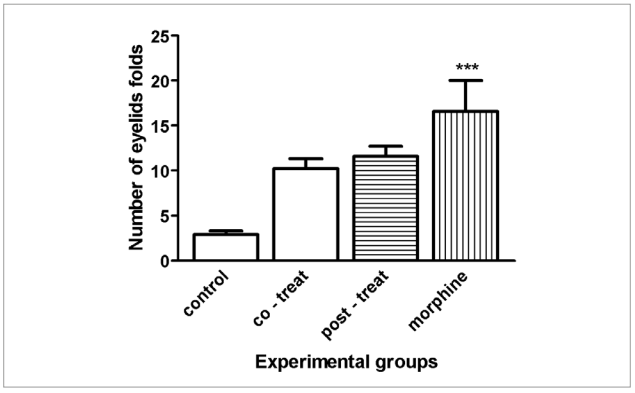

FIGURE 4 - The effects of *Artemisia dracunculus* essential oil co-treatment and post-treatment on the frequency of falling eyelids after naloxone administration in morphine-dependent mice. The post-treatment group received morphine for 4 days and then naloxone on the fourth day; one group received 75 mg/kg of essential oil before naloxone administration; the co-treatment group received morphine along with essential oil at 75 mg/kg; and the control group received normal saline for 4 days; *** $P<0.001$ (morphine-dependent vs. control).

The effect of *A. dracunculus* essential oil on the frequency of the number of standing on two legs

The effects of the *A*. *dracunculus* essential oil co-treatment and post-treatment on the frequency of the number of standing on two legs in morphine withdrawal syndrome mice are illustrated in Figure 5. The frequency of standing on two legs was significantly higher in the morphine-dependent mice than in the control mice ($P<0.05$). Essential oil co-treatment significantly decreased the frequency of standing on two legs compared to the morphine-dependent group ($P<0.05$) but its post-treatment did not cause any significant decrease in this variable compared to the morphine-dependent group ($P>0.05$). No significant difference in this variable was noted between the co-treatment and post-treatment groups ($P>0.05$).

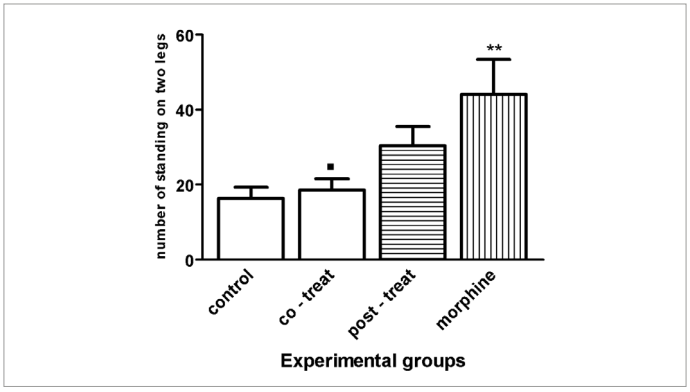

FIGURE 5 - The effect of *Artemisia dracunculus* essential oil co-treatment and post-treatment on the frequency of standing on two legs after naloxone administration in morphine-dependent mice. The post-treatment group received morphine for 4 days and then naloxone on the fourth day; one group received 75 mg/kg of essential oil before naloxone administration; the co-treatment group received morphine along with essential oil at 75 mg/kg; and the control group received normal saline for 4 days; ** $P<0.05$; ▪ $P<0.01$ (morphine-dependent vs. co-treatment).

The effect of *A. dracunculus* essential oil on stool weight

As illustrated in Figure 6, stool weight was not significantly different between the morphine-dependent group after naloxone administration and the control group (P>0.05). In addition, stool weight in the co-treatment and post-treatment groups was not significantly different compared to that in the morphine-dependent group. No significant difference in this variable was observed between the co-treatment and post-treatment groups (P>0.05).

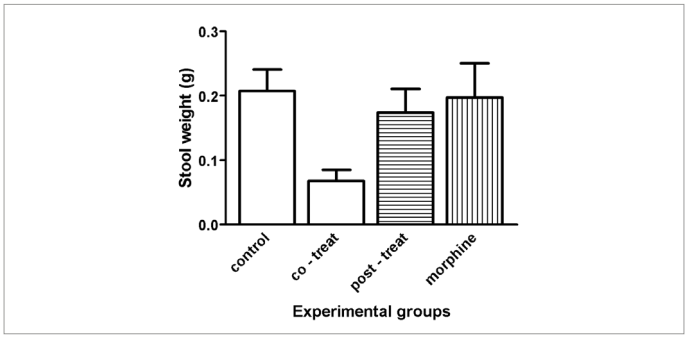

FIGURE 6 - The effect of *Artemisia dracunculus* essential oil co-treatment and post-treatment on stool weight after naloxone administration in morphine-dependent mice. The post-treatment group received morphine for 4 days and then naloxone on the fourth day; one group received 75 mg/kg of essential oil before naloxone administration; the co-treatment group received morphine along with essential oil at 75 mg/kg; and the control group received normal saline for 4 days.

The effect of *A. dracunculus* essential oil on the frequency of shaking the claw

As illustrated in Figure 7, the frequency of shaking the claw was significantly higher in the morphine-dependent group after naloxone administration than in the control group (P<0.01). In addition, shaking the claw significantly decreased in the co-treatment and post-treatment groups compared to the morphine-dependent group (co-treatment (P<0.01) and post-treatment (P<0.05). No significant difference in this variable was observed between the co-treatment and post-treatment groups (P>0.05).

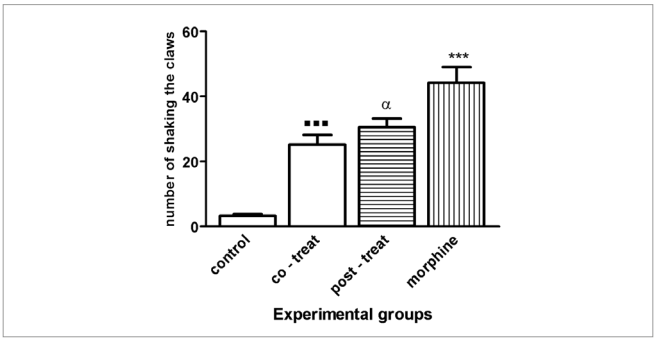

FIGURE 7 - The effect of *Artemisia dracunculus* essential oil co-treatment and post-treatment on the frequency of shaking the claws after naloxone administration in morphine-dependent mice. The post-treatment group received morphine for 4 days and then naloxone on the fourth day; one group received 75 mg/kg of essential oil before naloxone administration; the co-treatment group received morphine along with essential oil at 75 mg/kg; and the control group received normal saline for 4 days; *** P<0.001 (morphine-dependent vs. control); ▪▪▪ P<0.05 (morphine-dependent vs. co-treatment); α P<0.05 (morphine-dependent vs. post-treatment).

The effect of *A. dracunculus* essential oil on the frequency of itching

The effects of the A. dracunculus essential oil co-treatment and post-treatment on the frequency of itching in morphine withdrawal syndrome mice are illustrated in Figure 8. The frequency of itching was significantly higher in the morphine-dependent group after naloxone administration than in the control group (P<0.01). Essential oil co-treatment significantly decreased the frequency of itching compared to the morphine-dependent group (P<0.05). However, no significant decrease was observed in the frequency of itching between the morphine-dependent and post-treatment groups (P>0.05).

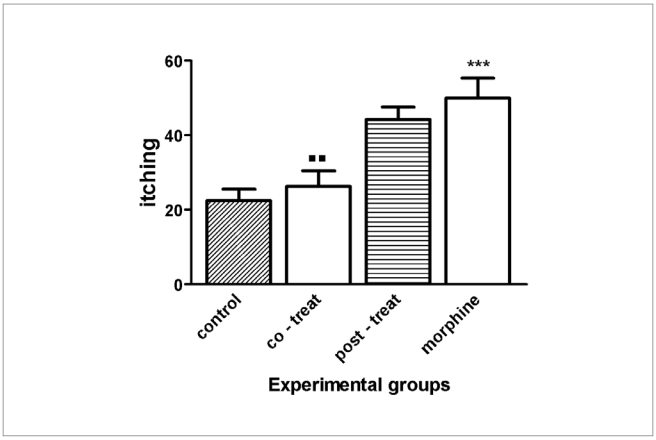

FIGURE 8 - The effect of *Artemisia dracunculus* essential oil co-treatment and post-treatment on the frequency of itching after naloxone administration in morphine-dependent mice. The post-treatment group received morphine for 4 days and then naloxone on the fourth day; one the group received 75 mg/kg of essential oil before naloxone administration; the co-treatment group received morphine with essential oil at 75 mg/kg; and the control group received normal saline for 4 days; *** P<0.001 (morphine-dependent vs. control); ▪▪ P< 0.01 (morphine-dependent vs. co-treatment).

The effect of *A. dracunculus* essential oil on the frequency of body stretching

As Figure 9 illustrates, the frequency of body stretching was significantly higher in the morphine-dependent group after naloxone administration than in the control group (P<0.01). Essential oil co-treatment and post-treatment significantly decreased the frequency of body stretching compared to the morphine-dependent group (co-treatment (P<0.01) and post-treatment (P<0.05). However, no significant decrease was observed in the frequency of this variable between the co-treatment and post-treatment groups (P>0.05).

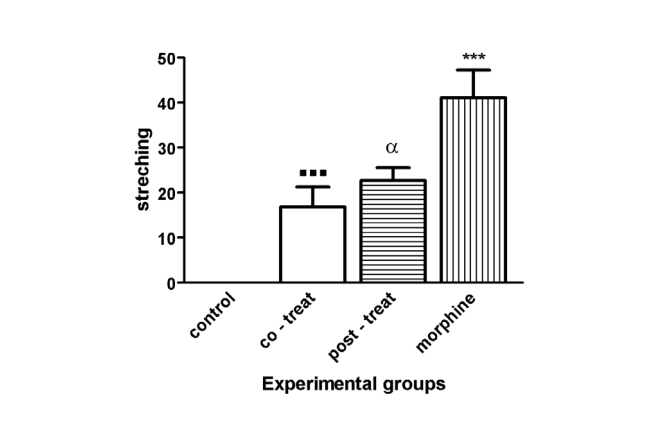

FIGURE 9 - The effect of *Artemisia dracunculus* essential oil co-treatment and post-treatment on the frequency of body stretching after naloxone administration in morphine-dependent mice; post-treatment group received morphine for 4 days and then naloxone on the fourth day; the group receiving 75 mg/kg of essential oil before naloxone administration; co-treatment group received morphine along with essential oil at 75 mg/kg; and control group received normal saline for 4 days; *** $P<0.001$ (morphine-dependent vs. control); ▪▪▪ $P<0.001$ (morphine-dependent vs. co-treatment); α $P<0.05$ (morphine-dependent vs. post-treatment).

DISCUSSION

The results of this study showed that *A. dracunculus* essential oil treatment could reduce the frequency of withdrawal syndrome symptoms such as standing on two legs, blinking, body scratching, shaking the claws and itching, as in all experiments, all withdrawal symptoms (except for stool weight) significantly increased in the morphine-dependent group, indicating the induction of addiction. The dopaminergic neuronal circuits of the mesolimbic pathway, especially the central part of the nucleus accumbent, are the most important locus of the effect of morphine in this area. Therefore, morphine, by inhibiting the inhibitory effects of GABAergic neurons on dopamine neurons in the ventral tegmentum area, increases the release of dopamine from these neurons in their ending region, ie, the nucleus accumbent, and produces two of its main effects, the induction of motor activity and pleasure. Various studies have also shown that metabotropic and ionotropic glutamate receptors are involved in this event (Nestler, 2001). This confirms the results of the current study in the morphine receiving group after naloxone administration. In the co-treatment group, the frequency of blinking, number of standing on two legs, and body itching significantly decreased compared to the morphine-dependent group. Furthermore, the frequency of shaking the claw and body stretching was significantly lower in the groups receiving essential oil as co-treatment and post-treatment than in the morphine-dependent group. However, the frequency of jumping and falling eyelids and stool weight in the co-treatment and post-treatment groups were not significantly different from those in the morphine-dependent group., Co-treatment caused a more pronounced decrease in the morphine withdrawal symptoms than the post-treatment. As a result, the essential oil and morphine co-treatment exhibited a comparatively greater effect in decreasing the symptoms of morphine withdrawal syndrome.

The identified main compounds in this essential oil included estragole (73.3%), limonene (5.4%), e-β-ocimene (5.3%), β-pinene (3.4%), and z-β-ocimene (3%) in the study of Fraternale (Fraternale, Flamini, Ricci, 2015), estragole (over 82%) in the study of Obolskiy (Obolskiy *et al.,* 2011), and estragole (79.5%), e-β-ocimene (7.2%), and z-β-ocimene (8.8%) in the study of Obistioiu (Obistioiu *et al.,* 2014). In this study, the main compounds of this essential oil were identified

as p-allylanisole (83.75%), e-β-ocimene (5.72%), z-β-ocimene (5.62%), and limonene (1.94%). Differences in the chemical composition of essential oils can be attributed to differences in harvesting season, climatic conditions, geographic region of growth, plant parts, and methods and duration of extraction. Estragole is a phenylpropene compound that is one of the major compounds of the essential oil of *A. dracunculus*. This compound can reduce the action of acetylcholinesterase (Kerachian *et al.,* 2007), thereby decreasing the withdrawal symptoms (Jain and Kulkarni 1999). This mechanism confirms the action mechanism of the *A. dracunculus* essential oil on morphine withdrawal syndrome. Various properties have been reported for the *A. dracunculus*, such as analgesia (Sayyah, Nadjafnia, Kamalinejad, 2004; Maham, Moslemzadeh, Jalilzadeh-Amin, 2014), nervous system relaxing, anti-flatulence, anticonvulsant, appetizing, antispasmodic, anticancer, refrigerant, gastric acid modulating, urinating, and anti-inflammatory activities. Previous studies have also shown that the antiepileptic effect of this plant is due to the presence of compounds such as estragole, methyl eugenol and benzodiazepine (Kavvadias *et al.,* 2000; Ribnicky *et al.,* 2011). In a 2014 study, Maham et al. examined the antinociceptive properties of the essential oil of *A. dracunculus* in Swiss albino mice and Wistar rats using hot plate tests, formalin, and acetic acid. *A. dracunculus* essential oil with 100 mg/kg and 300 mg/kg doses significantly reduced pain in the first and second stages of formalin test. The results of the hot plate and acetic acid tests also showed that the pain in mice receiving *A. dracunculus* essential oil was significantly reduced. Two main chemical components of the essential oil of *A. dracunculus* were pulegone and estragole. It is more likely that the antinociceptive effect of the essential oil of *A. dracunculus* is caused by the presence of pulegone (Maham, Moslemzadeh, Jalilzadeh-Amin, 2014). In vitro studies revealed that probably pulegone inhibited the production of inflammatory mediators from the cascade of cyclooxygenase (Kawata, Kameda, Miyazawa, 2008). In addition, estragole is probably involved in blocking nerve stimulation (Leal-Cardoso *et al.,* 2004). Finally, it is interesting to note that a-pinene and limonene, two monoterpenes of the essential oil of *A. dracunculus*, can also increase the antinociceptive activity of essential oil of *A. dracunculus*, since they have shown anti-inflammatory and antinociceptive effects in several animal models (Guimarães, Quintans, Quintans-Júnior, 2013). Other essential oils of *A. dracunculus* constituents also appear to be involved in its antinociceptive action. Thus, the presence of these compounds prevented the development of severe pain during the withdrawal and reduced the severity and difficulty of the withdrawal syndrome, which is consistent with the results of our study. Further studies are needed to clarify the mechanism of action and the components responsible for these pharmacological effects. It is also recommended to study the consequences of *A. dracunculus* essential oil, as a co-treatment and post-treatment in the acquisition, tolerance, and dependence of morphine with different doses, to select the most effective dose.

CONCLUSION

A. dracunculus essential oil co-treatment and post-treatment significantly reduced most withdrawal symptoms. In our experiments, co-treatment reduced the symptoms of withdrawal syndrome more pronouncedly than post-treatment and can be used for this purpose.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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