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Original Article

The Effects of *Cymbopogon citratus* (lemon grass) on Morphine Withdrawal Signs in Male Mice

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Abstract

Background and Aim: The antispasmodic, analgesic, antioxidant, anti-inflammatory and sedative effects of *Cymbopogon citratus* (*C. citratus*) have been already examined in various studies. Hence, the present study was conducted to investigate the effect of *C. citratus* hydroalcoholic extract on morphine withdrawal signs in male mice.

Materials and Methods: Male NMRI mice (20-30g) were rendered dependent by intraperitoneal (i.p.) injections of morphine three times daily at doses of 50, 50 and 75 mg/kg, respectively, for 3 days. After the last administration of morphine on the fourth day, different doses of *C. citratus* extract (140, 280 and 560 mg/kg, i.p.) and clonidine (0.3mg/kg, i.p.) were administered 30 min before the administration of naloxone (5 mg/kg, i.p.). The mice were observed for 30 minutes for the withdrawal signs, i.e., the characteristic jumping, grooming, teeth chattering, climbing, rearing, wet dog shakes, writing and diarrhea.

Results: The findings revealed that all doses of *C. citratus* ($p<0.01$, $p<0.001$ and $p<0.01$, respectively) and clonidine ($p<0.001$) could reduce the number of jumps. Moreover, all doses of the extract reduced the grooming ($p<0.05$), climbing ($p<0.05$), diarrhea ($p<0.01$), and writhing behavior ($p<0.05$). Rearing and wet dog shakes were reduced only by the high dose of the extract ($p<0.05$). Clonidine decreased the other checked signs (except rearing and wet dog shake behaviors) such as grooming ($P< 0.01$), teeth chattering ($P< 0.05$), climbing ($P<0.05$), writing ($P<0.01$) and diarrhea ($P<0.01$).

Conclusion: The results indicated that *C. citratus* extract could attenuate morphine withdrawal signs. However, further studies are required to clarify its exact mechanism of action.

Keywords: *Cymbopogon citrates*, Morphine dependence, Naloxone, Withdrawal signs

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Introduction

Opioid dependence is widely acknowledged as a chronic and relapsing disease of the brain that brings about influential medical, social and economic problems to both the individual and to the society. The individuals who depend on opioid are exposed to substantial health risks including overdose, transmission of infectious diseases, poor physical and mental health and frequent hospitalization (1).

Morphine is considered as one of the most effective opioid pain relievers for controlling the moderate to acute pain. However, the chronic consumption of morphine usually has unwanted adverse impacts, including analgesic, tolerance and physical dependence (2). Hence tolerance gradually diminishes the effect of morphine, it usually requires escalating doses to relieve the pain. Intensive physical and affective disorders, including irritability, anxiety, nausea, and diarrhea as well as muscular and abdominal pain upon the discontinuation of morphine are commonly attributed to morphine dependence. These symptoms, which are extremely aversive, might turn out to be effective obstacles to abstinence treatment (3). Nevertheless, no approved treatment has been developed so far for opioid tolerance and dependence. To find an appropriate treatment, herbal therapy, complementary, and traditional medicine are extremely appreciated. The number of studies mentioned above indicate the variety of researches conducted on systems or drugs that alleviate morphine withdrawal syndrome. They include drugs that influence dopaminergic, serotonergic (4) and adrenergic agents (5) as well as excitatory amino acid (6), GABAergic systems (7) and herbal medicines (8-12). Apart from the involvement of these neural systems, a study demonstrated the possible role of oxidative stress and nitric oxide (NO) synthesis in the development of morphine dependence and tolerance (13). Meanwhile, previous studies have shown the role of inflammatory cytokines, such as interleukin 12 (IL12) and tumor necrosis factor alpha (TNF-α) on morphine withdrawal signs (14).

Cymbopogon citratus (*C. citratus*) Stapf (Poaceae family), known as lemon grass, is commonly used in folk medicine for the treatment of nervous and gastrointestinal disturbances. It is also used as an antispasmodic, analgesic, anti-inflammatory and sedative agent (16). A study indicated that *C. citratus* is capable of having antioxidant activities (17). In this regard, pre-treatment with antioxidants (free radical scavengers) and anti-inflammatory agents could attenuate some aspects of the morphine withdrawal signs (14, 18).Given this background, hence, the purpose of the present study was to investigate the possible effects of *C. citratus* hydroalcoholic extract on morphine withdrawal signs in male mice.

Materials and Methods

Preparation of the Extract

Fresh leaves of *C. citratus* (lemon grass) were washed and air dried in the laboratory for two weeks. They were ground with Excella mixer grinder, and then sieved with a mesh of size 0.5mm. The obtained powdered sample was stored in clean air tight containers at ambient temperature until the time of its utilization. The powder (50g) was placed in a 500ml conical flask. Subsequently, 250ml of ethanol was added to the powder, and then it was stirred vigorously with a magnetic stirrer. The resulting substance was then allowed to stand for 36h after which it was stirred and filtered. The extract was concentrated using a rotary evaporator to 50ml. It was then cooled and stored in a refrigerator before its utilization (19).

Animals

The male NMRI mice, weighing 25-35g, which were used in this study, were housed in ventilated rooms at the temperature of 24±2°C with a 12h light/dark cycle and 60±5% humidity. They were provided with food and water *ad libitum*. All experiments were carried out in accordance with the guidelines of Urmia University of Medical Sciences for animal care and use.

Morphine Dependence

For the induction of morphine dependence, the mice were treated intraperitoneally (i.p.) with morphine three times a day (10 a.m., 1 p.m. and 4 p.m.) for three days, and the doses of morphine were 50, 50 and 75 mg/kg respectively. The higher daily dose, injected at 4 p.m., was aimed at minimizing any overnight withdrawal. On the fourth day, they received the last dose of morphine (50 mg/kg, 10 a.m.) (20).

Naloxone-Precipitated Withdrawal Syndrome

Withdrawal signs were elicited by i.p. injection of naloxone hydrochloride (5 mg/kg) 2 h after the last injection of morphine. The counted and checked signs were evaluated during a 30 min period starting just after naloxone injection. Jumps were counted, and the checked signs including diarrhea, grooming, climbing, rearing, teeth chattering, writing and wet dog shakes were evaluated over 30 min with one point given for the presence of each sign during each period (range of scores: 0-3) (8-12).

Experimental Groups

Forty mice were randomly divided into 5 groups with 8 animals per group: 1-One chronically intraperitoneally (i.p.) morphine (as a negative control group): in this group normal saline (10ml/kg) was administered i.p. 30 min after the last dose of morphine, and 30 min later naloxone was injected. 2-One chronically i.p. morphine (as a positive control group): in this group clonidine (0.3 mg/kg) was administered i.p. 30 min after the last dose of morphine, and 30 min later naloxone was injected. 3-Three chronically i.p. morphine (as a treatment group): in this group, different doses of *C. citratus* (140,280 and 560 mg /kg,i.p.) hydroalcoholic extract were administered i.p. 30 min after the last dose of morphine, and 30 min later naloxone was injected.

Statistical Analysis

The data were expressed as mean ± S.E.M. One-way ANOVA followed by Duncan test was used for the comparison of data, and *P* values less than 0.05 were considered significant. The Mann-Whitney U test was used for the comparison of checked signs data. All statistical calculations were done with SPSS for Windows (SPSS 19) software.

Ethics statement

Ethical approval has been received from the Ethical Committee of Urmia University of Medical Sciences, No: 42, Date: 25.9.2015).

Results and Discussion

Our results demonstrated that the i.p. administration of different doses (140, 280 and 560 mg/kg) of *C. citratus* compared to the control group (106.09±47.68) could significantly reduce the number of jumps in morphine-dependent mice (18±19.97, 12.75±10.17 and 16.5±15.67; $p<0.01$, $p<0.001$ and $p<0.01$, respectively). Moreover, clonidine (0.3mg/kg), as a reference drug, could reduce (24.3±4.75, $p<0.001$) the number of jumps (Table 1). Furthermore, our results exhibited that diarrhea could be decreased with all doses of the extract ($p<0.01$). Rearing, wet dog shakes and teeth chattering behaviors decreased only by high (560mg/kg) dose of the extract ($p<0.05$, $p<0.05$and $p<0.01$, respectively). Writing ($p<0.05$), grooming ($p<0.05$) and climbing ($p<0.05$) behavior were decreased with all doses of the extract ($p<0.05$). In addition, clonidine significantly reduced other signs, such as grooming ($p<0.01$), climbing ($p<0.05$), teeth chattering ($p<0.05$), writhing ($p<0.01$) and diarrhea

Table 1: Effects of Different doses of *Cymbopogon citratus (C. citratus)* on checked signs of morphine withdrawal signs in morphine-dependent mice.

Treatment/Group	Number of jumping	Grooming	Teeth chattering	Climbing	Rearing	Wet dog shakes	writhing	Diarrhea
Negative control (Normal saline)	106.09±47.68	2±(2-3)	2±(2-2)	2±(1-2)	2±(1-3)	1±(1-2)	2±(1-2.5)	3±(2-3)
Positive control (Clonidine 0.3 mg /kg)	24.3±4.75 ***	1±(1-0) **	1±(1-0) *	1±(1-1) *	1±(1-1.5)	1±(1-1)	0±(0-0.5) **	1±(0.5-2) **
***C. citratus* 140 mg/kg**	18±19.97 **	0±(0-1) *	1±(1-2)	1±(0-1) *	1±(1-1)	1±(1-2)	1±(0-1) *	1±(0-2) **
***C. citratus* 280mg/kg**	12.75±10.17 ***	0.5±(0-1.75) *	1±(1-1.75)	1±(1-1) *	1±(1-1.75)	1±(0.25-1)	1±(0.5-1.5) *	1±(1-1.75) **
***C. citratus* 560mg/kg**	16.5±15.67 **	0.5±(0-1.75) *	0.5±(0-1) **	1±(1-1) *	1±(0.5-1) *	0±(0-0.75) *	1±(0.5-2) *	1±(1-1) **

The data was expressed as Mean ± SEM for eight mice in each group with Tukey-Karamer test and Mann-Whitney U test for number of jumping and other checked signs, respectively.* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ compared to control group, respectively.

($p<0.01$). Nevertheless, clonidine could not decrease the rearing and wet dog shake behaviors ($p>0.05$) (Table 1).

The repeated administration of morphine produced physical dependence to the extent that naloxone administration to the mice after the repeated morphine generated a specific set of behavioral responses including jumping, climbing, teeth chattering, writhing, wet dog shakes, grooming and rearing. In the control group that was chronically treated with morphine, significant behavioral responses (as detailed above) were shown after naloxone administration. Our results demonstrated that the different doses of CC extract could reduce the number of jumps in morphine-dependent mice. Confirming our results, another study indicated that clonidine, as a reference drug, could significantly reduce the number of jumps (11, 21).

Several investigations have reported that jumping is an important sign for evaluating opioid dependence, though an effective drug should equally counteract other signs of withdrawal. Furthermore, diarrhea and rearing behavior are the other common signs found during morphine withdrawal (22, 23). However, our results exhibited that diarrhea would be decreased with all doses of the extract. These findings supported previous studies and demonstrated the anti-diarrheal activity of the extract. Rearing behavior decreased only by the high doses of the extract. Confirming our findings, another study reported that the *C. citratus* essential oil could reduce rearing in open-field tests. Writing behavior was decreased with all doses of the extract. Our results are in agreement with previous reports that indicate the antispasmodic activity of *C. citratus* extract. Moreover, the oral or i.p. administration of *C. citratus* dose-dependently cause the inhibition of abdominal contractions induced by acetic acid in mice (24). Climbing decreased with all doses of the extract. In accordance with others, grooming behavior was decreased with all doses of the extract (25). Wet dog shakes and teeth chattering decreased only with the high doses of the extract. Furthermore, clonidine significantly reduced the other checked signs except rearing and wet dog shakes compared to the control group.

The exact mechanism of the action of the *C. citratus* extract could not be predicted from present study experiments. However, *C. citratus* contains active ingredients like myrcene, citronellal, citronellol and geraniol. The essential oil consists mainly of citral, a volatile oil with strong lemon fragrance (26). On the other hand, it seems that the main chemical constituent of the extract, citral, was responsible for their anti-diarrheal activity (27). Costa et al, reported that acute treatment with *C. citratus* essential oil (EO) did not result in neurotransmitters (e.g. dopamine and serotonin), and its metabolites changes were evaluated in cortex, striatum, pons, and hypothalamus. They showed that the anxiolytic-like effect of its EO is mediated by the GABAA receptor-benzodiazepine complex (28). However, these data reinforce the idea that the major compounds are not always responsible for biological activity. Furthermore, according to Silva et al's findings, the i.p. administration of *C. citratus* extract had anticonvulsant effect, which was blocked by the pretreatment with flumazenil (as a competitive antagonist of benzodiazepine binding) suggesting and enhancing a possible effect on the GABAergic neurotransmission system. Moreover, it seems that GABAergic system has a significant role in some biological effects of *C. citratus* (29). Consistent with these findings, our previous study demonstrated that the flavonoids of *Rosa damascena* essential oil with GABAergic activity could attenuate morphine withdrawal signs (9).

Apart from these findings, one of the other proposed mechanisms that is involved in the opiate dependency and withdrawal is oxidative stress. There are two mechanisms involved in the development of oxidative stress: accumulation of free radicals and reduction of the antioxidant activity (30). The neurotransmitter and gasotransmitters involved are predominantly NO and glutamate (31). In this regard, previous studies have shown that L-NA(NG-nitro-L-arginine) and 7-NI (7-Nitroindazol), as nitric oxide inhibitors synthase (NOS) inhibitors, could attenuate naloxone-precipitated withdrawal signs, such as rearing, jumping, ptosis, rhinorrhoea, and irritability on touch, in morphine-dependent rats (32). Confirming this view, previous studies demonstrated that pre-treatment with free radicals' scavengers could attenuate the expression of morphine-induced withdrawal signs (18). In this study, we are trying to explore the ability

and efficacy of *C. citratus* extract as a supplementary therapy to attenuate opiate withdrawal signs. In this regard, previous studies have reported the antioxidant activity of *C. citratus* (17), which is due to the fact that *C. citratus* contains tannin, flavonoid and phenolic compounds that have higher antioxidant properties (33). Antioxidants reduce free radicals in oxidative stress pathway. Hence, it blocks oxidative stress in opioid dependence and tolerance.

Meanwhile, previous studies have confirmed the role of inflammatory cytokines on morphine withdrawal signs. On the other hand, during the chronic or long-term usage of morphine, the expressions of these inflammatory cytokines such as IL12 and TNF-α were increased (14). In support of this view, the suppression of these inflammatory cytokines reduced some aspects of morphine withdrawal signs (e.g. hyperactivity and weight loss) in rats (34). In this regard, previous studies have shown that polyphenol rich extractants and citral are the chief components of *C. citratus* extracts exhibiting anti-inflammatory activities (35). Moreover, citral and the other monoterpenes of *C. citratus* extract exhibited anti-inflammatory activity by using carrageenan-induced paw edema in rats (36). Furthermore, a study showed that the secretion of inflammatory cytokines (e.g. TNF-α) could be inhibited by *C. citratus* extracts (37).

Conclusion

The results described in this study indicate, for the first time, that *C. citratus* could attenuate some major morphine withdrawal signs. However, further studies are required to clarify their exact mechanisms of action.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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