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Original Article

Comparing the Effect of Saffron Aqueous Extract with Purslane on Cocaine-induced Locomotor Activity in Mice

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Introduction: Cocaine can increase motor activity by activating the dopaminergic system. The aim of this study is investigating the effect of saffron and purslane extract on cocaine-induced motor activity in mice.

Materials and Methods: 63 mice divide in 9 groups of 7. Group one was the control group and receive saline by intraperitoneal injection and their locomotor activity was measured. The second group received a medium dose of saffron, 150 mg/kg, and the third group received a medium dose of purslane, 50 mg/kg. The other 6 groups were first injected with cocaine at a dose of 10 mg/kg for 10 days. The motor activity of the mice was measured and the results were recorded. On the 10th day, after one hour of cocaine injection, groups 4, 5 and 6 were treated with saffron at doses of 50, 150 and 250 mg/kg respectively and groups 7, 8 and 9 were treated with purslane at doses of 20, 50 and 80 mg/kg respectively.

Results: The injection of saffron and purslane extract alone in the second and third group mice caused a decrease in the motor activity of the mice compared to the first group. Injection of 10 mg/kg of cocaine in mice causes an increase in their motor activity. After the induction of addiction the injection of saffron and purslane extract caused a dose-dependent decrease in motor activity in mice.

Conclusion: The findings show that the aqueous extract of saffron and purslane may play important role in reducing the symptoms of cocaine withdrawal and motor activity.

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Introduction

Cocaine addiction is defined as a mental illness characterized by uncontrollable and compulsive drug seeking and drug abuse, which has negative health and social consequences [1]. Cocaine is a strong and addictive psychostimulant. The available evidence shows that this substance, by blocking the dopamine transporter and subsequently increasing extracellular dopamine, firstly causes stimulation and secondly causes rewarding effects [2, 3]. Dopamine is an important neurotransmitter involved in many vital functions including motor control, emotion, motivation, memory and reward. Various researches have shown that the reward dopamine pathway, i.e. the path of the ventral tegmentum to the nucleus accumbens and prefrontal cortex, plays the main role in the occurrence of drug sensitivity [3, 4]. Dependence on drugs is a common and debilitating disease. Patients' interest in herbal treatments for this disease and the lack of valid documents in this field have disrupted the treatment process of patients. It is believed that herbal medicines can be used as a substitute for chemical medicines in many cases, including the treatment of opioid addiction, and for this reason, research on these plants is increasing. Purslane with the scientific name Portulaca oleraceae is a herbaceous and fleshy plant that is distributed in almost all parts of Iran and is cultivated as a vegetable in the southern regions of Iran. Phytochemical tests of purslane extract showed that this plant is a rich source of omega-3 fatty acids, beta-carotene, dopamine and noradrenaline [5]. This plant is used as an antiseptic, antispasmodic, diuretic, antipyretic, antioxidant and immune system booster. Research shows that the aqueous and alcoholic extracts of the aerial parts of this plant have various effects on the nervous system, such as: reducing motor activity, anticonvulsant effects, inhibition of neuromuscular contractions following electrical stimulation, analgesic and anti-inflammatory [6]. Also, histological studies show that purslane plant extract reduces the inflammatory damage of the mouse brain and has a protective effect on hypoxic nerve tissue [7]. Saffron is one of the plants that has been used as a medicinal plant in different parts of the world since ancient times. It is a perennial plant of the Iridaceae family, 10 to 30 cm high, and is mainly cultivated in Central Asia, China, India, Turkey, Iran, Algeria and Europe. Saffron is obtained from the flower of the Crocus sativus plant. The four major bioactive compounds in saffron are crocin, crostin, picrocrocin and safranal, which are involved not only in the sensory characteristics of saffron but also in its health-improving properties. Many studies have shown that crocin and crostin are able to exert various pharmacological protective effects that are attributed to the antioxidant capacity of these compounds. [8]. Saffron has about 150 chemical components in its stigma, which include minerals, sugars, vitamins, fats and secondary metabolites such as anthocyanin, terpenes, carotenoids and various flavonoids. Saffron and its active parts have been tested and their therapeutic benefits have been determined in various brain conditions such as Alzheimer's disease, Parkinson's disease, depression, multiple

sclerosis, anxiety disorder, and drug withdrawal. [9, 10] Saffron is a neuroprotective agent that modulates the effects. It shows the nervous system in pathological conditions [11]. Evidence shows that changes in the dopamine transporter can affect drug responses and animal behavior. It is widely believed that addiction to stimulants can increase locomotor activity by activating the dopaminergic system [12]. Considering the neuroprotective effects of saffron and purslane and their effects on dopamine pathways, in this study we aim to compare the effect of saffron and purslane on cocaine-induced motor activity in mice.

Materials and Methods

All experiments were performed at Shahid Sadoughi University of Medical Sciences. 63 mice with an approximate weight of 25 to 30 mg and an approximate age of 40 to 60 days were purchased from the Tehran Breeding Center. Initially, the animals will be kept in the animal house of Shahid Sadoughi university of medical Sciences for one week to adapt to the laboratory environment. These mice are kept in a colony room with 12 hours of light and 12 hours of darkness and a temperature of 21 ± 2 °C. Animals have access to food and water and are in accordance with the rules of the Ethical committee of Shahid Sadoughi faculty of pharmacy. Mice were randomly divided into 9 groups in groups of 7. The first group was the control group and received saline. Locomotion was measured for 5 minutes by an activity measurement device [LO-5800 Locomotion from Borj sanat Azma Company] and the results were recorded. All injections were done intraperitoneally. The second group of mice received a dose of 150 mg/kg of aqueous saffron extract and after one hour their motor activity was recorded. The third group of mice received a dose of 50 mg/kg of water purslane extract and after one hour their motor activity was recorded by an activity meter. Aqueous extracts of saffron and purslane have been prepared by Yazd Genetics Company. The remaining 6 groups of rats received cocaine at a dose of 10 mg/kg for ten days. On the tenth day after the injection of cocaine, after ten minutes, the movement activity of the rats in each group was measured by the device and the results were recorded. Then, the fourth group of mice, after injecting cocaine and recording their motor activity, were injected with a dose of 50 mg/kg of saffron extract and after about an hour, their motor activity was recorded. Also, the rats of the fifth group were treated in the same way with a dose of 150 mg/kg of saffron extract and the results were recorded over time, and the sixth group received a dose of 250 mg/kg of saffron extract and the results were recorded. The seventh group, after injecting cocaine and recording the results, they were injected with purslane extract at a dose of 20 mg/kg and after one hour, their motor activity was measured. In the same way, the eighth group received a dose of 50 mg/kg of purslane extract and the motor results were recorded. The ninth group was also treated with a dose of 80 mg/kg of purslane extract and after one hour the movement activity of the mice was recorded.

Additional behavioral, biochemical, or molecular assessments were not performed or reported because of budget limitation.

Statistical analysis

SPSS version 25 software and one-way ANOVA and Tukey's post-test were used in this study to analyze the data. In all studies, $p<0.05$ is considered as a significant level.

Results

The results obtained from the data were compared with each other on linear graphs. As shown in Fig. 1, saffron extract causes a decrease in the movement activity of mice compared to the positive control group, i.e. cocaine. It has also been shown that this effect is dose-dependent, and with increasing the dose of saffron extract, the effect of reducing motor activity also increases. Also, in Fig. 2, the results of different doses of purslane extract with the control and control groups are shown that, like saffron extract, purslane extract also causes a decrease in motor activity and this effect is dose-dependent, and with increasing the dose of the extract, the effect increased the movement activity of the mouse. In chart number 3, the control group, saffron extract and purslane are compared side by side. As it shows, the reducing effects of saffron extract in the tested doses were more than the purslane groups and both plants had a decreasing effect on motor activity compared to the control group.

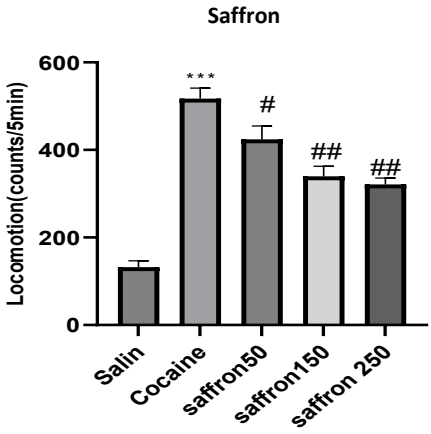

Fig. 1. The effect of different doses of aqueous saffron extract on motor activity caused by cocaine injection in mice. Cocaine caused significant increase in locomotor activity compare with control (saline) group***$p<0.001$. Two doses of the extract show a significant difference with the control group (Cocaine) ##$p<0.01$. The other dose (50mg/kg) also showed a significant difference with the control group (Cocaine) #$p<0.05$.

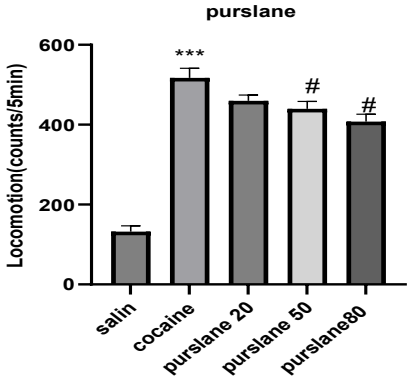

Fig. 2. Cocaine caused significant increase in locomotor activity compare with control (saline) group***$p<0.001$ The effect of different doses of water purslane extract on the number of motor activity caused by cocaine injection in mice. Only doses of 50 mg/kg and 80mg/kg of extract show a significant difference with the control group (Cocaine) (#$p<0.05$).

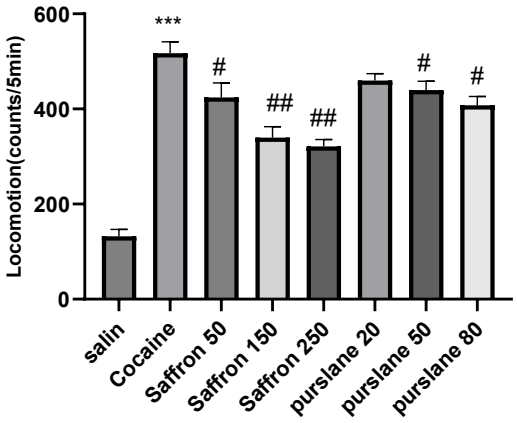

Fig. 3. Comparison of the effect of different doses of aqueous extracts of saffron and purslane with control groups on motor activity in cocaine-dependent mice, significance levels of ##p<0.01(for Saffron) and #p<0.05(for Purslane) have been showed.

Discussion

Dopamine transporter (DAT) is one of the known high-affinity targets for cocaine. Cocaine is a strong psychostimulant that causes reward and stimulation of motor activity in humans and animals, and the results state that the inhibitory effect of cocaine on DAT is necessary for its rewarding effect. Studies show that inhibition of DAT is necessary for the rewarding effect of cocaine (reward cocaine) and motor stimulation [13]. It is believed that herbal medicines can be used as a substitute for chemical medicines, including in the treatment of drug addiction, and for this reason, research on these plants is increasing. Crocin and safranal are two effective substances in saffron that prevent the reabsorption of dopamine, norepinephrine, and serotonin, and it seems that they are effective in cocaine addiction with this action. According to the study of Ghoshooni et al. in 2011, aqueous saffron extract in doses of 80, 160 and 320 mg/kg and ethanolic extract in doses of 400 to 800 mg/kg significantly decreased motor activity in morphine-dependent mice. It seems that the administration of aqueous and ethanolic extracts of saffron interferes with the opioid system and reduces withdrawal symptoms [14]. In a study conducted by Ettehadi et al. in 2013, intraperitoneal injection of aqueous saffron extract in doses of 50, 100, 150 and 250 mg/kg significantly increased the release of the neurotransmitter dopamine and a dose of 250 mg/kg increased the release of the neurotransmitter. Glutamate in the brain of rats. It has also been shown that the effect of the extract on dopamine release is dose-dependent. It is now known that the concentration of dopamine and glutamate in reward regions is affected by drug abuse. These neurotransmitters play an essential role in behavioral activity and sensitivity in addicted animals. It is possible that saffron extract has an effect on opioid addiction by changing the

release of dopamine and glutamate in rewarding areas [5]. Purslane is a plant species with a wide range of biological activities, including antioxidant and neuroprotective, which in addition to antioxidant and neuroprotective effects has dopamine precursors. Histological studies show that purslane plant extract reduces the inflammatory damage of rat brain and has a protective effect on hypoxic nerve tissue. According to a study conducted by Karimi et al. in 2008 on the effect of aqueous purslane extract on morphine addiction, the decrease in motor activity and movement caused by morphine addiction can be due to the inhibitory effects of purslane extract on the central nervous system or its relaxing activity peripheral muscle. Dopamine has been shown to be one of the main bioactive components of purslane. It is possible that purslane affects opioid dependence through this mechanism [15, 16].

Conclusion

The main approaches in the field of drug addiction treatment and withdrawal are reducing the desire for drugs and minimizing or eliminating the unpleasant symptoms caused by drug withdrawal, i.e. the symptoms that occur with the sudden cessation of drug use. Evidence shows that changes in the dopamine transporter can affect drug responses and animal behavior. It is widely believed that addiction to stimulants can increase motor activity by activating the dopaminergic system. According to the results obtained from the tests and the reducing effect of purslane and saffron extract on the motor activity of mice in a dose-dependent manner after developing cocaine dependence and withdrawal syndrome, according to the results of previous studies on the effect of these two plants on substance withdrawal and Considering the effect of cocaine on the dopamine pathway and the creation of dependence and the neuroprotective effects of saffron and purslane and the effect of the extracts of these two plants on the dopaminergic system, it can be concluded that these two plants may be effective in quitting cocaine dependence.

Ethical Considerations

Ethics and study registrationThe relevant ethics committee approved the study protocol and the informed consent procedures with the number of IR.SSU.AEC.1402.018.

Funding Statement

Shahid Sadoughi University of Medical Sciences, Yazd, Iran and Mahdieh Kargar covered the experiment and other associated costs.

Conflict of Interest

The authors declared no conflict of interest.

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Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Authors' Contributions

HR. J. and M.K were responsible for designing the research, conducting the experiments, and interpretation of the results. HR. J was responsible for writing the manuscript. All authors have read and approved the final version of the manuscript.

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