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Research Article

**COMPARING THE EFFECTS OF ALOE VERA EXTRACT AND
BUPRENORPHINE ON REDUCING BEHAVIORAL
SYMPTOMS OF METHADONE WITHDRAWAL SYNDROME
IN MICE****Fahimeh Davari¹, Mehrdad Modaresi^{2*}**¹ Dept. of Psychology, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, IRAN² Dept. of Physiology, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, IRAN**Abstract:**

Current study was carried out to compare the effects of Aloe Vera and buprenorphine on reducing behavioral symptoms of methadone withdrawal syndrome in mice. Sixty mature mice in the weight range of 25 to 30 were divided randomly into six groups including 50, 100, and 200 mg of Aloe Vera extract, buprenorphine, addiction and control. All groups except control received 0.4 mg/ml of oral methadone for 21 days and became addicted. After that, methadone was discontinued for 48 hours. Aloe Vera was injected in peritoneum at concentrations of 50, 100, and 200mg. Buprenorphine was also injected with a dose of 1.2 mg/kg. Each animal was placed inside a glass cylinder for 50 minutes after injection and withdrawal behavioral symptoms (including jumping up, climbing the glass wall, standing on rear legs, body and leg tremors, diarrhea, bruxism, body stretch and restlessness) were recorded for 30 minutes. Obtained data were analyzed using SPSS program. Results showed that Aloe Vera extract reduced the symptoms significantly in 100 and 200mg/kg doses. Consequently, the extract is effective dose dependently ($p < 0.001$) and can have the same effect as buprenorphine.

Keywords: *Aloe Vera, methadone, buprenorphine, behavioral symptoms, animal model****Corresponding Author:****Mehrdad Modaresi,**

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INTRODUCTION:

Mental and behavioral problems caused by psychoactive substances are common. Many of these substances can be problematic, such as alcohol, opium-like and cannabis-like substances, tranquilizers, stimulants, hallucinations, tobacco and volatile substances [1]. Drug withdrawal after a period of medication taking and existence of significant amount of drug in the body (for example, after a few days) causes an unwanted body reaction known as withdrawal syndrome. The effects of drug withdrawal are almost always the opposite of the initial effects of the drug [2]. Methadone is a drug that is under the control of the Ministry of Health with high dependence possibility. It has low mortality risk but in the first two weeks, overdose is a risk [3].

According to researches of *National Institute on Drug Abuse (United States)*, many people who gave up heroin believed that heroin withdrawal was less horrible than methadone withdrawal. Therefore, most of heroin addicts became methadone addicts and the fear of methadone withdrawal causes treatment to fail or continue for many years [4].

Today, descending doses of buprenorphine tablets are used for methadone withdrawal. Buprenorphine is an analgesic drug from narcotics which is also used to treat addiction. This drug was made in 1968 and is a relative agonist which simultaneously has the property of the GABA receptor antagonist. So that in low doses, the effect is agonist and in higher doses its antagonistic effect predominates. Increasing the dose of drug more than 30 mg does not increase the effect of it and since this drug is a relative agonist, it has weaker withdrawal symptoms in proportion to other narcotics such as methadone and morphine. Due to mentioned properties, this drug has been used widely in recent years for curing addiction, detoxification, or as a preservative [5].

Although, most of diseases are treated now by using industrial drugs with decisive effects on curing diseases, side effects of these drugs encourage people to pay more attention to use medicinal plants [6]. Aloe Vera (*Aloe barbadensis* Miller and *Aloe ferox* Miller) is from Liliaceae family. This plant is called crocodile tongue in Indonesia and crocodile tail in Thailand. Aloe Vera is native to North Africa and has been used worldwide for many years. Known pharmacological properties of this plant has caused it to be called the 20th century plant. Aloe Vera has about 99% water and its pH is about 4.5 The rest of the substance contains about 200 compounds including vitamins, non-organic salts, mineral, enzymes, sugars, phenolic compounds,

anthraquinones, lignin, saponins, sterols, amino acids, salicylic acid, calcium oxalate, amorin, barbaloin, sulfates, tannins and steroids, sulfates, tannins and steroids [7]. For thousands of years, Aloe Vera leaves are widely used as medications in different countries. The numerous therapeutic and pharmacological effects claimed for Aloe Vera are often based on the history of traditional medicine, but clinical studies have also taken place in recent years on the therapeutic effects of this plant [8].

MATERIALS AND METHODS:

To compare the effects of buprenorphine and Aloe Vera on reducing methadone quitting effects this research was carried out as a post-test type research with control group.

Sixty female mature mice in the weight range of 25 to 30 gr were divided randomly into six groups and were kept for 15 days to adapt to environment. The first step was to treat the mice with methadone in order to establish dependence. Methadone (0.4mg/ml) was added to drink water of mice (except control group) for 21 days. According to previous studies, addiction occurs in mice after 21 days.

After the 21st day, methadone was discontinued for 2 days and mice showed withdrawal symptoms. Then, buprenorphine and Aloe Vera extract were injected to groups in peritoneum by using 1cc insulin syringe. Fifty minutes after injection, each animal was placed inside a glass cylinder for 30 minutes and withdrawal behavioral symptoms were recorded.

Independent variables in this study were buprenorphine (2.1 mg) and Aloe Vera (50, 100, and 200 mg) whereas methadone withdrawal symptoms were dependent variables. Symptoms were divided into two groups: nominal symptoms (jumping up, climbing the glass wall, standing on rear legs) and relative symptoms (body and leg tremors, diarrhea, bruxism, body stretch and restlessness). Nominal variables were measured by counting the frequency whereas relative variables were evaluated by measuring the time using a chronometer.

Extract production

The plant was divided into small pieces and dried in the shade at normal temperature. Dried pieces were powdered using mill and 100mg of this powder was weighed and poured in a sterilized erlen plus 40cc of ethylic alcohol. Erlen was shaken completely, sealed and kept in a cool place for 48 hours. After that, erlen contents were mixed again using a shaker for five minutes, and were filtered using whatman paper: At first, the weight of paper was measured by a digital

scale. Then, the extract was filtered using the paper and residuals were dried using oven (50 °C) for one and half an hour. Dried powder was weighed using a digital scale. Filtered mixture was separated from alcohol by rotary device and the extract was prepared. Base extract was used to prepare desire doses (50, 100, and 200 mg/kg) [9].

Statistical calculations

Obtained data were analyzed at two descriptive and inferential levels. In descriptive level, average and standard deviation were calculated and one-way analysis of variance was used for inferential level. Tukey test was used to compare group's pairs. To compare significance of non-counting behaviors,

various groups were compared using χ^2 test. SPSS program was used to analyze obtained data at 5% probability level.

RESULTS AND DISCUSSION:

Groups were not significantly different in nominal symptoms including jumping, climbing and standing ($P < 0.05$) but differences between groups were significant in relative symptoms (body and leg tremors, diarrhea, bruxism, body stretch and restlessness) ($p = 0.0001$). As it is shown in figure 1 to 3, Aloe Vera extract affected relative symptoms and groups were different. The effects of extract were similar to buprenorphine effects.

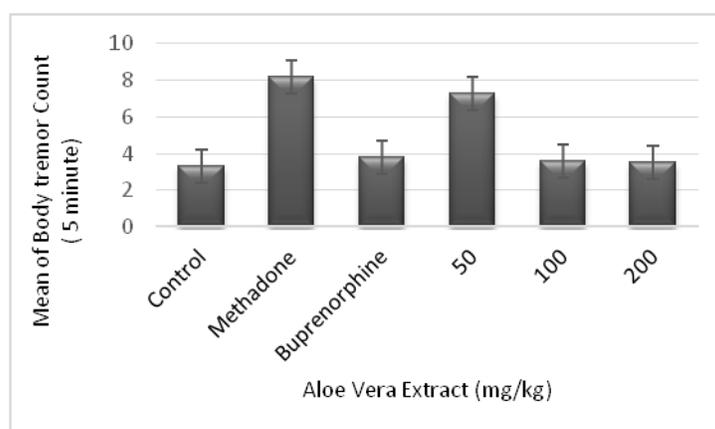


Figure 1. The effects of Aloe Vera extract and buprenorphine on body tremor in all groups

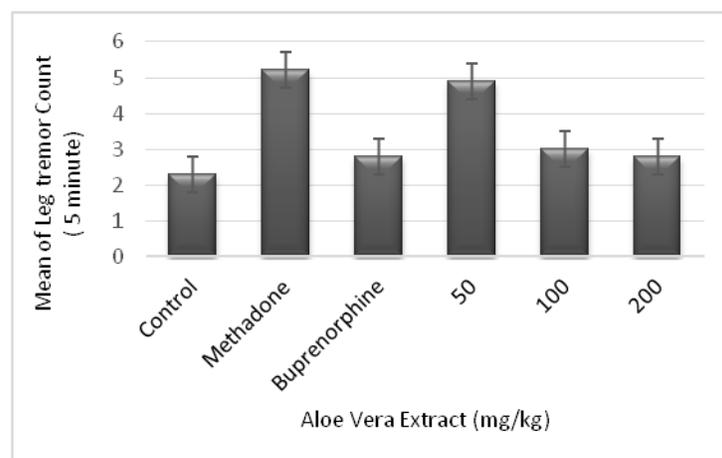


Figure 2. The effects of Aloe Vera extract and buprenorphine on leg tremor in all groups

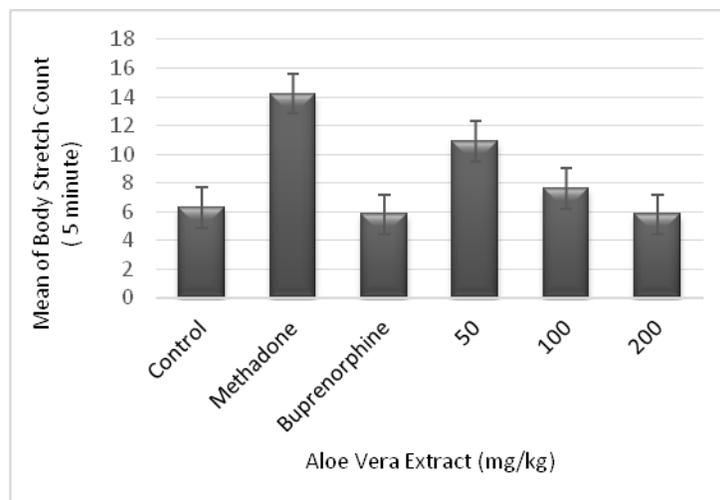


Figure 3. The effects of Aloe Vera extract and buprenorphine on body stretch in all groups

Determining and identifying the appropriate dose plays an important role in the performance and effectiveness of the medicinal plants. Chemical compounds in certain dose-drug medicinal plants have the same function as chemical drugs and can be a suitable substitute for similar synthetic drugs. Clinical studies of Wagner and Ernest (1999) about medicinal activities of Aloe Vera have confirmed energetic, anti-inflammatory and analgesic properties of this plant plus detoxification ability [10]. Anti-inflammatory and analgesic properties of the plant can be very effective in controlling drug withdrawal symptoms. Significant decrease in symptoms by Aloe Vera indicates the importance of this plant. Extract in 50 mg/kg could not affect the symptoms but in 100 and 200 mg/kg doses reduced duration of relative symptom similar to buprenorphine.

There is a direct relationship between the activity of dopaminergic system and motion activity of animal, so that, any activity decreasing factor of dopaminergic system, will reduce the motion activity [8]. The process of Aloe Vera effect is not well known but probable mechanisms can be reduced or increased secondary messengers, stimulating production and release of ACTH and cortisol, preventing the metabolism of endogenous opioids and injecting opioids in the body and affecting dopaminergic and glutaminergic systems [7].

Available evidences show that glutamate plays an important role in appearance of addiction withdrawal syndrome, so that each drug which struggle with glutamate can reduce the symptoms of this syndrome highly. It is very logical that Aloe Vera extract

prohibits the emergence of syndrome by blocking glutaminergic receptors.

CONCLUSIONS:

We can conclude that Aloe Vera can control withdrawal syndrome in mice dose dependently similar to buprenorphine.

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CONFLICT OF INTEREST

Authors claim that there is no conflict of interest.

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