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Original Article

An Evaluation of Antidepressant-Like Effects of the Aqueous Extract of the *Myrtus Communis L.* Fruit in Male Mice

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Abstract

Background and Aim: This study aimed to investigate the potential antidepressant-like effect of aqueous extract from fruits of *M. Communis L*. on mice.

Materials and Methods: To carry out this investigation, after weighting, coding, and classifying the mice, they were divided into the following groups (n = 6): test groups (175, 350, and 700 mg/kg of *M. Communis* aqueous extract; i.p), the control group (20 mg/kg Fluoxetine, and 30 mg/kg Imipramine; i.p) and the blank group (normal saline i.p). Different doses of the extract, fluoxetine, and Imipramine were administrated daily for 28 days. Behavioral evaluations were performed using the tail suspension and forced swimming tests.

Results: The aqueous extract of the *M. Communis* fruit did not reduce the immobility time in both TST and FST($P>0.05$). Moreover, the extract did not increase the climbing behavior in FST, which reveals the depressant-like effect of this herbal extract ($P>0.05$). This depressant-like effect increased dose-dependently.

Conclusion: The results of this study suggest that the aqueous extract of the *M. Communis* fruit has a depressant-like activity in mice models.

Keywords: Psychopharmacology, Antidepressant agents, M. Communis L, Aqueous extract, Depression

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Introduction

As a major depressive disorder, depression is a common and serious medical disease that affects about 20% to 25% of women and 7% to 12% of men in their lifetime (1). The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 revealed that depressive and anxiety disorders are the most disabling mental disorders worldwide (2). Depression has a pessimistic effect on the cognitive behavior and may lead to suicidal ideation in some patients (3). Most patients report physical symptoms of depression contrary to non-physical criteria, including gastrointestinal complaints, and skeletal muscle as well as cardiovascular diseases (4). Antidepressants that are commonly used in clinics are either first-generation (three cyclic antidepressants and monoamine oxidase inhibitors) or second-generation antidepressants (selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors) developed in the

late 1980s and early 1990s. They are generally regarded as the next generation of clinical therapy(5). Adverse effects of antidepressants can reduce admission and delay recovery. Thus, it is essential to consider potential side effects while choosing an antidepressant (6).

In addition to the classes of antidepressants mentioned above, we have seen a significant rise in the use of herbal medicines in the recent decade to treat various ailments, including anxiety and depression (7). Based on a report by WHO (World Health Organization), about 80% of people, particularly in developing countries, consume herbal medicines as their primary medications (8). Low costs, availability, and safety are the most important advantages of herbal medicines (9). These items make them a great option for self-medication worldwide (10). Furthermore, among different types of self-medication, which is considered a serious challenge of our health system around the globe (11-14), self-treatment with herbal medicines is safer and has a very long history (9).

Truly myrtle (Myrtus Communis L., Myrtaceae family), known as Mourd in Persian, is a small flowering shrub with a height of 1–3 meter (15). *M. Communis* has bright green leaves with white flowers and spherical, dark blue to black fruits (16). According to traditional medicine documents, *M. Communis* has several biological activities such as astringent, wound healing, haemostatic, heart tonic, lung tonic, and antitussive effects (15). Moreover it has sedative, mood elevating, antidepressant, anti-Alzheimer's and anti-Parkinson's like properties (17). Furthermore, recent studies have revealed some other effects of this plant such as antiviral (18), antioxidant (19), anti-inflammatory (20), and antipyretic (21) properties.

Based on the aforementioned evidence, we carried out this research to evaluate the antidepressant-like effects of the aqueous extract of *M. Communis* fruit on mice and find out its mechanism of action.

Materials and Methods

Animals and Grouping

In this experimental study, 72 Male albino NMRI mice weighing 22-32 g were randomly divided into 12 groups of 6. The mice were purchased from the Pasteur Institute (Iran) and were housed in a 12-h light/12-h dark cycle, controlled temperature (24–26°C) and relative humidity of 45-55%. The animals were kept in groups of 6 in Plexiglas animal cages with free access to tap water and standard rodent chow. The entire experiments were carried out between 8:00 A.M and 2:00 P.M, from May to August 2021 at school of pharmacy, Tehran Medical Sciences, Islamic Azad University, and each animal was used only once. The negative control group received normal saline (10ml/Kg, i.p). The positive control groups were treated with Imipramine (30mg/Kg, i.p) and Fluxetine (20mg/Kg, i.p). The other experimental groups were treated with different doses of the *M. Communis* aqueous extract (175, 350, 700mg/Kg, i.p) for 28 days. Each mouse was used only once for either the FST or TST test. The experimental protocol was observed according to the rules of the National Institute of Health. The proposal was approved and evaluated by the Research Ethics Board at Islamic Azad University. (IR.IAU.PS.REC.1400.290).

Plant Materials

Fruits of *M. Communis* were obtained from a grocery store in Tehran, Iran. Identity confirmation was carried out by botanists at the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran (No: HMS-558).

The fruits were dried in shadow until they were desiccated. The dried fruits were crushed into powder and kept at room temperature in a container. One hundred fifty gram of the dried powder was infused for 30 min in 1500 ml of boiled distilled water by filtration. The extract was concentrated by vacuum evaporation and dried at low temperatures.

Dose Preparations

The doses of 175, 350, and 700 mg/kg of the M. Communis aqueous extract were used based on the extract dry weight and traditional medicine suggestions. Normal saline was used as the solvent, and

all doses were administered intraperitoneally.

Behavioral Models

Forced Swimming Test (FST)

The mice were drooped individually in a cylinder-shaped jar (height 25 cm, width 10 cm), containing 14 cm of fresh water at 25°C. Each mouse was considered immobile when ceased the attempt and remained motionless floating on water, making merely necessary movements to keep its head above the water. Immobility, swimming, and climbing duration of each animal were registered during the 4-minute test after 2 min of adaptation. The decrease in immobility time reflects the anti-depressive-like effect (22).

Tail Suspension Test (TST)

In this behavioral model, the animals were suspended separately by their tail at a height of 50 cm above the floor of the table edge by the help of adhesive tape at approximately 1 cm from the tip of the tail. The mice were separated both acoustically and visually from each other during the whole procedure. The entire duration of immobility caused by tail suspension was calculated manually with a stopwatch for 6 min. The mice without any body movement were considered immobile (23).

Statistical Analysis

All the results have been presented as Mean ± SEM of measurements made on six mice in each group. The data were analyzed using one-way analysis of variance (one-way ANOVA) followed by Tukey's post-hoc test. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) for Windows version 25, and statistical differences were considered to be significant at P<0.05.

Results and Discussion

Figure 1 illustrates the effects of the *M. Communis* L. aqueous extract (175, 350, and 700mg/Kg ip.) on climbing behavior in FST. According to our data, Imipramine significantly (P<0.001) increased climbing in comparison with the control (Saline) group, but this behavior did not increase significantly in the Fluoxetine-treated and *M. Communis* extract-treated groups (P>0.05).

Figure 2 indicates the effect of the *M. Communis* extract in different doses, Fluoxetine, and Imipramine

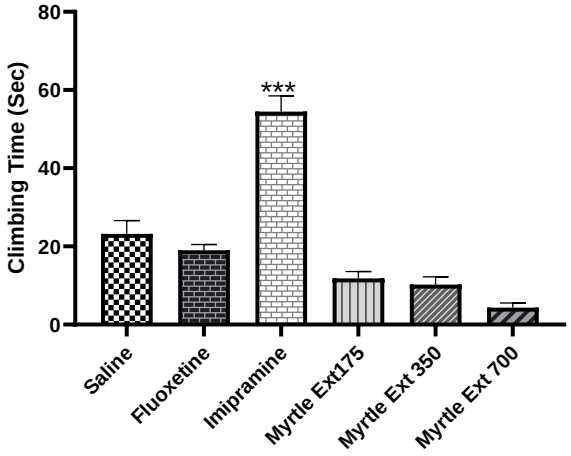

Figure 1. Effects of different doses of the Myrtus Communis L. aqueous extract (175, 350 and 700mg/Kg ip.), fluoxetine (20 mg/kg; i.p), and Imipramine (30 mg/kg; i.p) on the climbing behavior in the forced swimming test in male mice. The data have been shown as Mean±SEM. ***significant at P<0.001 compared with the control group.

on the immobility time of the mice in FST. Our investigation revealed a significant reduction in the duration of immobility with Fluoxetine (p<0.001) and Imipramine(p<0.001), but no significant reduction was observed in the duration of immobility with our different doses of the *M. Communis* extract (P>0.05, for all the administered doses).

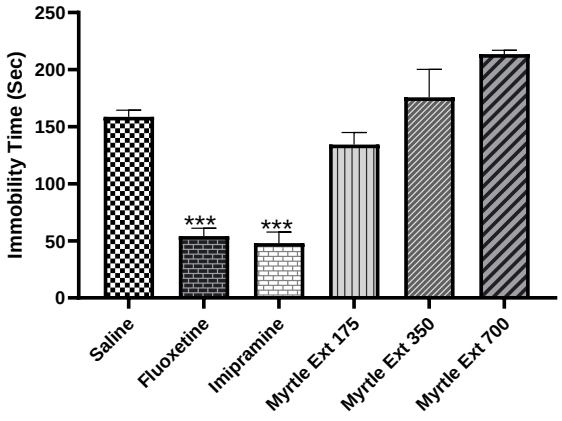

Figure 2. Effects of different doses of the Myrtus Communis L. aqueous extract (175, 350 and 700mg/Kg ip.), fluoxetine (20 mg/kg; i.p), and Imipramine (30 mg/kg; i.p) on immobility in the forced swimming test in male mice. The data have been shown as Mean±SEM. ***Significant at P<0.001 compared with the control group.

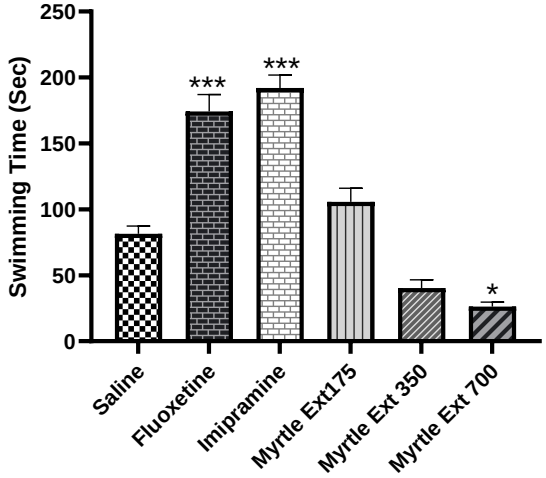

Figure 3. Effects of different doses of Myrtus Communis L. aqueous extract (175, 350 and 700mg/Kg ip.), fluoxetine (20 mg/kg; i.p), and Imipramine (30 mg/kg; i.p) on the swimming behavior in the forced swimming test in male mice. The data have been shown as Mean±SEM. ***significant at P<0.001 compared with the control group. *Significant at P<0.05 compared with the control group.

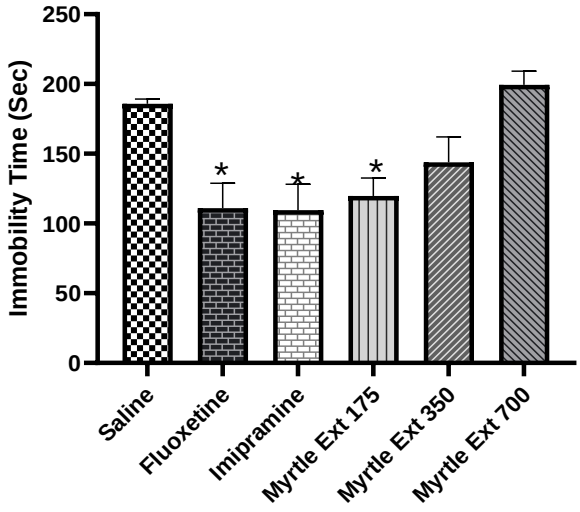

Figure 4. Effects of different doses of Myrtus Communis L. aqueous extract (175, 350 and 700mg/Kg ip.), fluoxetine (20 mg/kg; i.p), and Imipramine (30 mg/kg; i.p) on the immobility time in the tail-suspension test in male mice. The data have been shown as Mean±SEM; *Significant at P<0.05 compared with the control group.

Figure 3 shows that the most effective agents in increasing the duration of swimming time in comparison with the control-treated group were Fluoxetine (P<0.001) and Imipramine(P<0.001), but we did not observe any significant increase in swimming duration with the *M. Communis* extract at all the mentioned doses (P>0.05 for all the administered doses).

The effects of Fluoxetine, Imipramine, and *M. Communis* extracts (175, 350, and 700mg/Kg) on the immobility time of the mice in TST have been shown in Figure 4. In this test, only Fluoxetine (P<0.05) and Imipramine (P<0.05) could remarkably reduce the immobility duration, in comparison with the control group. However, there was no significant decrease in the duration of immobility with *M. Communis* extract doses compared with the control group (P>0.05, for all administered doses).

Depression is a common and serious illness. This chronic condition is associated with a high rate of recurrence and suicide. Many different antidepressant agents have been developed and are available for patients, but a certain proportion of these patients show limited responses to these agents that are often accompanied by undesirable side effects (24, 25).

A wide variety of herbal medicines have been used in the psychiatric practice, and several studies have been conducted to find new agents with better efficacy and fewer side effects among herbal and traditional sources (26).

One of the well-known models for evaluating depressive-like behaviors is the Forced Swimming Test (FST) (27). FST is characterized by relatively fast results and easy operation (28). Moreover, it is sensitive to a broad range of antidepressant medications and can differentiate between medications that have not been developed to manage depression such as benzodiazepines. That is, they are mostly antianxiety or neuroleptic agents (28-30). Tail Suspension Test (TST) is also another model to evaluate the antidepressant activity. This test does not result in a decrease in body temperature and stress caused by FST (31).

In the present study, we used FST and TST as two mouse models to evaluate the antidepressant effect of the *M. Communis* L. aqueous extract (22). The results of this study indicated an increase in the duration of immobility in FST and TST in different doses of the *M. Communis* extract compared with the control group as well as a reduction in the swimming time. Both results suggest a depressive-like behavior in mice. Nevertheless, the use of Fluoxetine and Imipramine led

to a highly remarkable decrease in immobility ($P<0.001$) and an increase in the swimming time ($P<0.001$), which is considered an antidepressant-like effect as it has already been reported in previous studies (32).

Previous studies have reported that agents with noradrenergic activity reduce the immobility time, while antidepressants with serotonergic activity increase the swimming time (33). However, the *M. Communis* extract neither increased the swimming time nor reduced the immobility time. Moreover, other studies have reported that increasing the immobility time in FST might be the cause of central GABAergic activity, which results in a depressant-like activity most likely through the α1 subunit of $GABA_A$ receptors (34). Thus, the effect of the *M. Communis* extract on increasing the immobility time might be because of its GABAergic activity.

Furthermore, the results of the present study showed a decrease in the duration of climbing (struggling) in FST in different doses, which again suggests a depressive-like behavior in the mice. In this study, only imipramine significantly increased the climbing (struggling) time, which is consistent with previous studies (32).

Another study conducted on the effect of the ethanolic extract of *M. Communis* leaves on anxiety and sleep reported anxiolytic, myorelaxant, and hypnotic effects, which is consistent with our depressive-like results, and this depressive-like results might be due to its GABAergic activity (34).

Conclusion

According to the results of this study, *M. Communis* extract has considerable depressive-like effects in animal models of depression. However, more studies should be undertaken to find the mechanism of depressive-like effects of this extract.

Acknowledgment

None.

Conflict of Interest

The authors declare that they have no conflict of interest.

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