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Echinophora platyloba Essential Oil: Chemical composition and Antidepressant-Like Effects in Reserpinized Mice

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Abstract

Background: Oxidative stress has been implicated as a contributing factor in the pathophysiology of depression and anxiety, potentially mitigated through the application of antioxidant-rich medicinal herbs. Among these, *Echinophora platyloba* DC., an endemic plant, was identified as a promising candidate for investigation. This study aimed to characterize the phytochemical profile of the essential oil of *E. platyloba* and evaluate its efficacy in alleviating depressive-like behaviors and oxidative stress in mice.

Methods: The essential oil extracted from the aerial parts of *E. platyloba* was subjected to gas chromatography-mass spectrometry (GC/MS) analysis to identify its chemical composition. A total of 60 adult male NMRI mice were randomly assigned to six groups: a negative control group, a reserpine-treated group, a positive control group, and three treatment groups receiving reserpine combined with *E. platyloba* essential oil at doses of 50, 75, or 100 mg/kg. Behavioral assessments, including the tail suspension test (TST) and forced swim test (FST), were conducted to evaluate depressive-like behaviors. Additionally, biochemical assays were performed to quantify antioxidant capacity and oxidative stress markers.

Results: Administration of the essential oil significantly reduced locomotor activity in the open field test and substantially decreased immobility times in both the FST and TST, suggesting robust antidepressant-like effects. At a dose of 50 mg/kg, the essential oil significantly enhanced antioxidant capacity in brain and serum samples while reducing malondialdehyde (MDA) levels, a key indicator of oxidative stress, in these tissues. The GC/MS analysis revealed that myristicin, α-phellandrene, and neocnidilide were the predominant constituents of the essential oil.

Conclusion: The essential oil of *E. platyloba* demonstrated significant antidepressant-like activity and effectively attenuated oxidative stress associated with depressive states, underscoring its potential as a therapeutic agent for depression management.

Keywords: Depression, Oxidative stress, *Echinophora platyloba*, Reserpine, Medicinal plant, Fluoxetine

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Introduction

Depression, affecting over 264 million individuals globally, according to the World Health Organization (WHO, 2020), is a prevalent psychological disorder and a major contributor to disability, diminished quality of life, and reduced occupational performance. It is classified based on severity—mild, moderate, or severe—or the presence of manic episodes, distinguishing recurrent depressive disorder from bipolar disorder. Core symptoms include social withdrawal, reduced motivation, sexual dysfunction, sleep disturbances, persistent sadness, and anhedonia, the inability to experience pleasure (1, 2). The biochemical basis of depression involves the dysregulation of neurotransmitters within the central nervous system (CNS), including serotonin, glutamate, γ-aminobutyric acid (GABA), and other critical mood and cognitive function regulators. Contributing factors to such neurochemical imbalances encompass a range of environmental, psychological, and biological influences, including adverse life events, occupational stress, poor health, and certain medications (3, 4).

Emerging evidence underscores the pivotal role of oxidative stress in the pathogenesis of depression and anxiety-related disorders (5, 6). Elevated levels of malondialdehyde (MDA), a well-established marker of lipid peroxidation resulting from oxidative stress, have been consistently associated with these conditions (7, 8). Consequently, synthetic and natural compounds exhibiting antioxidant properties alongside targeted anti-depressant effects in the CNS hold significant therapeutic

promise for managing psychiatric disorders.

Natural antioxidants, particularly medicinal plants and their essential oils, have been utilized historically for their accessibility and perceived efficacy in treating psychological conditions (9). The present study focused on *Echinophora platyloba* DC. Umbelliferae, an endemic plant native to Iran, is locally known as "khosharizeh." Infusions prepared from the aerial parts of this plant have traditionally been employed to alleviate digestive complaints, such as gastric discomfort (10, 11). Additionally, extracts of *E. platyloba* have demonstrated antimicrobial, antifungal, and antibacterial properties (10, 12). Given its reported antioxidant capabilities (13, 14), the primary objective of this study was to characterize the phytochemical composition of the essential oil extracted from the aerial parts of *E. platyloba* and to evaluate its antidepressant-like effects in an in vivo murine model of depression.

Methods

Plant Preparation and Essential Oil Extraction

In the spring of 2018, the aerial parts of *E. platyloba*, including leaves and stems, were collected from their natural habitat in the Ghale Sefid region, located in Shimard village, Chaharmahal and Bakhtiari province, Iran (latitude: 51°27'38" E, longitude: 31°25'09" N, altitude: 3101 m). Dr. Shimardi Hamzeh-Ali, a botanist at the Research Center of Agriculture and Natural Resources, Shahrekord, Iran, authenticated the plant. For reference, a voucher specimen (Herbarium No. 249) was deposited at the Medical Plants Research Center, Shahrekord University of Medical Sciences. The plant material was air-dried, pulverized, and subjected to hydrodistillation for four hours using a Clevenger-type apparatus following British Pharmacopoeia guidelines. The resulting essential oil was dehydrated using anhydrous sodium sulfate and stored at -20°C until further analysis.

Identification of Essential Oils Components

The composition of the essential oil was assessed via gas chromatography-mass spectrometry (GC-MS) using a ThermoQuest-Finnigan system (TRACE MS) fitted with a DB-5 capillary column measuring 30 meters by 0.25 millimeters. Helium (99.999% purity) served as the carrier gas, with a split ratio of 1:100 and a flow rate of 1.1 milliliters per minute. The injection port was maintained at 250°C, and 0.2 microliters of the sample were introduced under split conditions with an ionization energy of 70 electron volts. The temperature program began at 60°C and was increased by 5°C per minute until it reached 250°C. Operational parameters and the column setup mirrored standard GC conditions, and the transfer line temperature was maintained at 250°C. Retention indices of the detected compounds were calculated using a series of n-alkanes. Determining constituents was based on comparing retention times and mass spectra with those available in the Wiley 275 and Adams libraries (15).

Laboratory Animals

All procedures were conducted to minimize the number of animals used and ensure their welfare, per national animal care regulations. The experimental protocols were approved by the Ethics Committee of Shahrekord University of Medical Sciences (Approval ID: IR.SKUMS.REC.1395.328). Sixty adult male NMRI mice weighing 20–30 g were utilized in the study. The animals were housed in a controlled environment maintained at 21 ± 2°C with a 12-hour light/dark cycle and provided ad libitum access to food and water. The mice were randomly allocated into six groups (n = 10 per group) and administered treatments via intraperitoneal (i.p.) injection as follows: Group 1 received normal saline (vehicle control); Group 2 was administered reserpine (5 mg/kg); Groups 3–5 received reserpine (5 mg/kg) combined with *E. platyloba* essential oil at doses of 50, 75, or 100 mg/kg, respectively; and Group 6, also treated with reserpine (5 mg/kg), received fluoxetine (10 mg/kg) as the reference drug (Figure 1).

Tail Suspension Test (TST)

The TST serves to evaluate behaviors resembling depression. A strap was attached to the mouse's tail, suspending the animal about 1 centimeter from the tip. The duration of complete stillness, unresponsiveness, and lack of activity was measured as immobility time, consistent with prior descriptions (16). The test was conducted in a noise-free environment, and the total suspension time was 7 min, the first 2 min of which were specified as the adaptation of the mouse to the environment, and the immobility duration within the remaining 5 min was calculated in seconds by the stopwatch. Increased immobility time is interpreted as a measure of depression-like behavior.

Open Field Test (OFT)

The OFT examined the mouse's movement patterns and anxiety-related behaviors. The test utilized a 60 × 60 cm box with a height of 40 centimeters. The floor was segmented

Figure 1. Overview of the experimental protocol

into 16 equal squares arranged perpendicularly, and a camera captured the animal's movements. The animal's crossing of the lines mentioned with all four hands and feet was considered a unit of motion. This test measured the motor activity over 5 min using video tracking software (17). The arena is thoroughly cleaned between tests to eliminate olfactory cues. Parameters measured include the number of entries into the center zone. Reduced center entries are indicative of anxiety-like behavior.

Forced Swim Test (FST)

The FST is a widely recognized and reliable method for assessing depressive-like behaviors in mice. The time the animal remained still was documented to determine immobility duration. Extended immobility was interpreted as an indicator of depression, while a decrease suggested an antidepressant effect (18). The FST lasts 6 min, and the first 2 minutes were set for the mouse's adaptation to the environment when the immobility duration was not recorded. The duration of immobility in the following 4 min was measured (19). Prolonged immobility time is interpreted as a measure of behavioral despair.

Estimation of Total Antioxidant Potential in Brain and Serum Samples

To evaluate the total antioxidant capacity in brain and serum samples, three reagent solutions were prepared: Solution I, a 0.02 M iron chloride solution in distilled water; Solution II, a 0.0365 M sodium acetate buffer; and Solution III, a 0.01 M triazine solution. A working solution was formulated by combining 10 mL of Solution I, 1 mL of Solution II, and 1 mL of Solution III. Serum samples (25 µL) or homogenized brain tissue samples (25 µL) were mixed with 1.5 mL of the working solution and incubated at 37°C for 10 minutes. The absorbance was measured at 593 nm using a spectrophotometer (Figure 2A) (20).

Determination of Brain and Serum Malondialdehyde (MDA) Levels

Serum MDA Levels

A reagent solution was prepared by dissolving 0.5 g of thiobarbituric acid (TBA) in 80 mL of 20% acetic acid. A 100 µL serum sample was mixed with 100 µL sodium dodecyl sulfate (SDS) solution and 2.5 mL of the TBA reagent mixture. The resulting mixture was incubated in a boiling water bath for 1 hour. After cooling, the samples were centrifuged at 4000 rpm for 10 minutes. The absorbance of the supernatant was measured at 532 nm using a spectrophotometer (21).

Brain MDA Levels

1.0 g of brain tissue was homogenized in Tris buffer and incubated at 37°C for 1 hour in a metabolic shaker. Subsequently, 1 mg of TBA and 1 mg of 5% trichloroacetic acid (TCA) were added sequentially, thoroughly mixing after each addition. The samples were centrifuged at 2000 rpm for 10 minutes, and the supernatant was collected and transferred to separate containers. The supernatant was then heated in a boiling water bath for 10 minutes. After cooling, the absorbance was measured at 532 nm using a spectrophotometer (Figure 2B) (21).

Statistical Analysis

Data were analyzed using the GraphPad Prism 5 software using Tukey's test and one-way ANOVA. In all calculations, data were considered significant when $P < 0.05$.

Results

Chemical Profile of E. Platyloba Essential Oil

The essential oil of *E. platyloba* aerial parts was obtained in a yield of 0.34%. To characterize the main components of the oil, GC/MS analysis was performed. The principal components of the essential oil consisted of myristicin (76.6%), α-phellandrene (5.9%), and neocnidilide (4.4%). According to Table 1, 21 substances were identified, representing a remarkable 99.6% of the essential oil content (Figure 3).

Effect of E. Platyloba Essential Oil on the Immobility Time in the TST

The antidepressant-like effect of the essential oil tested at three doses (50, 75, and 100 mg/kg) and the positive

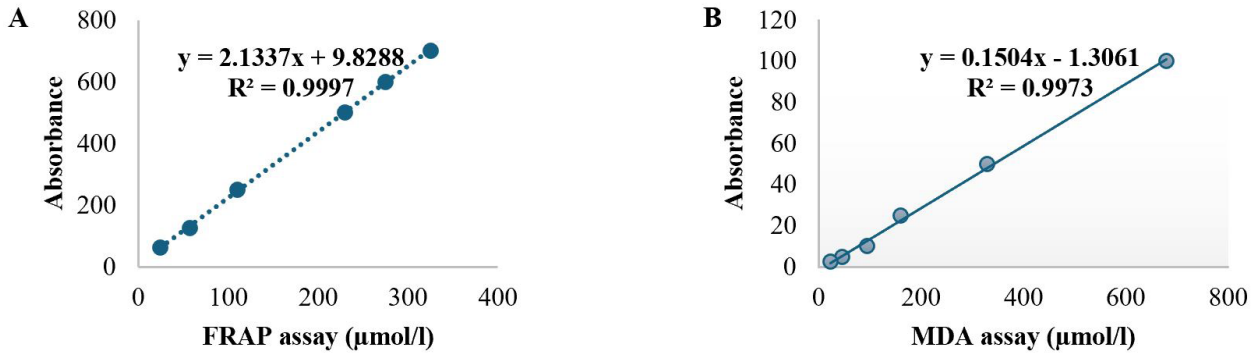

Figure 2. A. The standard curve at 593 nm for the FRAP assay. **B.** The standard curve at 535 nm for the MDA assay

control, fluoxetine (10 mg/kg), is shown in Figure 4A. In the TST experiment, reserpine injection increased immobility duration by three to four times. The essential oil at all tested doses and fluoxetine notably counteracted the reserpine-induced effect. The effect of *E. platyloba* essential oil, although significant, was lower than that of fluoxetine ($P<0.001$) and did not show a dose-dependent response for the tested concentrations (Figure 4A).

Table 1. List of volatile components identified in the essential oil of *E. platyloba*

No.	Compound	Area %	RI[a]
1	α-Pinene	2.3	938
2	Sabinene	0.1	977
3	β-Pinene	0.1	982
4	β-Myrcene	0.1	994
5	α-Phellandrene	5.9	1011
6	p-Cymene	1.5	1028
7	β-phellandrene	1.6	1033
8	(Z)-β-Ocimene	0.1	1039
9	γ-Terpinene	0.1	1061
10	Fenchone	0.1	1092
11	linalool	1.8	1104
12	4-Terpinenol	0.1	1183
13	α-Terpieol	0.3	1197
14	α-phellandrene epoxide	1.5	1210
15	β-Citronellol	0.8	1233
16	Carvacrol	0.2	1313
17	α-Terpinyl acetate	1.1	1352
18	Unknown	0.7	1403
19	Myristicin	76.6	1542
20	Neocnidilide	4.4	1740
21	(Z)-Ligustilide	0.9	1747

RI[a]: Retention indices calculated against n-alkanes.

Impact of E. Platyloba Essential Oil on the Immobility Duration in the FST

The FST (Figure 4B) also showed that injection of reserpine caused a significant ($P<0.001$, Tukey's test) increase in immobility time, which was reversed by the antidepressant drug fluoxetine ($P<0.001$). Similarly, the essential oil at 50 and 75 mg/kg doses could reduce the reserpine response ($P<0.05$), but strangely, a 100 mg/kg dose did not show statistically significant activity. The differences between the various groups (ANOVA analysis) are shown in Figure 4B.

Impact of E. Platyloba Essential Oil on the Motor Activity Rate in the OFT

The effect of the test compounds in this assay (Figure 4C) system is marginally seen since the motion units increased by reserpine was not as great as those of the FST and TST tests, though statistically significant ($P<0.05$). Fluoxetine was the most active ($P<0.01$) in suppressing motion unit enhancement by reserpine, while the essential oil at the dose of 50 mg/kg ($P<0.05$) but not higher doses (75 or 100 mg/kg) were effective (Figure 4C).

Effect of E. Platyloba Essential Oil on Serum Antioxidant Capacity

One-way ANOVA (Figure 5A) shows a significant difference in serum antioxidant capacity in the examined

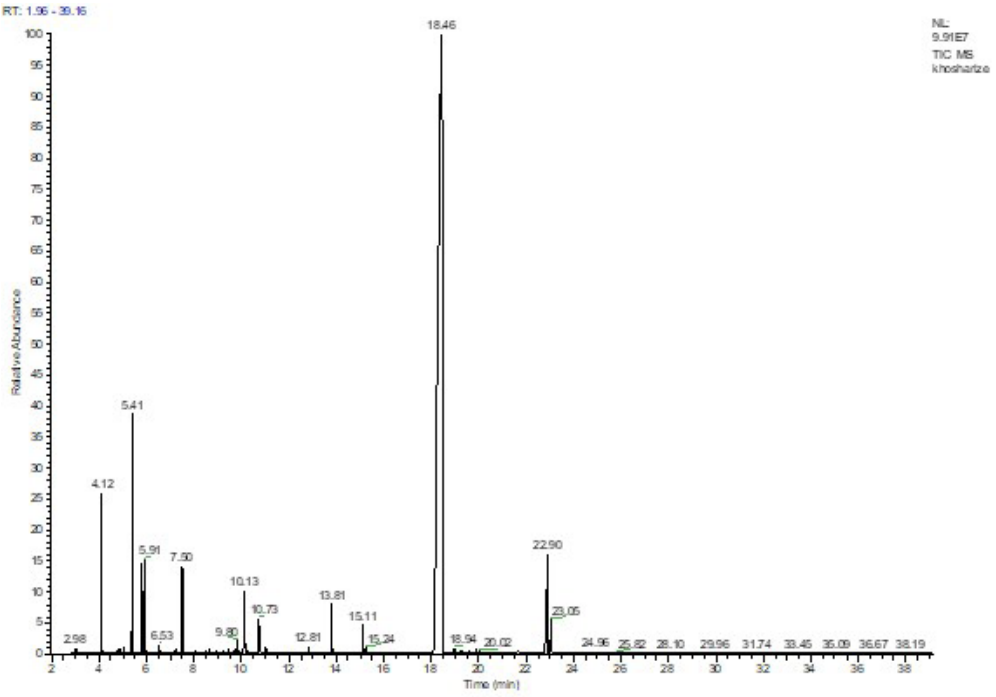

Figure 3. Representative chromatogram from GC/MS analysis of the volatile oil extracted from *Echinophora platyloba*

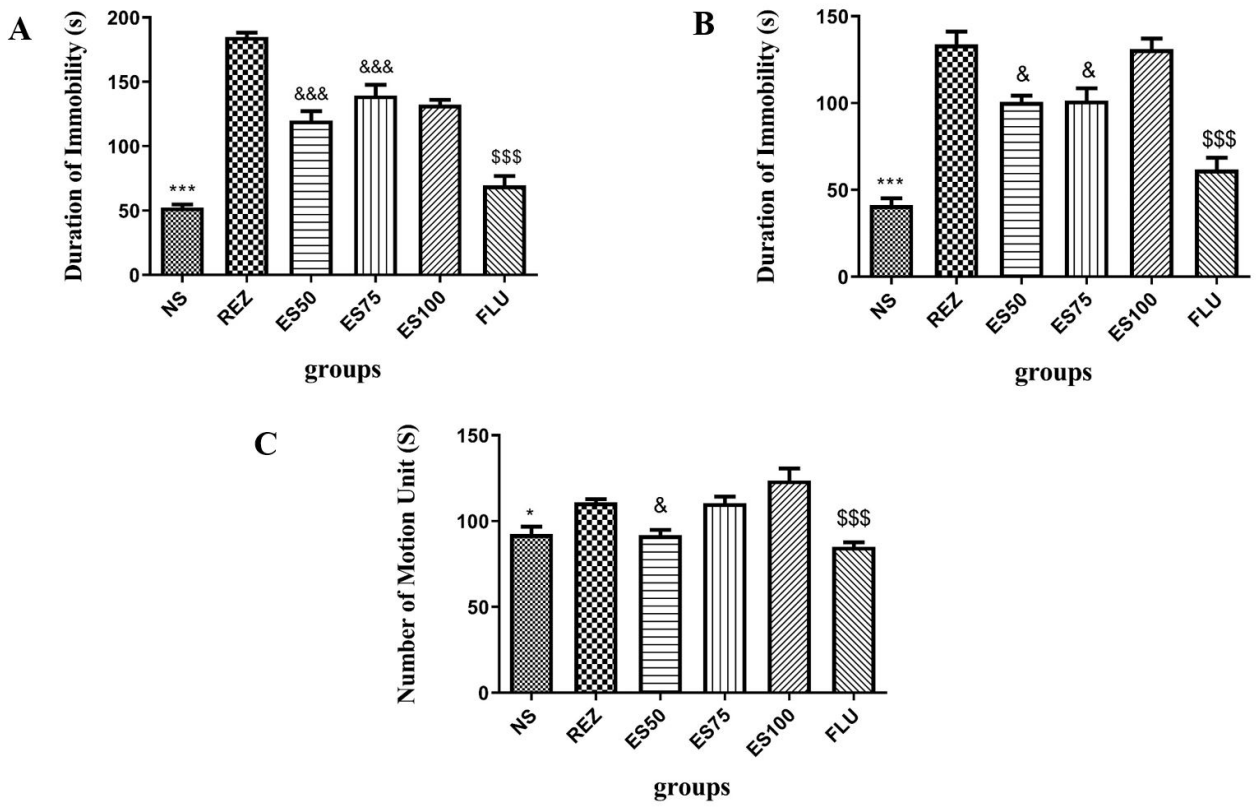

Figure 4. A. Effect of *Echinophora platyloba* Essential Oil on the Duration of Immobility in the TST, **B.** Effect of *Echinophora platyloba* Essential Oil on the Duration of Immobility in the Forced Swim Test, **C.** Effect of *Echinophora platyloba* Essential Oil on the Number of Motion Units in the OFT; (REZ: Reserpine; (REZ: Reserpine; ES50: Essential Oil at 50 mg/kg; ES75: Essential Oil at 75 mg/kg; ES100: Essential Oil at 100 mg/kg; NS: Normal Saline; FLU: Fluoxetine). *** and * Comparison of reserpine and normal saline ($P<0.001$), ($P<0.05$), respectively; &&& Comparison of reserpine and essential oil at 50, 75, and 100 mg/kg ($P<0.001$); & Comparison of reserpine and essential oil at 50 and 75 mg/kg ($P<0.05$); $$$ Comparison of reserpine and fluoxetine ($P<0.001$)

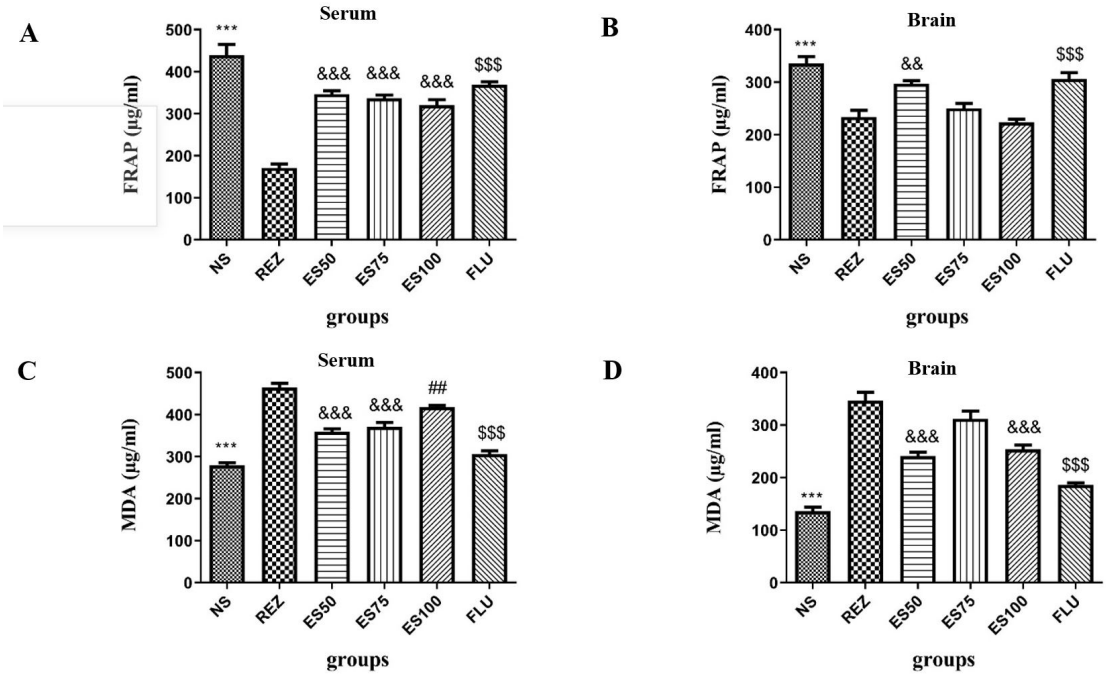

Figure 5. A,B. Effect of *Echinophora platyloba* Essential Oil on Serum **(A)** and Brain **(B)** Antioxidant Capacity; **C,D.** Effect of *Echinophora platyloba* Essential Oil on Serum (**C**) and Brain **(D)** Malondialdehyde Level; (REZ: Reserpine; ES50: Essential Oil at 50 mg/kg; ES75: Essential Oil at 75 mg/kg; ES100: Essential Oil at 100 mg/kg; NS: Normal Saline; FLU: Fluoxetine). *** Comparison of reserpine and normal saline ($P<0.001$); &&&, && Comparison of reserpine and essential oil at 50, 75, and 100 mg/kg ($P<0.001$), ($P<0.01$), respectively; $$$ Comparison of reserpine and fluoxetine ($P<0.001$)

groups ($P<0.001$). Tukey's post-test confirmed that the antioxidant capacity of serum was lower in the reserpine group than in the normal saline group ($P<0.001$). Serum antioxidant capacity in the essential oil (50, 75, and 100 mg/kg) group and those receiving fluoxetine was higher than the reserpine group ($P<0.001$). No significant difference was observed in the serum antioxidant capacity between the fluoxetine and essential oil at 50, 75, and 100 mg/kg groups ($P>0.05$). No significant difference was also seen in serum antioxidant capacity between the essential oil groups at different concentrations ($P>0.05$) (Figure 5A).

Impact of E. Platyloba Essential Oil on Brain Antioxidant Capacity

Figure 5B shows that the brain antioxidant capacity was lower in mice receiving reserpine than in the normal saline group ($P<0.001$, Tukey's test). Also, slightly lower than fluoxetine, all doses of the essential oil effectively increased the brain's antioxidant capacity ($P<0.01$) in reserpine-treated mice. The activity profile and the difference between the various groups (One-way ANOVA) are shown in Figure 5B no significant difference was seen in brain antioxidant capacity between the groups treated with essential oil at 75 and 100 mg/kg and the reserpine group ($P>0.05$), and also between the essential oil group (50 mg/kg) and the fluoxetine group ($P>0.05$).

Impact of E. Platyloba Essential Oil on Serum MDA Level

One-way ANOVA showed a significant difference in the serum MDA level between the studied groups ($P<0.001$). Administration of reserpine could induce a significant increase ($P<0.001$) in the serum level of MDA (Figure 5C). The essential oil could reverse this at all doses ($P<0.01$). Still, the lowest dose (50 mg/kg) was the most active ($P<0.05$) (Figure 5C). The positive control, fluoxetine, showed significantly better activity ($P<0.001$) than the essential oil groups (Figure 5C).

Impact of E. Platyloba Essential Oil on Brain MDA Level

The one-way ANOVA results confirmed that the brain MDA levels were significantly different between the studied groups ($P<0.001$). Tukey's test showed that the MDA level in mice receiving reserpine was significantly higher than in the normal saline group ($P<0.001$). Fluoxetine was the most effective treatment ($P<0.001$) in reducing the brain MDA level, while the most effective dose of the essential oil was 50 mg/kg, followed by 100 and 75 mg/kg (Figure 5D).

Discussion

This investigation revealed that administering reserpine to mice can provoke depressive-like behaviors. As a result, mice exposed to reserpine demonstrated extended immobility periods in the FST and TST depression assessments. These findings align with the results of earlier research that utilized reserpine as an established rodent model for evaluating antidepressant effects (22, 23). At the biochemical level, reserpine induces a depressive state by discharging monoamine transmitters such as serotonin and norepinephrine at post-nodal terminals (24, 25). However, other mechanisms, such as increased inflammatory signaling and the induction of nitrosative and oxidative stress, also contribute to the effects of reserpine (26). In the FST assay, no significant difference was seen in immobility time between the essential oil (100 mg/kg) and the reserpine groups.

This study showed that intraperitoneal injection of *E. platyloba* essential oil at different doses in the TST reduced the prolonged immobility time induced by reserpine. Furthermore, intraperitoneal injection of *E. platyloba* essential oil (50 and 75 mg/kg) in the FST decreased immobility time induced by reserpine, attributed to reserpine. Similarly, the locomotor activity decreased in the OFT in the groups receiving essential oil at the dose of 50 mg/kg. The overall trend is that the dose of 50 mg/kg appears to be optimum, and there may not be a benefit in increasing the dose further, as 100 mg/kg had a lower activity profile in some experiments. Although the positive control, fluoxetine, tested at a lower dose (10 mg/kg), was more effective than the essential oil, it is important to note that the essential oil is a crude mixture and cannot be directly compared with the purified antidepressant drug.

Gas chromatography-mass spectrometry (GC/MS) analysis revealed that the primary constituents of *E. platyloba* essential oil were myristicin (76.6%), α-phellandrene (5.9%), and neocnidilide (4.4%). In contrast, Hassanpouraghdam et al reported myristicin (52.7%), α-phellandrene (44.2%), β-ocimene (38.9%), and p-cymene (7.4%) as the main components (12). Similarly, Rahimi Nasrabadi et al identified β-ocimene (26.71%), limonene (6.59%), spathulenol (4.57%), and myristicin (4.48%) (27), while Mazloomifar et al reported β-ocimene (26.7%), limonene (6.6%), myristicin (4.5%), and α-pinene (4.1%) (28). Variations in the chemical composition of *E. platyloba* essential oil may be attributed to differences in harvesting season, climatic conditions, geographical location, plant developmental stage, plant parts used, and extraction methods (29, 30). Given that myristicin, the predominant component is a known serotonin receptor agonist and a weak monoamine oxidase inhibitor, the antidepressant-like effects of the essential oil may be mediated by increased serotonin availability, akin to the mechanisms of selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) commonly used in depression treatment (27, 31).

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, is increasingly recognized as a key contributor to major

depressive disorder (32, 33). Antioxidants, therefore, hold significant therapeutic potential for depression management (34, 35). Essential oils from medicinal plants, including *E. platyloba*, can mitigate oxidative stress due to their diverse antioxidant compounds (36, 37). Previous studies have confirmed the antioxidant properties of *E. platyloba* (12), with Saei-Dehkordi et al reporting both antioxidant and antimicrobial activities, suggesting its potential as a natural antioxidant agent for pharmacological and food applications (36). In the present study, 50 mg/kg of *E. platyloba* essential oil exhibited the most consistent anti-depressant and antioxidant effects. In contrast, higher doses showed reduced efficacy in some parameters, potentially indicative of a bell-shaped dose-response curve. The diminished efficacy at higher doses may be linked to a pro-oxidant effect, as certain antioxidants can exhibit pro-oxidant activity at elevated concentrations (38). Further research is needed to elucidate this dose-response relationship and determine the optimal therapeutic dose.

MDA is a final peroxidation product of unsaturated fatty acids in the cell, and its higher level is a typical marker of oxidative stress (39). The results of the present study confirmed that the MDA levels of serum and brain in the essential oil groups were significantly decreased at all three doses. Hence, the reserpine-induced oxidative stress in the brain and serum could be ameliorated by *E. platyloba* essential oil. It should be noted, however, that antioxidants may also act as pro-oxidants in certain conditions and may exacerbate oxidative stress (39). The reduced efficacy of the essential oil as the dose increased in some experiments may be linked to such an effect, though further studies are required to establish the exact mechanism.

Overall, the antidepressant-like effects of *E. platyloba* essential oil are likely attributable to its antioxidant capacity in mitigating oxidative stress, potentially combined with myristicin's serotonin receptor agonist and monoamine oxidase inhibitory properties. Given that numerous plants exhibit antioxidant activity (40–43), the hypothesis that antioxidant properties contribute to the antidepressant effects of *E. platyloba* suggests that other antioxidant-rich plants may also hold therapeutic potential for depression. Further studies are warranted to explore this hypothesis and validate the efficacy of such plants in preclinical and clinical settings.

Conclusion

The essential oil extracted from the aerial parts of *E. platyloba* exhibited significant antidepressant-like effects in a reserpine-induced murine model of depression. Additionally, it effectively mitigated depression-associated oxidative stress in both brain and serum samples. Although the pharmacological efficacy of *E. platyloba* essential oil was less pronounced compared to fluoxetine, a well-established antidepressant, these findings underscore its therapeutic potential. Further preclinical and clinical studies are warranted to validate the efficacy and safety of *E. platyloba* essential oil in human populations. Moreover, investigations on the potential synergistic effects with conventional antidepressants could yield valuable insights. Additionally, exploring the broader therapeutic applications of this essential oil for other oxidative stress-related disorders is recommended.

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Project administration: Mehrdad Shahrani, Zahra Lorigooini.
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Competing Interests

The authors declared no competing interests.

Ethical Approval

The study protocol was performed according to the relevant guidelines by the SKUMS Bioethics Committee (IR.SKUMS.REC.1395.328).

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