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Short communication

Antidepressant Potential of *Ferula gummosa* Essential Oil in Mouse Models

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Abstract

Background and objectives: Earlier researches have exhibited the antioxidant, antinociceptive, and antiepileptic effects of *Ferula gummosa*. Considering that antioxidants play a key role in the pathogenesis of depression, the antidepressant potential of the *F. gummosa* essential oil was assessed by using a mouse models. **Methods:** Lorke's method was used to access the acute toxicity of the *F. gummosa* essential oil. The *F. gummosa* essential oil (5-40 mg/kg), standard agents, and vehicle were administered to animals. The forced-swimming test (FST), tail suspension test (TST), and open-field test (OFT) were used for the evaluation of depression. **Results:** The *F. gummosa* essential oil LD_{50} was found to be 316.22 mg/Kg b.w. β-Pinene, α-pinene, guaiol, δ-3-carene, bulnesol, α-Bisabolol, and β-myrcene were the major components of the *F. gummosa* essential oil, respectively. In both FST and TST, 10-40 mg/kg of the essential oil decreased the duration of immobility. Furthermore, 10-40mg/kg of the *F. gummosa* essential oil enhanced the duration of swimming with no significant effect on the duration of climbing in FST. The *F. gummosa* essential oil did not change the animal locomotion in the OFT. **Conclusion:** According to the results, the *F. gummosa* essential oil showed antidepressant activity similar to fluoxetine which may have a potential clinical value for the treatment of depression.

Keywords: antidepressive agents; essential oil; *Ferula gummosa*; mice; monotrepens

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Introduction

Major depression is a prevalent mood disorder that is characterized by depressed mood, diminished interests, impaired cognition, sleep, or appetite disorder [1]. Most commonly available antidepressant agents target the monoaminergic system including the serotonergic system [2]. Nevertheless, the treatment of major depression with standard agents provides a complete treatment only for 60-70% of the patients; also, their most prevalent side effects limit their clinical use [3,4]. Hence, it is necessary to use alternative therapies with minimal side effects [5].

Ferula gummosa Boiss. ("Barijeh" in Persian, Apiaceae) grows in the western and northern areas of Iran. In Iranian folk medicine, this plant is used for the control or treatment of different diseases including, colic, epilepsy, and stomach pain [6]. The important constituents of the *F. gummosa* essential oil (FGEO) are monotrepens (e.g., β-pinene) [7]. Monoterpenes are also known to have antidepressant properties [8,9]. Several pharmacological activities including antiepileptic [7], antioxidant [10], antinociceptive

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and anti-inflammatory effects have been attributed to *F. gummosa* [11]. However, no studies have yet evaluated its antidepressant-like effects. Hence, the antidepressant potential of the *F. gummosa* essential oil was assessed in this study by using mouse models.

Material and Methods

Ethical consideration

The experiments were approved by the ethical committee of the Khoy (IR.KHOY.REC.1399.007). The animal experimental practice was carried out in accordance with the NIH for laboratory animal use and care.

Chemicals

Imipramine (Sobhandaru, Iran) and fluoxetine (Abidipharma Co, Iran) were used in this study.

Plant material

Ferula gummosa essential oil was obtained from Tabib Daru Co (Kashan, Iran; Bath No.009). The content of the essential oil was analyzed with GC-MS method by Tabib Daru Co.

Animals

Male Swiss albino mice (8 weeks old) (Urmia University of Medical Sciences), weighing 20-30 g, were used. The mice were kept under standard animal facility conditions (23 -25 °C with 45–60% humidity, 12 h light/dark cycle, and food, and water ad libitum).

Acute toxicity

Lorke's method was used to access the acute toxicity of the *F. gummosa* essential oil [12].

Open-field test (OFT)

To assess the animal's locomotion, the mouse was subjected to OFT 5 min before FST [13].

Forced-swimming test (FST)

The forced-swimming test was conducted according to Porsolt et al. [14].

Tail suspension test (TST)

Tail suspension test was performed following the method of Steru et al. [15].

Experimental design and treatments

A total of 84 male albino mice were divided into 14 groups (n=6) as follows: groups 1-2: received the vehicle and served as a negative controls for FST, TST, and OFT. Groups 3-6: received imipramine (IMP; 30 mg/kg) and fluoxetine (FLX; 20 mg/kg) and served as positive controls for FST and TST. Groups 7-14: received the *F. gummosa* essential oil (5, 10, 20, and 40 mg/ kg, i.p.) and served as treatment groups for FST, TST, and OFT. After 45 min of the *F. gummosa* essential oil or drug injections, the animals were subjected to behavioral tests. The doses of the treatment groups were chosen based on earlier works [8,16]. All drugs were dissolved in saline except *F. gummosa* essential oil which was dissolved in 5% DMSO (in saline).

Statistical analysis

The data were expressed as the mean ± standard deviation (SD) using GraphPad Prism software (9.0.). Differences were analyzed by one-way ANOVA, followed by Tukey's test. P values <0.05 were considered statistically significant.

Results and Discussion

The *F. gummosa* essential oil mainly composed of 55 compounds (representing 99.52%): β-pinene (53.31%), α-pinene (7.72%), guaiol (4.15%), δ-3-carene (4.0%) bulnesol (3.59%), α-Bisabolol (3.16%), and β-myrcene (2.78%).

The oil LD_{50} was found to be 316.22 mg/Kg b.w. Additionally, toxic signs observed in doses 1000 to 5000 mg/kg included increased activity, ataxia, sleepiness, hyperpnea, and death.

As shown in Figure 1, the essential oil (10-40 mg/kg) decreased the immobility time [$F_{6, 35}$=160.2, p<0.001] and increased the swimming time [$F_{6, 35}$=76.59, p<0.001] without influencing the climbing behavior (p>0.05). FLX decreased the immobility time [$F_{6, 35}$ =76.59, p<0.001] whereas it increased swimming time [$F_{6, 35}$ =76.59, p<0.001] without any considerable effect on the climbing time (p>0.05). Contrarily, IMP decreased immobility time [$F_{6, 35}$ =76.59, p<0.001] while increasing climbing time [$F_{6, 35}$ =76.59, p<0.001] without any considerable effect on the swimming time (p>0.05).

Figure 2 shows that 10-40mg/kg of the *F. gummosa* essential oil, FLX, and IMP decreased the immobility time [$F_{6,35}$ =76.67, p<0.001], while the *F. gummosa* essential oil did not alter the line crossings and rearings (Table 1, p>0.05).

The findings of the present study show that *F. gummosa* essential oil is effective to induce considerable antidepressant activity. Our results also indicated that the *F. gummosa* essential oil did not alter animal locomotion in the OFT. In

this regard, agents that can increase animal locomotion (e.g., stimulants) tend to create a false positive result in mice models [17].

Table 1. Effect of *Ferula gummosa* essential oil on animal locomotion in open-field test (OFT)

Groups	Dose (mg/kg)	Number of crossing	Number of rearing
Vehicle	-	36.17 ± 6.01	10.67 ± 2.09
FGEO	5	41.17 ± 2.65	15.67 ± 1.80
FGEO	10	38.00 ± 6.23	13.67 ± 2.48
FGEO	20	44.67 ± 4.60	14.50 ± 1.66
FGEO	40	25.33 ± 4.73	11.00 ± 1.78

Data represent the mean±SD (n= 6); FGEO: *Ferula gummosa* essential oil

According to previous studies, the pharmacological properties of the essential oil are attributed to pinenes [10,18]. Earlier research has also shown that monoterpenes (e.g., β-pinene) have potential antidepressant activity [8,9], while β-pinene creates an antidepressant-like effect partly by activating 5-HT1A receptors [9].

Studies have shown that oxidative stress may play a significant role in the pathophysiology of depression [19]. Hence, antioxidants are new candidates to control or used as treatment for depression with enhancing the reuptake of serotonin in the synaptic cleft [20]. Earlier research indicated the antioxidant potential of the *F. gummosa* essential oil [21]. Our findings also confirm the significant role of the serotonergic system in the antidepressant-like effect of the *F. gummosa* essential oil.

Overall, a considerable reduction in immobility time and an increase in swimming time after the treatment with the *F. gummosa* essential oil was related to the principal compounds of the essential oil (particularly β-pinene), which are likely to create antidepressant activity via the modulation of the serotonergic system.

Conclusion

According to the results, the *F. gummosa* essential oil showed antidepressant activity similar to fluoxetine which might have a potential clinical value for the treatment of depression.

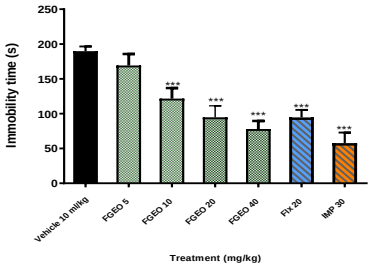

Figure 2. Effects of *Ferula gummosa* essential oil (FGEO), fluoxetine (Flx), and imipramine (Imp) on active behavior in mouse in tail suspension (TST); data represent the mean±SD (n= 6); *** p <0.001 *vs*. vehicle group on immobility time

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Author contributions

Saeid Abbasi-Maleki and Hadi Yousefi were involved in preparing, writing and editing of the manuscript and data collection; Rahim Sharafkhani and Mohammad Azarsa were involved in data collection and statical analysis.

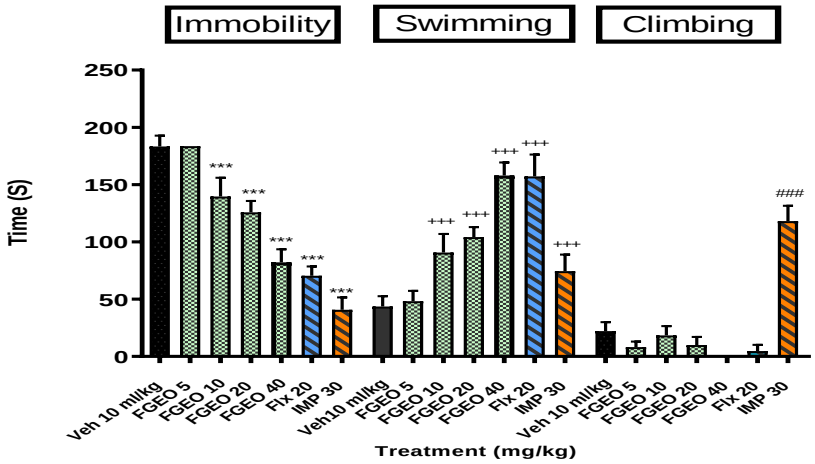

Figure 1. Effects of *Ferula gummosa* essential oil (FGEO), fluoxetine (Flx), and imipramine (Imp) on active behaviors in mice in forced-swimming test (FST); data represent the mean±SD (n= 6); *** p <0.001 vs. vehicle group on immobility time; +++ p<0.001 vs. vehicle group on swimming time; ### p <0.001 vs. vehicle group on climbing time

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

DMSO: dimethyl sulfoxide; FGEO; *Ferula gummosa* essential oil; FLX: fluoxetine; FST; forced-swimming test; 5-HT1A: 5-hydroxytryptamine receptor 1A; IMP: imipramine; i.p.: intraperitoneally; OFT: open-field test; TST: tail suspension test