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Original Article

Effects of Essential Oil of *Satureja Bachtiarica* Bunge in a Rat Model of Reserpine-Induced Depression

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Abstract

Background: Due to the unfavorable side effects of some commonly used chemical drugs, the trend in the public has shifted towards using herbal medicines to treat central nervous system disorders like depression. The present experimental study was designed to evaluate the effect of Marze (*Satureja bachtiarica* Bunge) essential oil on reserpine-induced depression in rats.

Methods: In total, 48 male Wistar rats were randomly divided into 6 groups: 1) control, 2) reserpine, 3-5) reserpine with 50, 75 and 100 mg/kg of Marze essential oil, respectively, and 6) reserpine and fluoxetine. The forced swimming test was used to evaluate the antidepressant activity of the essential oil. Total antioxidant capacity (TAC) and MDA levels of serum and brain were also determined.

Results: Reserpine induced a significant increase in the immobility time of rats in the forced swimming test (P=0.02) and treatment with Marze essential oil (50, 100 mg/kg) ameliorated the reserpine induced changes (P=0.04, P=0.03, respectively). Reserpine-induced reduction in brain TCA was improved using Marze essential oil at a dose of 100 mg/kg (P=0.04). Marze essential oil at 100 mg/kg dose significantly decreased the MDA level in the brain tissues of reserpine-treated rats (P=0.04).

Conclusion: Marze (*Satureja bachtiarica* Bunge) essential oil has the ability to prevent depression induced by reserpine probably via its antioxidant activity.

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Keywords ● *Satureja bachtiarica* Bunge ● Marze ● Antidepressant activity ● Antioxidant activity ● Forced swim test

What's Known

- *Satureja bachtiarica* exhibit antioxidant, antimicrobial, anti-inflammatory and analgesic properties in vitro and in animal models

What's New

- For the first time, the anti-depression effects of *Satureja bachtiarica* is reviewed

Introduction

Anxiety and depression, highly comorbid psychiatric conditions, are chronic and recurring disorders associated with biochemical, cognitive, behavioral, and psychological changes that can cause a significant socioeconomic burden.[1,2] The prevalence rate of depression is about 15% during the lifecycle and is considered as one of the main reasons of disability. It is ranked fourth among the top ten main reasons of disease load in the world. It is also reported that about 500 million people suffer from anxiety disorder around the world.[1] The increasing number of patients with these disorders encourages research on developing effective drugs to prevent or treats such diseases.[3]

Due to unfavorable side effects of some commonly used chemical drugs, there is an increasing trend in the public to use herbal medicines to treat various diseases.[1,4] Herbal medicine has been widely used for the treatment of mood and anxiety disorders since the ancient times. Nowadays, about 25% of all prescribed drugs are derived from herbs or medicinal plants.[1] Many medicinal plants are recently identified for the treatment of specific disorders, but some others have been used for thousands of years without being recognized by scientists.[3]

Satureja is a member of Lamiaceae family that encompasses more than 30 species. It is scattered mainly in the Mediterranean region. In Iran, 14 species of Satureja with the Persian name of "Marze" are present in which 9 are endemic. One of these endemic species is *Satureja bachtiarica. Satureja bachtiarica* exhibited antioxidant, antimicrobial, anti-inflammatory, and analgesic properties in vitro and in animal models.[5] The major reported constituents of *Satureja bachtiarica* essential oil are Thymol, carvacrol, terpinene, p-Cymene, and beta-caryophyllene.[5,6] Until now, few studies have been conducted on the neuroprotective effect of *Satureja bachtiarica*. Soodi et al. (2016) reported the protective effect of *Satureja bachtiarica* against β-amyloid-induced neurotoxicity and oxidative stress in a mice model.[7] In the present study, we aimed to investigate the effect of *Satureja bachtiarica* Bunge essential oil on reserpine-induced depression in rats.

Materials and Methods

Preparation of Marze (Satureja Bachtiarica Bunge) Essential Oil

The leaves of *Satureja bachtiarica* Bunge were collected in the plains and mountainous regions of Chaharmahal-Bakhtiari province (Iran) during the spring and summer. After approval from an herbalist, it was kept in the herbarium (tag number: 137654) of the Medical Faculty of Shahrekord University of Medical Sciences (Iran). The dried leaves of *Satureja bachtiarica* Bunge were ground and used for essential oil extraction using the Clevenger method. Briefly, 142 grams of the powdered plant was weighed by analytical balance and transferred to a 3-liter flask attached to the Clevenger. Distilled water (1,500 ml) was added to the flask containing the powder. Extraction was carried out for 4 hours and then the oil was collected and dehydrated by anhydrous sodium sulfate. The prepared essential oil was kept at -20 °C until injection to the GC/MS.

GC-MS Analysis of Essential Oil

GC-MS analyses were carried out using Agilent 5975 GC-MS system equipped with the HP-5MS fused silica column (30 m × 0.25 mm I.D.), oven temperature 50-240 °C with a rate of 7 C/min, injector temperature 280 °C, carrier gas He with a flow rate of 0.8 mL/min, Ionization energy 70 eV, scan time 1 second, and mass range 40-300 amu. The essential oil compounds were identified by comparing their mass spectra with those of a computer library, authentic compounds, or data published in the literature.[2]

Animals and Treatments

The experiments were performed on 48 adult male Wistar rats weighing 250-300 g. Rats were kept under standard laboratory conditions (12 h light/12 h dark cycle at 22±2 °C) with free access to water and standard laboratory food. The rats were randomly divided into 6 groups. The control group received normal saline (1 mg/kg, i.p.) and the reserpinized group received reserpine (5 mg kg, *i.p.*) 18 hours before the behavioral test. The intervention groups received fluoxetine (20 mg/kg, i.p.) or Marze essential oil (50, 75, 100 mg/kg, ip) 18 hours after reserpine injection. Doses of essential oil were selected based on the previous study.[7] The behavioral test was conducted 30 minutes after essential oil or fluoxetine injection. After performing the behavioral test, the animals were subsequently put under deep anesthesia, cardiac blood samples were collected, and the brain was removed and used for biochemical analysis. Blood was centrifuged and serum was separated and used for biochemical analysis.

All experiments were performed in accordance with the Guide for Laboratory Animals Care and Use.[8] The study was approved (number: 2237654) by the Ethics Committee of Islamic Azad University of Izeh (Iran).

The Forced Swimming Test

The forced swimming test was developed by Porsolt et al. (1979).[9] Rats were forced swim for 15 minutes on the final day of administration. After 24 hours, the rats were forced swim again for 5 minutes and were videotaped for further behavioral analyses such as calculating the duration of immobility, swimming, and struggling using the forced swim scan™ software (Clever Sys. Inc., Reston, VA, USA). The definition of these different behaviors is based on the activity of the four limbs and the ratio of body area that was below or above the water surface.[10]

Measurement of Plasma Antioxidant Capacity

Three solutions were used for this measurement. Solution 1: 1.5 ml of sodium acetate and 8 ml of

concentrated acetic acid, diluted to 500 mL with distilled water. Solution 2: 270 mg of Iron (III) chloride, dissolved in 50 mL of distilled water. Solution 3: 47 mg of treeazin, dissolved in 40 mL of HCl. The working solution was prepared by mixing 10 mL of solution 1, 1 ml of solution 2, and 1 ml of solution 3. Thereafter, 25 microliters of the serum sample were added to 5.1 ml of the working solution. The resulting mixture was incubated at 37 °C for 15 minutes and then the absorbance was measured at 593 nm.[11]

Measurement of Brain Antioxidant Capacity

The antioxidant capacity of the brain was determined by ferric reducing antioxidant power (FRAP) assays. The FRAP working solution was prepared by mixing 25 ml of acetate buffer, 2.5 ml of TPTZ (2, 4, 6-tripyridyl-s-triazine), and 2.5 ml of $FeCl_3$. Brain tissue was homogenized and the homogenate was centrifuged at 1000 g for 10 minutes. 50 ml of the resulting supernatant was mixed with 5.1 mL of FRAP working solution. After 10 minutes of incubation, Fe^{3+} TPTZ complex was reduced to the ferrous (Fe^{2+}) producing an intense blue color. The absorbance of mixture was measured at 590 nm.[12]

Measurement of Serum MDA Level

Briefly, 50 µL of serum was mixed with 50 µL of 0.05% BHT, 400 µL of 0.44 M H_3PO_4, and 100 µL of 42 Mm TBA. The mixture was vortexed and then heated in a boiling water bath for 1 hour. After cooling at 0 °C for 5 minutes, 250 µL of n-butanol was added to the mixture, vortexed, and then centrifuged at 14000 rpm for 5 minutes. The absorbance of the supernatant was measured at 532 nm.[13]

Measurement of Brain MDA Level

Brain tissue was homogenized in (1:10 wv^{-1}) pre-chilled KCL solution and transferred into a 20 ml tube. After incubation for 60 minutes at 37 °C, the suspension was mixed with 1 ml of 5% tetrachloroacetic acid and 1 ml of 67% TBA, and centrifuged for 15 minutes at 2,000 rpm. The resulting supernatant was transferred into a new tube and placed in a boiling water bath for 10 minutes. After cooling, its absorbance was measured at 535 nm.[14]

Statistical Analysis

All data were expressed as the mean±SD. The Kolmogorov-Smirnov test was used for the normality test. All data had P values greater than 0.05, which indicated the normal distribution of data. The homogeneity of variances was determined using the Levene's test. One-way ANOVA was used to compare the mean between the experimental groups. In the case of homogeneous variances and in the case of non-homogeneous variances Duncan test and Dunnett's T3 were used, respectively. P<0.05 was considered statistically significant.[15]

Results

The results of behavioral testing (immobility during forced swimming test) are shown in figure 1. Compared with the control group, treatment with reserpine significantly increased the immobility time during the forced swimming test (P=0.02). Prescription of 50 and 100 mg/kg Marze essential oil as well as fluoxetine significantly ameliorated the reserpine-induced incremental changes in the immobility time during the forced swim (P=0.04, P=0.03, P=0.04, respectively).

Table 1 shows the results of serum total antioxidant capacity (TAC) among different treatments. The analysis of ANOVA showed no significant difference for serum TAC among different treatments (P=0.69). The administration of reserpine decreased the serum TAC level compared with that of the control group, but not significantly (P=0.69). Prescription of Marze essential oil as well as fluoxetine increased the reserpine-induced changes in serum TAC, but not significantly (P=0.69).

The results of brain TAC among different treatments are shown in table 2. The administration of reserpine significantly (P=0.03) decreased the brain TAC level compared with that of the control group. Prescription of Marze essential oil and fluoxetine increased the brain TCA of reserpine treated mice. Such increase was significant at 100 mg/kg of Marze essential oil compared with that of reserpine, fluoxetine as well as 50 and 75 mg/kg MEO (P=0.04).

As presented in table 3, the analysis of ANOVA showed no significant difference

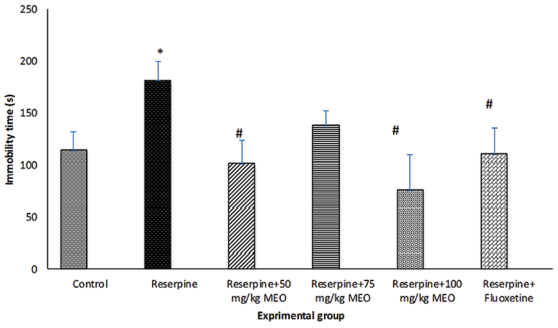

Figure 1: The results of behavioral testing (immobility time during the forced swimming) among different studied groups. *Significant differences with control at P=0.02; #Significant differences of reserpine plus 50, 75, and 100 mg/kg MEO with the reserpine group at P=0.04, P=0.03, and P=0.04, respectively.

for the serum MDA among different groups (P=0.43). Reserpine increased serum MDA compared with that of the control group, but not significantly (P=0.43). The use of fluoxetine or Marze essential oil at different concentrations decreased the reserpine-induced increase in the serum MDA, but these changes were not significant (P=0.43).

The results of brain MDA among different treatments are shown in table 4. Reserpine increased brain MDA compared with that of the control group, but not significantly (P=0.06). The use of fluoxetine, as well as MEO at 50, 75, and 100 mg/kg decreased the brain MDA as compared with that of the reserpine group. However, this reduction was only significant for the dose of 100 mg/kg of MEO (P=0.04) (table 4). Based on table 5, the major components of Marze essential oil were carvacrol (63.34%), 2-cyclohexen-1-one (10.2%) and caryophyllene (4.1%).

Discussion

The antidepressant effects of Marze (*Satureja bachtiarica* Bunge) were studied in reserpine-induced depression model in rats. Based on the results, reserpine significantly increased the immobility time in the forced swimming test and treatment with Marze essential oil at doses of 50 and 100 mg/kg significantly ameliorated the

Table 1: The results of serum total antioxidant capacity among different study groups

Treatment	Serum TCA (μmol/ml) (mean±SD)	P value
Control	1.04±0.13	0.69
Reserpine (5mg/kg)	0.98±0.13	
Reserpine+50 mg/kg MEO	1.2±0.17	
Reserpine+75 mg/kg MEO	1.04±0.07	
Reserpine+100 mg/kg MEO	1.1±0.13	
Reserpine+20 mg/kg fluoxetine	1.3±0.25	

Table 2: The results of brain total antioxidant capacity among different study groups

Treatment	Brain TCA (μmol/ml) (mean±SD)	P value
Control	7.78±0.28	0.005
Reserpine (5mg/kg)	5. 87±0.64*	
Reserpine+50 mg/kg MEO	6.00±0.58	
Reserpine+75 mg/kg MEO	7.02±0.50	
Reserpine+100 mg/kg MEO	8.89±0.76#	
Reserpine+20 mg/kg fluoxetine	6.17±0.66	

*Significant differences with control at *P*=0.03; #Significant differences with the reserpine group at *P*=0.04

Table 3: The results of serum malondialdehyde level among different study groups

Treatment	Serum MDA (μmol/ml) (mean±SD)	P value
Control	19.2±1.8	0.43
Reserpine (5mg/kg)	35.05±10.8	
Reserpine+50 mg/kg MEO	21.6±5.4	
Reserpine+75 mg/kg MEO	19.9±5.8	
Reserpine+100 mg/kg MEO	16.4±1.6	
Reserpine+20 mg/kg fluoxetine	19.9±6.8	

Table 4: The results of brain malondialdehyde level among different study groups

Treatment	Brain MDA (μmol/ml) (mean±SD)	P value
Control	0.43±0.06	<0.001
Reserpine	0. 50±0.03	
Reserpine+50 mg/kg MEO	0.50±0.07	
Reserpine+75 mg/kg MEO	0.54±0.08	
Reserpine+100 mg/kg MEO	0.27±0.06#	
Reserpine+20 mg/kg fluoxetine	0.38±0.06	

#Significant differences with the reserpine group at *P*=0.04

Table 5: Phytochemical composition of Marze (***Satureja bachtiarica*** Bunge) essential oil

Number	Phytochemical	Retention time	CAS	Maximum (%)	Kowats index
1	2-cyclohexen-1-one	20.6773	2,244-16-8	10.22	1,277
2	Anethole	20.9353	104-46-1	1.94	1,288
3	Thymol	21.1398	89-83-8	0.7	1,296
4	Carvacrol	21.5877	499-75-2	63.34	1,317
5	Piperitenone	22.3716	491-09-8	0.7	1,354
6	Carvacryl acetate	22.8925	6,380-28-5	1.4	1,379
7	Caryophyllene	23.8565	87-44-5	4.11	1,428
8	Aromadendrine	24.2168	489-39-4	0.73	1,447
9	Alpha-curcumene	24.9812	644-30-4	0.51	1,488
10	Ledene	25.2635	21,747-46-6	0.65	1,503
11	Beta-bisabolene	8.22	1,516		
12	Cyclohexene	25.7309	20,307-83-9	0.63	1,530
13	Alpha-bisabolen	26.0425	17,627-44-0	0.96	1,548
14	Spathulenol	26.7388	77,171-55-2	1.2	1588
15	Caryophyllene oxide	26.8507	1,139-30-6	1.31	1,594
16	Tricyclo	31.7778	281-46-9	0.52	1,944

reserpine-induced changes. Other studies have also used reserpine to induce depression-like disorders and reported increased immobility time during the forced swimming test.[13] Reserpine is the blocker of vacuolar monoamine reuptake that can result in the evacuation of monoamines in the brain, which subsequently can lead to the depressive-like symptoms in animals.[13]

The antidepressant effect of Marze essential oil observed in our study may be related to its major component, carvacrol. The major component of Marze essential oil was carvacrol (63.34%). Falsafi et al. (2014) reported that carvacrol (45.5%) and thymol (27.9%) were the primary constituents of Marze essential oil.[14] The difference between the main components in different studies might be related to the geographic localities, harvesting time, and extraction method.[15]

The antidepressant effect of carvacrol has been shown in previous studies. In a study conducted by Melo et al. (2011), carvacrol significantly decreased the immobility time of physically stressed mice in the forced swimming and tail suspension tests. They reported that the antidepressant effect of carvacrol was not prevented with adrenergic and serotonergic antagonists, but prevented with dopaminergic antagonist. These results demonstrated that carvacrol shows antidepressant effects through the interaction with the dopaminergic system.[16] In Melo et al. study (2010), carvacrol exhibited sedative and anxiolytic-like activities in plus maze and barbiturate-induced sleeping tests. The anxiolytic effect of carvacrol was significantly inhibited by flumazenil that shows the involvement of the GABAergic system.[17]

The results also showed that reserpine significantly decreased the total antioxidant capacity of the brain and partially increased serum and brain levels of MDA. The use of Marze essential oil at 100 mg/kg significantly increased the reserpine-induced reduction in the brain TAC and decreased the reserpine-induced increase in brain MDA level. Our results are consistent with the results of other researchers who reported a decrease in the marker of oxidative stress after *Satureja bachtiarica* treatment.[7] In another study, Khosravinia et al. (2013) reported that the addition of Marze essential oil to the drinking water of chickens significantly decreased the level of lipid peroxidation and increased the activity of antioxidant enzymes including catalase, glutathione peroxidase, and superoxide dismutase compared to the control group.[18] Samarghandian et al. (2016) reported the protective effects of carvacrol against oxidative stress induced by chronic stress in mice. Carvacrol significantly reduced lipid peroxidation in the brain, liver and kidney tissues and improved the activity of antioxidant enzymes.[18] Thus, it can be concluded that the positive effects of Marze essential oil on depression may be related to the increased activity of antioxidant defense system and prevention of oxidative stress in the brains of *reserpined* rats. In this regard, studies have shown that antioxidants could prevent the injury or death of nerve cells by reducing oxidative stress.[19-21]

In the present study, Marze essential oil showed the antidepressant effect against reserpine-induced depression. Some of the observed antidepressant effects of Marze essential oil can be attributed to its anti-oxidant activity. Its antidepressant effect may also contribute to the

interaction of its main component, carvacrol, with GABAergic and dopaminergic system. However, it is recommended that the role of monoaminergic systems in the antidepressant effect of Marze essential oil be further studied using different agonist and antagonist.

Conclusion

It is suggested that *Satureja bachtiarica* Bunge essential oil has the ability to prevent reserpine-induced depression. This effect may be related to its antioxidant activity. The monoaminergic system may also be involved in the antidepressant effect of Marze, but this mechanism should be evaluated further.

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Conflict of Interest: None declared.

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