Phytochemical Study and Antidepressant Effect of Essential Oil of *Apium graveolens* L.

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Authors' contributions

This work was carried out in collaboration among all authors. Author MS designed the study. Author AA performed the statistical analysis and managed the analyses of the study. Author HAK wrote the protocol. Author ZLG wrote the first draft of the manuscript. Authors NA and MS managed the literature searches. Author ZM did the experiments. All authors read and approved the final manuscript.

| Original Research Article |

ABSTRACT

Background and Purpose: Depression is a common and debilitating disease.The aim of this study was to investigate the chemical composition of *Apium graveolens* essential oil and its anti-depressant effect in mice and the effect on motor balance, serum and brain antioxidant capacity.

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Materials and Methods: 60 mice were randomly divided into 6 groups (N=10), Control, reserpine 5mg/kg IP, reserpine + fluoxetine 20 mg/kg, reserpine + essential oil (50, 75 and 100 mg/kg). The intervention group received 5 mg/kg reserpine and 18 hours later, essential oil (50, 75 and 100 mg/kg). Assessment of depression done with forced swimming and open field tests and motor balance with a Rotarod. Serum and brain antioxidant capacity and malondialdehyde levels were measured.

Results: Reserpin increased the immobilization time in the forced swimming test, the number of motor units in the open field test, serum and brain malondialdehyde and reduced the antioxidant capacity and the motor balance. Fluoxetine and essential oil of *Apium graveolens* 50 and 75 mg/kg reduced the time of immobilization time, number of motor units, serum and brain malondialdehyde and increased serum and brain antioxidant capacity and motor balance. *Apium graveolens* essential oil 100 mg/kg increased serum antioxidant capacity and reduced number of motor units.

Conclusion: Chemical compounds of essential oil of *Apium graveolens* have antioxidant, anti-inflammatory and regulating of chemical neurotransmitters properties that are known mechanisms of depression.

1. INTRODUCTION

Depression is one of the major causes of ill health and economic burden worldwide. Antidepressant medication is a standard treatment and the first choice for depressed patients in current psychiatric guidelines [1].

Depression is a primary determinant of years lost due to disability accounting for 24.5% of all disability-adjusted life years due to mental and neurological disorders. Prevalence of lifetime depression ranges from 7.6 to 16.6% across countries and the economic burden has been estimated in 210 billion dollars per year in the USA only [2].

Over the past few decades, depression has become one of the most common neuropsychiatric disorders, affecting the quality of life of millions of people worldwide [3].

The pathophysiology of depression has not been fully elucidated; increasing evidence has shown that neuro inflammation may play a role in the development of this disorder. Specifically, it has been reported that patients with depression frequently show immune system alterations, such as elevated proinflammatory cytokines levels in plasma and cerebrospinal fluid [4]. Disturbance of affective cognition constitutes a core aspect of the symptomatology of many psychiatric disorders, particularly depression and anxiety. These cognitive dysfunctions represent one of the main features of depressive disorders, of which the number of patients is increasing globally [5].

According to the World Health Organization, Major Depressive Disorder also carries the heaviest burden of disability among mental and behavioral disorders [6]. The generation of excessive free radicals due to oxidative stress and subsequently defective antioxidant defense along with enhanced lipid peroxidation are implicated in depressive disorders. In addition, impaired hypothalamic-pituitary adrenal axis (HPA-axis) is known to participate in the induction of depressive like behavior. The disproportionate elevation of serum corticosterone level in response to impaired HPA axis is responsible for neuronal damage which is manifested to hippocampal atrophy in depressed patients [7].

Reserpine is a sympatholytic and sedative agent and was once used as a primary treatment for hypertension. However, evidence in research and clinical trials have shown that Reserpine has a serious side-effect, causing major depression after chronic use of the medication in a percentage of the drug's users. Reserpine-mediated depression is thought to be caused by the depletion of monoamines in the brain, such as the catecholamine's adrenaline, dopamine, and nor epinephrine. This is referred to the monoamine theory of depression. The mechanism of Reserpine is the irreversible binding to storage vesicles in monoaminergic neurons. The gathered evidence indicating Reserpine causes depression has led to the usage of the medication in animals, most commonly mice and rats, to produce a practical animal model for depression [20].
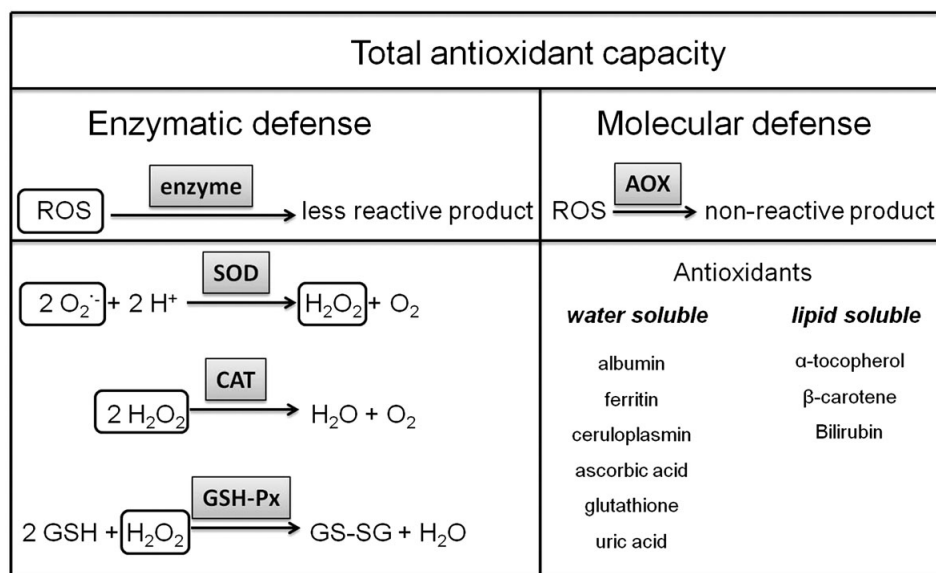
Fig. 1. Overview of the oxidative defense mechanism in human blood and tissues. AOX, antioxidant; GSH-Px, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; ROS, reactive oxygen species

Lipid peroxidation is associated with depression and a variety of chronic health diseases, such as cancer and atherosclerosis numerous studies suggest that antioxidants can prevent the oxidation of various macromolecules, such as DNA, proteins, and lipids, thus preventing the depression, aging process and increasing the lifespan of the organism [8]. In this study, we investigated one type of antioxidants *Apium graveolens*. Oxidative stress occurs when there is an imbalance in oxidant and antioxidant in excess of oxidant [9]. Free radicals, because of their nature of attack on cellular organelles behave like oxidants. The attack of free radical on polyunsaturated membrane lipid gives hydroperoxide with subsequent production of malondialdehyde (MDA). This attack on membrane lipid is termed as lipid peroxidation, and malondiadehyde is now measured as the product of free radical injury on membrane lipid. The attack of free radical on polyunsaturated membrane lipid results in hydroperoxide with subsequent production of malondialdehyde (MDA) [10]. The oxidative defense mechanism is shown in Fig. 1 [11].

Apium graveolens is classified as a member of the Apiaceae family known as celery. It is a well-known plant used consistently throughout history in medicinal preparations, food flavoring or in spices. The whole part of this plant has a specific taste and aromatic smell, especially the leaves and roots [5]. Medicinal and aromatic substances are presented in the roots, stem and leaves. Reports in literature reviews have claimed to show that *A. graveolens* extracts have healing properties and their active compounds possess a wide range of biological activities including anti-inflammatory activity, anti-oxidative activity, enhanced memory, and neuroprotective effects mostly found in vitro models. In addition *A. graveolens* seed has been found to help regulate the nervous system. Despite the numerous scientifically proven pharmacological activities of *A. graveolens*, there are no scientific data on its potential as an antidepressant agent. Hence, this study was initiated to determine the potential effect of essential oil of *A. graveolens* on depression and antioxidant capacity in mice.

2. MATERIALS AND METHODS

2.1 Essential Extraction

The Clevenger device works by distilling water for hydrodistilation method extraction. The powdered plant was weighed by an analytical balance and transferred to the Clevenger attached balloon. Distilled water was added to the balloons containing *A. graveolens* powder and extracted for 4 hours. Then the essential oil was collected and added sodium sulfate without water and stored at -20°C until GC-MS was injected [12].

2.2 Determination of Chemical Composition of Essential Oil by GC-MS

The GC-MS is a device that removes chemical mixtures by gas chromatography and mass spectrometry, and we used it to determine the essential oil composition.

2.3 Animals

60 Adult Balb/c mice (6-7 weeks old, weighing 18-22 g) were purchased from the Experimental Animal Centre of Tehran. The mice allowed to acclimatize for 1 week in an environment with a controlled temperature (25-27°C), and 12 h light/dark cycle, and were given free access to food and water. The animal protocols for this study were approved by the Shahrekord University of Medical sciences Animal Care Committee according to the Guidelines on the Humane Treatment of Laboratory Animals.

The groups were divided as follows (N=10): Control (Do not get any medication or negative control), reserpine 5 mg/kg IP, reserpine + fluoxetine 20 mg/kg (positive control), reserpine + essential oil (50, 75 and 100 mg/kg). The intervention group received 5 mg/kg reserpine and 18 hours later, essential oil (50, 75 and 100 mg/kg).

2.4 Rotarod Test

Locomotors activity of mice was assessed using a Rotarod system (borjsanat company, Iran). Before measuring, mice were adapted to the rod with a constant speed of 4 rpm for 3 minutes. Mice were conditioned on the rod (diameter: 3.5 cm) with an increasing speed of 4 to 40 rpm (accelerated by 1 rpm per 5 s). Motor ability was measured as the time until the mouse falls off the rod, up to 300 s. The average latency time of 3 trials was calculated for statistical analyses. The interval period between trials was 20 min [13].

2.5 Open Field Test (OFT)

The open-field apparatus was a square, Plexiglas, arena measuring 60 cm _ 60 cm _ 40 cm. To start a session, mice were gently placed in the center of the open-field and were allowed to freely explore the whole arena. Mice were allowed to habituate to the open-field arena for 2 min to eliminate the bias of novelty. This test was used to evaluate the motor activity of the mouse. The floor area of this box was divided into 16 squared houses of equal size, and within 5 minutes, when four limbs of rats in one squared houses were counted as a one unit of movement.

2.6 Forced Swimming Test (FST)

In FST, we assessed the ability of mice to cope with an inescapable stressful situation, which reflects depressive-like behavior. Mice were individually placed in a 2 L Pyrex beaker (13 cm diameter, 24 cm height), filled with 23°C water with a depth of 17 cm. All mice were forced to swim for 6 min, and the duration of immobility was measured during the final 5 min of the test. The immobility was defined as the time that the mouse spent floating without struggling and making only the movements necessary to keep its head above the water level. The observers were blinded to the groups. The time spent immobile was measured and compared by two observers to minimize the bias [13].

2.7 Assay of Plasma and Brain MDA Levels

Malondialdehyde (MDA) was estimated using method of Sikar et al. it is a thiobarbituric acid reacting substance. After the initial precipitation by trichloroacetic acid (TCA), the reaction of MDA with thiobarbituric acid gives a red colored complex. Thiobarbituric acid (TBA) reacts with lipoperoxidation aldehydes, such as MDA, as the most common method to assess lipid peroxidation in biological samples. Briefly, 0.5 mL of plasma or brain homogenate was added to a reaction mixture (1.0 mL) formed by equal parts of 15% trichloroacetic acid, 0.25 N HCl and 0.375% TBA, plus 2.5 mM butylated hydroxytoluene (BHT) and 0.1 mL of 8.1% sodium dodecyl sulphate (SDS), followed by 30 min heating at 95°C; the pH value of the analytical reaction mixture was about 0.9. After cooling, the chromogen was extracted with N-butanol and read spectrophotometrically at 532 nm against reaction mixture blank lacking plasma but subjected to the entire procedure and extracted with n-butanol. The results were expressed as mol/L in plasma and nmol/gr in wet tissue according to a standard, which was prepared with serial dilutions of standard 1,1,3,3 tetramethoxypropane [14].

2.8 Measurement of Total Antioxidant Capacity (TAC)

The ferric reducing antioxidant power (FRAP assay) is a method to determine TAC (total antioxidant capacity). According to this method, a blue ferrous complex is formed by reduction of colorful ferric-tripyridyltriazine complex in the presence of antioxidant. The absorbance of samples was determined at a wavelength of 593 nm. After comparing the absorbance of each sample to the standard curve, the quantity of antioxidant power was calculated and the TAC has reported in µmol/L [15].

2.9 Data Analysis Method

Graphpad PRISM software version 6 was used to plot the graphs. One way ANOVA was used to determine the significant difference and Tukey's post hoc test was used for comparison of the means. $P < 0.05$ was considered statistically significant.

3. RESULTS

3.1 Chemical Composition of Essential Oil of *Apium graveolens* by GC-MS

Analysis identified 19 components in the *Apium graveolens* essential oil. The main components of essential oil composition were α-Terpinyl acetate (29.5%), limonene (19.7%), Neocnidilide (19.2%), γ-Terpinene (9.1%), Myristicin 6%) and (Z) -Ligustilide (4%) as shown in Fig. 2.

3.2 The Effect of *Apium graveolens* Essential Oil on the Duration of the Balance

Analysis of One Way Anova showed that the duration of balance in the reserpine group was significantly reduced compared to the control group ($P < 0.001$). The duration of balance in 75 and 100 mg / kg groups of essential oil was significantly increased compared to the reserpine group ($P < 0.01$). The duration of balance in the reserpine + fluoxetine group increased significantly compared to the reserpine group ($P < 0.01$) (Fig. 3).

3.3 The Effect of *Apium graveolens* Essential Oil on the Number of Unit Movements

Analysis of One Way Anova showed that the number of motor units in the reserpine group was significantly decreased compared with the control group ($P < 0.01$). The number of motor units in groups 75 and 100 mg / kg of essential oil was significantly higher than the reserpine group ($P < 0.001$). The number of motor units in the reserpine + fluoxetine group increased significantly compared to the reserpine group ($P < 0.05$) (Fig. 4).
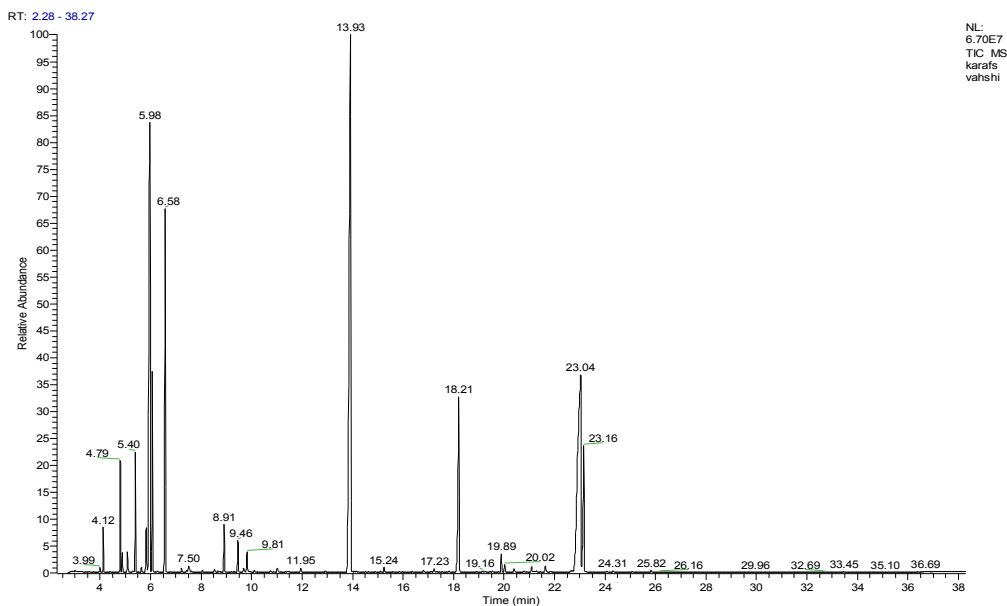
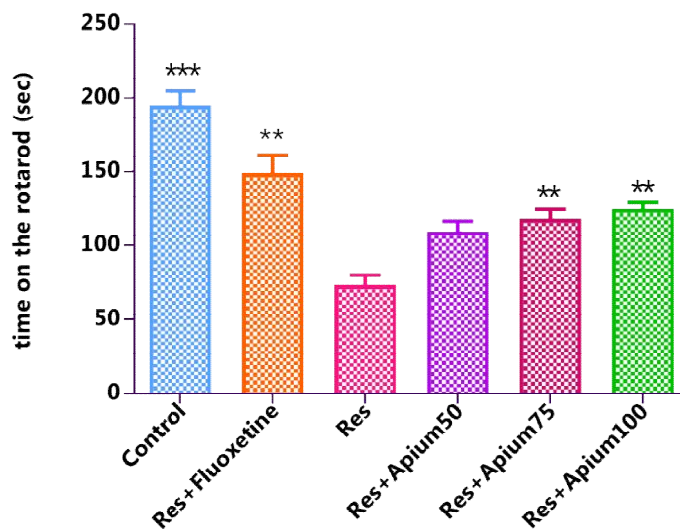**Fig. 2. GC /MS chromatogram from *Apium graveolens* essential oil**

Fig. 3. Duration of balance in rotarod test. Res = Reserpine, Apium = *Apium graveolens*
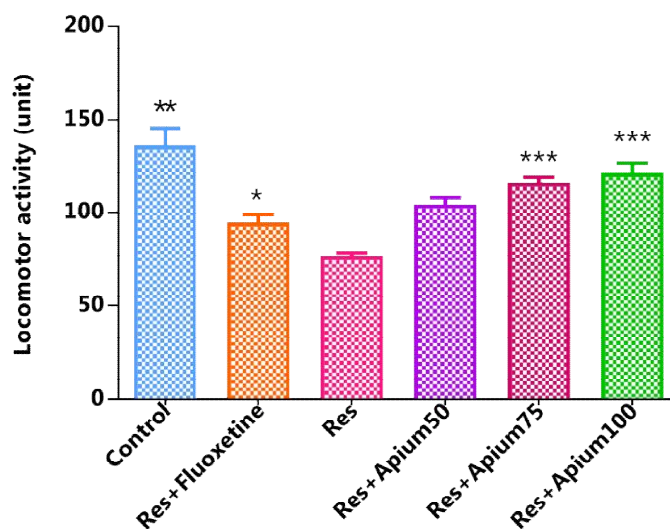**** and ** Comparison with Reserpin P <0.001, p<0.01*

Fig. 4. Locomotor activity in open fild test. Res = Reserpine, Apium = *Apium graveolens*
*** comparison with reserpine p<0.001; ** comparison wih reserpine p<0.01 * comparison with reserpin p<0.05

3.4 Effect of *Apium graveolens* Essential Oil on the Immobility Time in the Swimming Test

Analysis of One Way Anova showed that, the immobility time was significantly increased in the reserpine group compared to the control group (P <0.001). The duration of immobility in 75 and 100 mg / kg essential oil was significantly lower than the reserpine group (P <0.05). The duration of immobilization in the reserpine + fluoxetine group was significantly lower than that of the reserpine group (P <0.05) (Fig. 5).

3.5 Effect of *Apium graveolens* Essential Oil on Serum Antioxidant Capacity

Analysis of One Way Anova showed that serum antioxidant capacity decreased significantly in reserpine group compared to control group (P <0.001). Serum antioxidant capacity in the groups 50, 75 and 100 mg / kg essential oil and reserpine + fluoxetine was significantly increased compared to the reserpine group (P <0.001) (Fig. 6).
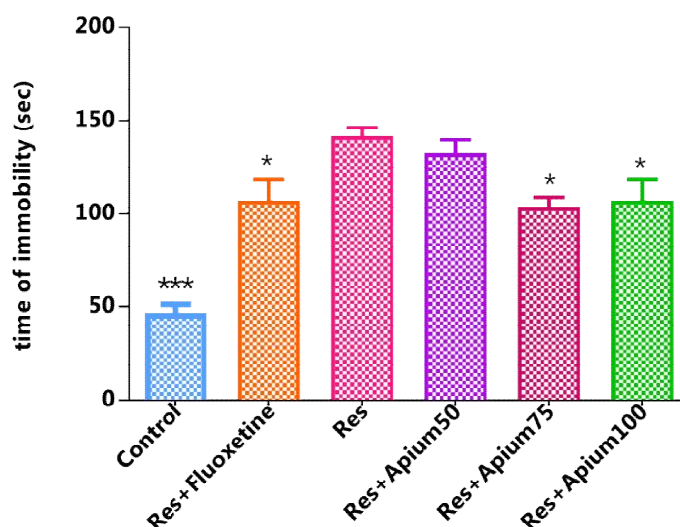
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Fig. 5. Duration of immobilization in the forced swimming test. Res = Reserpine, Apium =
Apium graveolens
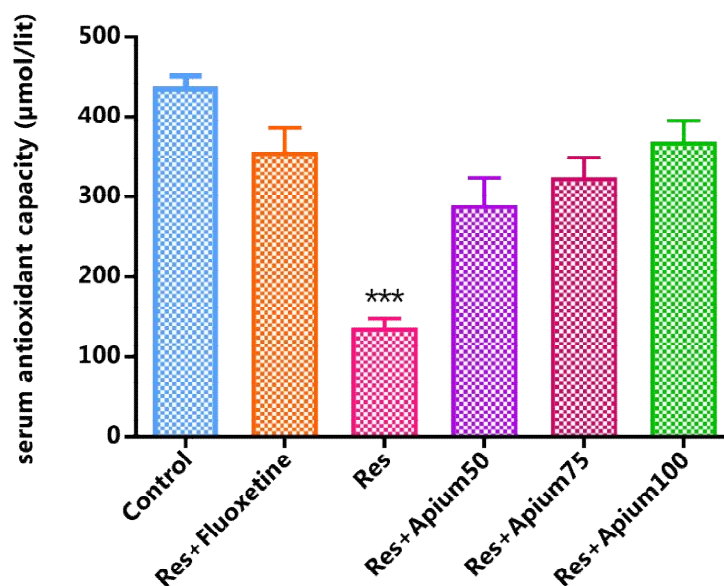*** comparison with all other groups p<0.001; * comparison with reserpine p<0.05*

Fig. 6. Serum antioxidant capacity Res = Reserpine, Apium = *Apium graveolens*
**** comparison all other groups p<0.001*

3.6 Effect of *Apium graveolens* Essential Oil on Serum Malondialdehyde

Analysis of One Way Anova showed that serum malondialdehyde increased significantly in the reserpine group compared with the control group (P <0.01). Serum malondialdehyde was significantly decreased in groups 75 and 100 mg / kg essential oil and reserpine + fluoxetine compared to the reserpine group (P <0.05) (Fig. 7).

3.7 The Effect of *Apium graveolens* Essential Oil on the Antioxidant Capacity of the Brain

Analysis of One Way Anova showed that the antioxidant capacity of the brain in the reserpine group, was significantly reduced compared with the control, 75 and 100 mg / kg essential oil and reserpine + fluoxetine groups(P <0.001, P <0.01, P <0.05) (Fig. 8).
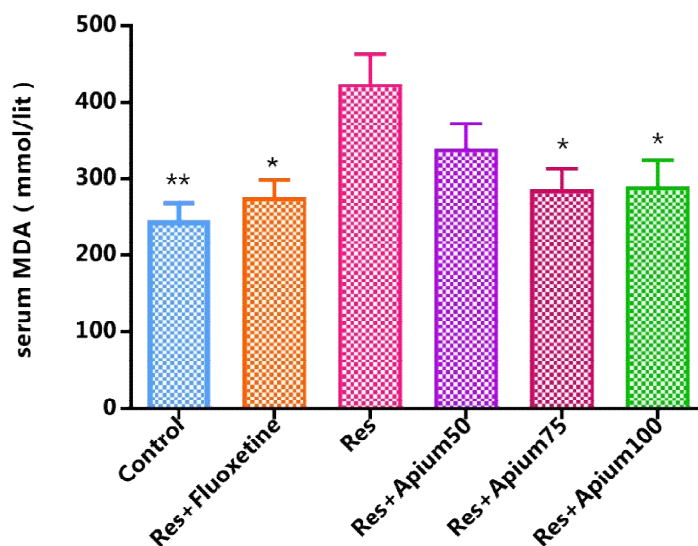
Fig. 7. Serum malondialdehyde Res = Reserpine, Apium = *Apium graveolens*
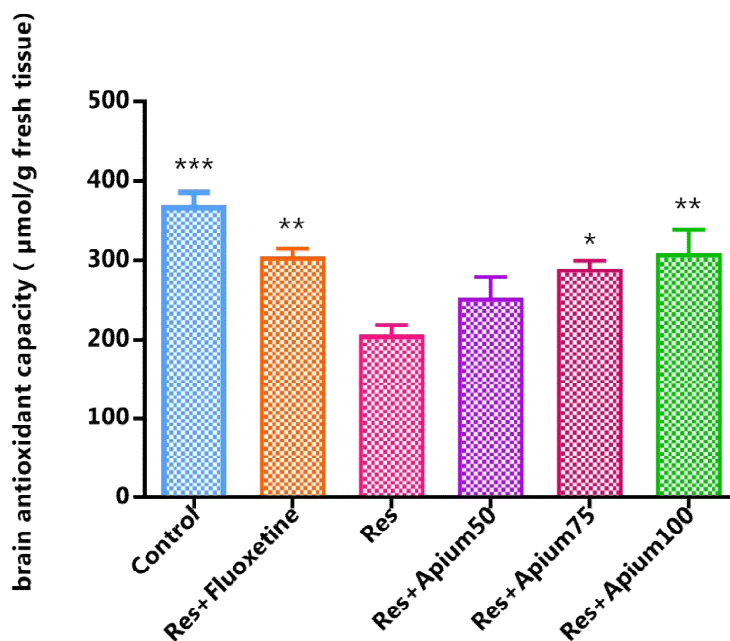*** and * comparison with reserpine p<0.01, p<0.05*

Fig. 8. Antioxidant capacity of the brain Res = Reserpine, Apium = *Apium graveolens*
**** , ** and * comparison with reserpine p<0.001, p<0.01, p<0.05*

3.8 Effect of *Apium graveolens* Essential Oil on the Level of Malondialdehyde in the Brain

Analysis of One Way Anova showed that the level of malondialdehyde in the brain in reserpine group, was significantly increased compared to the control and 100 mg / kg essential oil groups (P <0.001). The level of malondialdehyde in the 75 mg / kg essential oil and reserpine + fluoxetine groups was significantly lower than the reserpine group (P <0.01, P <0.05) (Fig. 9).
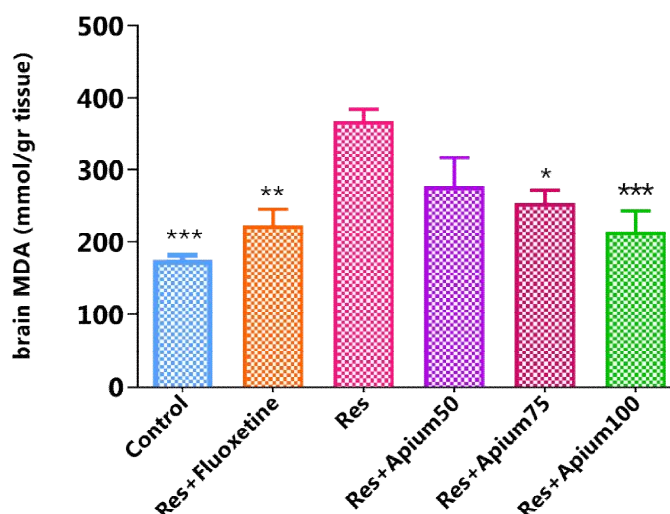
Fig. 9. Brain malondialdehyde Res = Reserpine, Apium = *Apium graveolens*
***, ** and *comarison with Res. p<0.001, p<0.01 and p<0.05

4. CONCLUSION

Oxidative stress has been hypothesized to play a role in the pathophysiology of depression and anxiety disorders and has previously been demonstrated to be increased in subjects with these disorders [16].

As oxidative stress is closely linked to the immuno-inflammatory system, the finding that oxidative stress markers are influenced by antidepressant use is in line with reports of the anti-inflammatory effects of antidepressant treatment, [17].

In the present study, reserpine injection induced depression behaviors and significantly increased the duration of immobilization in forced swimming test and decreased number of motor units in open field test compared to control group. Reserpine induces depression by depletion of monoamine transmitters [18-20]. Reducing levels of inflammatory factors and oxidative and nitrate parameters also contribute to depression by reserpine [21]. In the present study, intra peritoneal injection of fluoxetine reduced the duration of immobilization and increased the number of motor units compared to the reserpine group.

In a study by Lingling et al., administration of 20 mg / kg fluoxetine to mice reduced the duration of immobilization and increased motor activity. Fluoxetine significantly increased norepinephrine in the prefrontal cortex and serotonin in the mouse hippocampus, but did not change the level of dopamine in the mouse brain [22].

Fluoxetine reduced depression has been reported to significantly increase the activity of serum antioxidant enzymes and non-enzymatic antioxidants in the brain [23]. The main mechanism of its effect is the selective retention of Serotonin reuptake in synaptic space. However, in higher concentrations, Fluoxetine can also inhibit norepinephrine and dopamine reabsorption [24]. In forced swimming and open field test *Apium graveolens* (75 and 100 mg / kg) showed anti-depressant effect.

Oxidative stress is one of the mechanisms associated with depression [25]. Increasing the production of free radicals and lipid peroxidation leads to oxidative stress due to the disruption of the enzyme and non-enzymatic antioxidant system [26,27]. Studies have shown that anti-oxidant compounds reduce the symptoms of depression in affected individuals [28]. Therefore, the results indicate that antioxidants have a special place in the treatment of depression. Among the potential sources of antioxidants, plants can be mentioned.

Previous studies confirmed the role of plants as antioxidants in serum and brain levels in the treatment of depression [29].

Various studies have examined the effects of the major chemical compounds of essential oil of

Apium graveolens such as limonene, α-Terpinyl acetate, γ-Terpinene, Myristicin and (Z) - Ligustilide, as well as many non-essential compounds such as β-pinene, β-thujene, α-pinene, p-cymene, α-terpineol, linalol sabinene and β-Myrcene [30,31].

On the other hand, in this study, reserpine significantly reduced the serum and brain anti-oxidant capacity of rats. Also, fluoxetine and *Apium graveolens* significantly increased the antioxidant capacity of serum and brain of rats.

Malondialdehyde is one of the final products of peroxidation of unsaturated fatty acids in the cell. Increasing the production of free radicals increases the production of malondialdehyde as a marker of oxidative stress [32]. In this study reserpine significantly increased malondialdehyde in serum and brain of rats. Fluoxetine and *Apium graveolens* reduced it. Other studies also showed that people with depression have lower serum antioxidant capacity and have higher levels of malondialdehyde than healthy subjects [25].

The precise mechanisms through which antidepressants could exert anti-inflammatory and antioxidant action are not fully understood. There are a number of possible pathways through which antidepressants might reduce oxidative damage. Antidepressants may replenish and/or reactivate antioxidants levels, increased mRNA levels of antioxidant enzymes, such as superoxide dismutase, have been demonstrated after antidepressant treatment [17].

As the next mechanism of depression, people with depression have higher levels of inflammatory factors such as IL-6 and tumor necrosis factor alpha compared with healthy subjects. Studies have shown the anti-inflammatory effect of some of the chemical compounds found in essential oil of *Apium graveolens* such as limonene, γ-Terpinene, Myristicin and (Z) -Ligustilide that can reduce levels of inflammatory cytokines in the body [33-35] On the other hand, decreased monoamine function including serotonin, norepinephrine and dopamine cause depression [22,36]. Study on lemon oil showed that the main chemical compounds of lemon essential oil are limonene and γ-terpinene, which have a strong effect on the release of monoamines from brain tissue [37].

A relative weakness of present study is the absence of a group receiving only fluoxetine, therefore results only may be compared with the combination of fluoxetine and reserpine. In conclusion, reserpine produced despair-like actions and motoric alterations in mice. High concentrations of essential oil of "*Apium graveolens*" although did not produce a clear antidepressant action, effectively reduced the actions of reserpine in a similar manner than the antidepressant drug fluoxetine in both, behavioral and chemical indicators.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The ethical code is IR.SKUMS.REC.1395.319.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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