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Effects of Lavender Aqueous Extract on the Levels of Oxidative Stress Markers in the Sera and Tissues from Male Sprague–Dawley Rats with Chronic Mild Stress Induced Depression

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Abstract

Background & Objective: Oxidative stress is associated with the pathology of various neuropsychiatric disorders, such as depression and anxiety. The aim of the study was to examine the impacts of the lavender aqueous extract (LAE) on the levels of oxidative stress markers in an animal model with chronic mild stress induced depression.
Materials & Methods: 36 adult male Sprague–Dawley rats were haphazardly split into 6 groups (n=6). Rats in the test groups were put through five weeks of chronic mild stress. The sucrose preference test (SPT) confirmed depressive-like behaviors in the rats. Rats in both unstressed and stressed control groups received LAE (200 or 400 mg/kg) and distilled water respectively. The specific activities of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione peroxidase (Gpx), malondialdehyde (MDA) and as well as the total content of glutathione (GSH) were examined in the serum, liver and prefrontal cortex (PFC) using colorimetric assays.
Results: The stress group experienced a significantly decreased level of GSH, SOD, GR, Gpx and CAT, and a statistically considerable augment in MDA level in in the serum, PFC and liver $p<0.05$. LAE at both doses significantly reversed the depression-caused oxidative stress markers in all the studied tissues. No significant difference was observed between the two used dosages of LAE.
Conclusion: LAE is able to ameliorate depression-induced pathology possibly through anti-oxidant activity.

Keywords: Chronic mild stress, Antioxidant activity, Lavender, Aqueous extract, Oxidative stress

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Introduction

Low spirits and depression is the most common psychiatric disease worldwide which contributes to the impairment of global health (1). It has been shown that depression is going to be the second main public health concern by the year 2020 (2). It is described by a wide range of signs such as sadness, low mood, loss of interest and pleasure, and alterations in cognitive ability (3). Additionally, several neural changes including volumetric reductions in various parts of the brain and reductions in the neurons and glial density have been associated with depressive disorders (4). Although the exact biological process involved in the etiology of depression is not well understood, long-term exposure to stressful environment, circadian rhythm aberrations, and

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genetic and oxidative stress (OS) have been claimed to have influence (5-10). Exposure to persistent stress has been reported to change the neuronal role and morphology over the prefrontal cortex (PFC) which is a brain area involved in cognition. In chronic stress-exposed rats, the PFC neural atrophy and reduction in the number of dendrites resulted in changes in synaptic plasticity and, therefore, behavioral faulty (11, 12). Recent facts and proof have suggested the involvement of OS in these changes in the PF (13). Oxidative stress, as the result of attenuated antioxidant enzymatic defense such as CAT, SOD, GSH, Gpx, GR and reactive oxygen species (ROS) overproduction, can damage the neurons and glial cells through lipid peroxidation, DNA modification, and protein degradation (14, 15). An investigation by Kodydková et al. demonstrated that the amount of glutathione peroxidase in the group of patients with depression is sharply reduced (16). Similarly, Maes et al. provided another proof to this finding (17). Interestingly, it has shown that there is a reverse relationship between the intensity of depression and the level of Gpx (18, 19). The brain, due to its high metabolism, is one of the most at risk organs to the destructive effects of free radicals and ROS which describes the association and role of ROS in neurological impairments (20, 21). Besides, several studies showed the increased activity of monoamine oxidase (MAO) in depressed patients as a result of excessive ROS production (22, 23). It can also trigger lipid peroxidation and alter the penetrability of the membrane, change the viscosity of the cells, and afterwards affect the discharge of nerve neurotransmitters such as serotonin (24). Regarding the role of OS in the pathogenesis of depressive impairments and the poor clinical efficacy of the available antidepressant medications, anti-oxidant compounds could be possible therapeutic agents. To prevent OS, therapeutic strategies have concentrated on using natural products as available, easy-to-use antioxidant components with fewer side effects (25, 26). Lavender (*Lavandula angustifolia Mill.*) is widely used in traditional medicine and it has been reported that this medicinal plant possesses several health benefits such as antidepressant (27), antioxidant (28), anti-inflammatory (29) and neuroprotective effects (27). Linalool and linalyl acetate, as major antioxidant ingredients of lavender essential oil, has been demonstrated to have anxiolytic and antidepressant activities (30). Although extensive research has been carried out on health benefits of lavender, there are few studies that have investigated the effect of LAE on oxidative stress markers and antioxidant enzymes in the chronic stress condition. Therefore, this study aimed to detect the effect of two doses of LAE on antioxidant enzymes including CAT, Gpx, GR and SOD as well as non-enzymatic markers including MDA and GSH in the serum, liver and prefrontal cortex tissues of the CMS-induced depression model in male rats.

Materials and Methods

Animals

In this study, 36 male Sprague Dawley rats (3–4 months, 280− 300 g) were used. All testing protocols were approved by the Medical and Research Ethics Committee of the Shiraz University of Medical Sciences (IR.SUMS.REC.1397.861). Based on sucrose preference consumption from the 3 tests the animals were randomly divided into two groups. The unstressed group and the chronic mild stressed group. Then, each group was subdivided into three groups (6 rats in each group), including the unstressed rats which were orally treated with distilled water and or LAE at a dose of 200 and or 400 mg/kg (based on our previous studies) (31). The non-stressed animals were held in a cage and under the conditions of a 12-h light/dark cycle (lights on at 7:00 a.m.) with free access to food and water. The chronic mild stress (CMS) method was performed as described previously (31). Paired housing, wet cage, water and food scarcity,

cage tilt, continues lighting and strobe light were used to form CMS model. Stressed animals were kept one in each cage with food and water available ad libitum except for when the CMS procedure required deprivation (for stressed rats) and during the stress procedure, CMS rats were housed separately in different rooms. To minimize nonspecific stress responses during the experiment, before beginning the experiment, the animals were allowed to adapt to the laboratory environment for one week. During the 5 weeks of treatment, water or a respective dose of LAE (200 and 400 mg/kg) was orally given to animals' every day 1 h before exposure to CMS procedure.

Preparation and Administration of aqueous extracts (LAE)

Dried flowers of Lavandula angustifolia Mill were obtained from a herbarium store. The taxonomic identity of the plant was verified by herbarium of the faculty of Pharmacy of Shiraz university of Medical Sciences, Shiraz, Iran. Lavender aqueous extracts were prepared as previously explained (31). Animals in stressed and unstressed groups were given LAE by gavage at a volume of 1.0 mL and by appropriate dosage.

Tissue preparation

At the end of 5th week, for biochemical analysis, the rats were immolated by beheading. The blood samples were obtained directly from the heart and collected into heparinized tubes. The liver and prefrontal cortex samples were quickly removed and then, the samples were washed completely in physiological saline to remove the blood. Tissues were separately homogenized in 10 volumes of 50 mM phosphate buffer (pH 7.4) using a Polytron homogenizer (Brinkmann Instruments, Westburry, NewYork) at 4°C twice each for 15 sec. To remove cell debris and unbroken cells, homogenate was centrifuged at 10,000 rpm for 20 min. The supernatant was used for various measurements.

Glutathione peroxidase (Gpx) activity measurement

The activity of Gpx was assayed using, the procedures of Fecondo and Augustey with minor changes (32). The Gpx activity of samples was checked by continual checking of the production of the reduced glutathione (GSH) from glutathione disulfide (GS-SG) by glutathion reductase in the presence of NADPH. Briefly, T-BUOOH was used as substrate in the presence of 0.1mM GSH, EDTA (3mM), NADPH (0.15mM), GR (2U/mL) and phosphate buffer (50mM, pH=7.2). Sample volume was 25 ul in total volume of 0. 5mL.The absorbance of the reaction products was observed after 3 min at 340 nm. We used disodium salt of NADPH for the measurement of Gpx activity with the oxidation of NADPH which is directly equal to the Gpx activity in samples, which were monitored at 340nm. The enzyme activity in tissue samples was expressed as μm of NADPH oxidized/min/mg cell protein. Molar extinction coefficient for NADPH was 6.22×10^{6} $M^{-1}cm^{-1}$.

Glutathione reductase (GR) activity measurement

GR activity was measured spectrophotometrically according to the method of Racker with minor modifications (33). Briefly the activity of GR was assayed in a cuvette that contained 270ul incubation buffer (60uM), 40ul BSA (10uM), 100ul GSSG (0.033M), 100ul NADPH (2mM) as substrate and 150ul sample in a total volume of 660ul. Reduction of glutathione disulfide (GSSG) by glutathione reductase in the sample, which reflects oxidation of NADPH, was checked by spectrophotometry at 340 nm for 3 min. One unit of GR was defined as mU/mg cell protein.

Determination of GSH

The glutathione (GSH) level was determined spectrophotometrically using Ellman's method with minor modifications (34). Which this method involves oxidation of glutathione by reagent of 5,5'-dithio-bis 2-nitrobenzoic acid or DTNB to produce yellow derivative of 5′-thio-2

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-nitrobenzoic acid (TNB) which can measure spectrophotometrically at 412 nm. To 0.2 mL of cell lysate supernatant potassium phosphate buffer (0.2 M, pH 7.6) was added, and then reagent of DTNB, 0.001 M was added to the solution. After 5 minutes absorbance of the yellow solution of TNB, was measured at 412 nm (35, 36).

Catalase activity (CAT) measurement

CAT activity levels were assessed according to the method of Aebi (37) using an ultraviolet spectrophotometer (UV- 160A, Shimadzu, Japan). The dissociation rate of the substrate, hydrogen peroxide was measured at 240 nm. Molar extinction coefficient of 36 $M^{-1}cm^{-1}$for H_2O_2 at 240 nm was used to calculate the activity. One unit of enzyme is equal to 1 µm of H_2O_2 dissociation /min.

Determination of MDA

The MDA level was determined by the method of Placer (38). Briefly, the samples were precipitated with a mixture of TCA and thiobarbituric acid (TBA) and the mix was heated for 60 min. Then the absorbance of cooled mixture was determined at 535 nm using spectrophotometer model of UV- 160A, Shimadzu, Japan. The results are expressed as units of enzyme activities per mg of protein. The concentration of protein was measured using the protein assay kit (Beyotime, Shanghai, China).

Superoxide dismutase (SOD) activity

The level of SOD in the studied tissues was measured using commercially available ELISA kit (Abcam, USA), according to the manufacturer's protocols. Briefly, in this kit superoxide anions are produced by the action of xanthin oxidase, which reacts with iodonitrotetrazolium chloride quantitatively to form a red formazan dye. SOD inhibits the reaction by converting the superoxide anion into hydrogen peroxide and O_2. The greater the activity of SOD in the sample, the less formazan dye is produced. Absorbance was measured at 450 nm using a ultraviolet spectrophotometer (UV- 160A, Shimadzu, Japan) for 30s after the addition of xanthine oxidase as start reagent and 3 minute after reaction as duplicates samples. The SOD activity was expressed as U/mL reagent. One unit is the amount of SOD that inhibits the rate of formazan dye formation by 50%. Data were normalized by detection of the protein concentration of the samples, using the protein assay kit (Beyotime, Shanghai,China).

Statistical Analysis

All data are shown as mean ± SEM. For statistical analysis SPSS statistical software (SPSS version 16 Inc, USA) was used. At first normal distribution of data was verified by the Shapiro-Wilk test and then differences between groups were assessed by one way ANOVA followed by Tukey's post hoc test. Differences were considered significant at $p<0.05$.

Results

Effect of LAE on biochemistry markers in the serum, liver and brain

The chronic administration of two doses of LAE (200 and 400 mg/kg) in CMS rats resulted in a significant reduction in sucrose intake as compared to the STC group (data not shown).

To determine whether LAE treatments influence the stress-induced oxidative parameters, we examined the amounts of MDA, GSH. CAT, Gpx and SOD in the serum, liver and prefrontal cortex tissues. Data displayed in Table 1.

Table 1. The effects of chronic treatment of two different doses of LAE on the level of GSH, SOD, GPX, GR, catalase and MDA in different tissues of rat model of depression

Tissue	Experimental group	GSH	Catalase	GR	GPX	SOD	MDA
Liver							
	Control	358.68±6.06	32.43±0.99	25.34±1.35	2.92±0.05	307.32±2.73	59.3± 5.23
	Cola 200mg/kg	307.20±7.84	40.14±0.86	35.36±0.71	3.80±0.06	323.57±8.63	51.35± 2.42
	Cola 400mg/kg	247.99±7.53	49.76±1.21	44.76±1.40	4.47±0.21	360.93±5.80	40.77± 4.92
	STC	449.51±5.26	15.86±2.25	16.99±1.07	1.40±0.22	251.78±6.36	68.40±5.25
	STC + Cola200mg/kg	360.99±22.25	31.28±1.41	23.72±1.32	2.94±0.14	297.33±5.32	57.95±1.22
	STC + Cola400mg/kg	325.45±13.70	39.13±1.63	28.69±2.02	3.48±0.05	322.11±6.41	53.90±2.57
Brain							
	Control	442.38±16.18	56.16±1.70	26.43±0.21	8.06±0.54	397.80±3.21	50.83±3.35
	Cola 200mg/kg	387.96±13.19	71.09±2.08	28.14±0.083	11.78±0.84	423.59±1.24	44.71±2.11
	Cola 400mg/kg	312.04±10.34	81.77±4.03	30.86± 0.44	13.84±1.47	464.44±6.59	35.38±2.33
	STC	555.17±20.60	34.59±2.78	20.45±0.26	4.45±1.07	307.84±3.95	64.59±4.87
	STC+ Cola200mg/kg	485.91±8.06	53.57±3.17	24.88±0.18	7.99±1.11	374.20±2.78	56.15±2.34
	STC+ Cola400mg/kg	413.47±19.71	63.52±2.53	26.96±0.29	10.41 ±1.75	405.70±4.46	45.03±2.77
Serum							

	Control	382.60±11.91	6.41±0.11	5.55±0.172	0.462±0.018	109.88±3.41	20.36±1.07
	Cola 200mg/kg	290.37±10.94	7.08±0.11	6.29±0.052	0.649±0.026	124.72±1.021	17.77±0.57
	Cola 400mg/kg	273.0±21.54	8.40±0.125	7.26± 0.204	0.817±0.011	144.17±3.97	12.26±0.98
	STC	512.59±22.27	5.27±0.126	4.13±0.272	0.269±0.017	81.83±5.39	38.98±0.98
	STC+ Cola200mg/kg	355.65±21.20	6.13±0.063	5.21±0.108	0.482±0.012	103.17±2.165	23.51±0.59
	STC+ Cola400mg/kg	337.88±26.53	6.79±0.14	5.56±0.082	0.590±0.0187	110.13±1.61	19.21±0.59

The changes in MDA levels, as a lipid peroxidation marker, in the considered groups are presented in Chart1. The outcomes revealed a statistically significant reduction in the MDA level in non-stress lavender-treated animals, compared to the normal group ($p<0.05$), in the serum, liver and prefrontal cortex. The MDA level of the stress group in all tissues was notably higher than the other groups ($p<0.001$). Interestingly, treatments with lavender (200 and 400 mg/kg) attenuated the elevated levels of MDA in comparison with the STC group, $p<0.05$. Additionally, there was a statistically significant decrease in the MDA level in the ST+LA400 ($p<0.05$) compared to the ST+ LA200 group (Chart 1).

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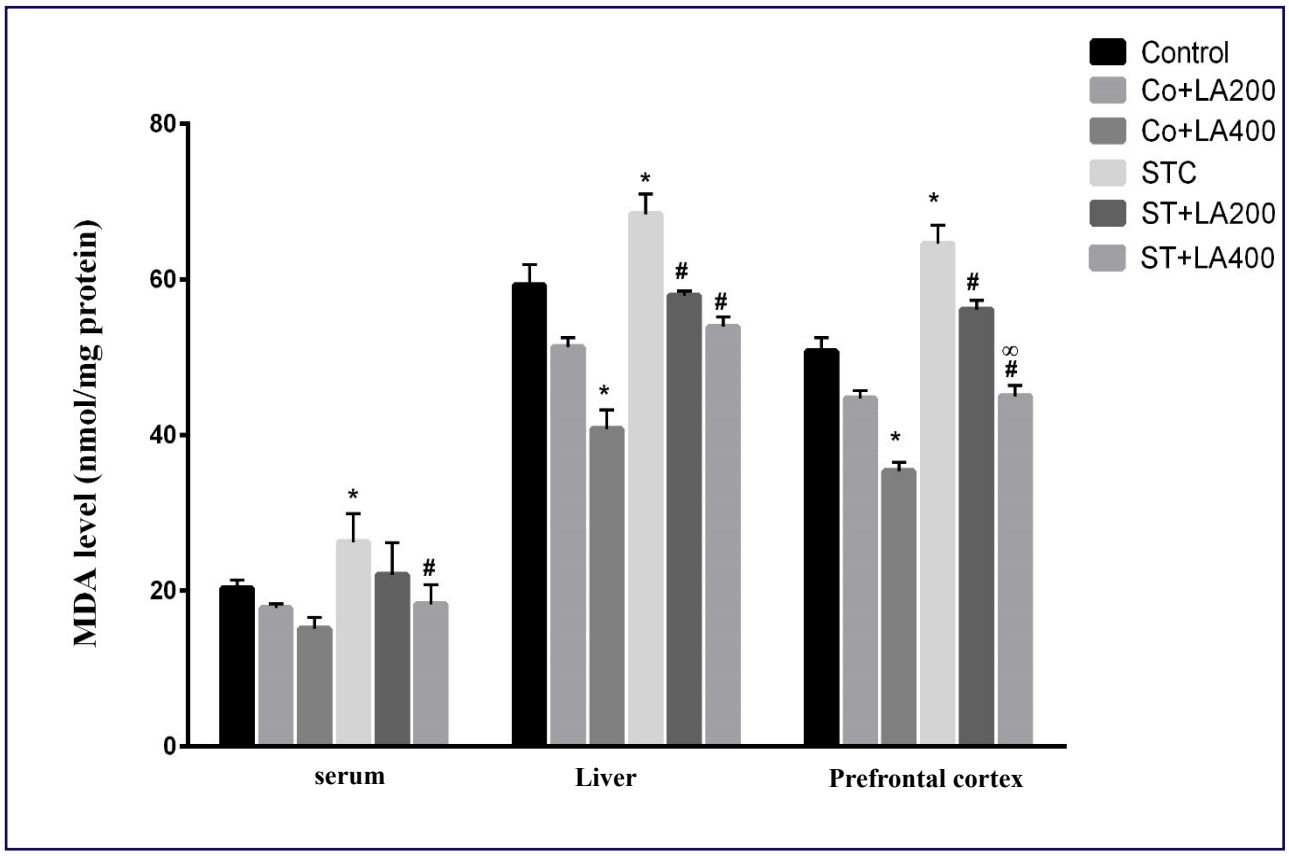

Chart 1. The effect of chronic treatment of 2 doses of lavender aqueous extract (LAE) on the MDA level in the serum, liver and prefrontal cortex in CMS model of rats. The rats were administered with 200 or 400mg/kg/day of LAE for 5 weeks and were sacrificed 24 h after the last gavage. Results are showed as the means ± SEM and $p<0.05$ is regarded as significant (one-way analysis of variance (ANOVA), pursued by Tuky's post hoc test). The asterisk (*) indicates the significant differences vs. control animals, and the hash (#) displays the significant differences vs stressed control (STC) group, n=6

One-way analysis of variance (ANOVA) results showed that the GSH level of the stress group in all the three tissues was significantly lower than the other groups ($p<0.05$ for the prefrontal cortex; $p<0.03$ for the liver; and $p<0.05$ for the serum). The GSH levels in the ST+LA200 and 400 groups in the liver, serum, and prefrontal cortex were significantly higher than those of the stress group ($p<0.001$). There was a significant increase in GSH level of ST+LA200 and 400 in the serum compared to the non-stress group ($p<0.05$). Our results also revealed no significant contrast between the GSH level in the ST+LA200 and 400 groups (Chart 2).

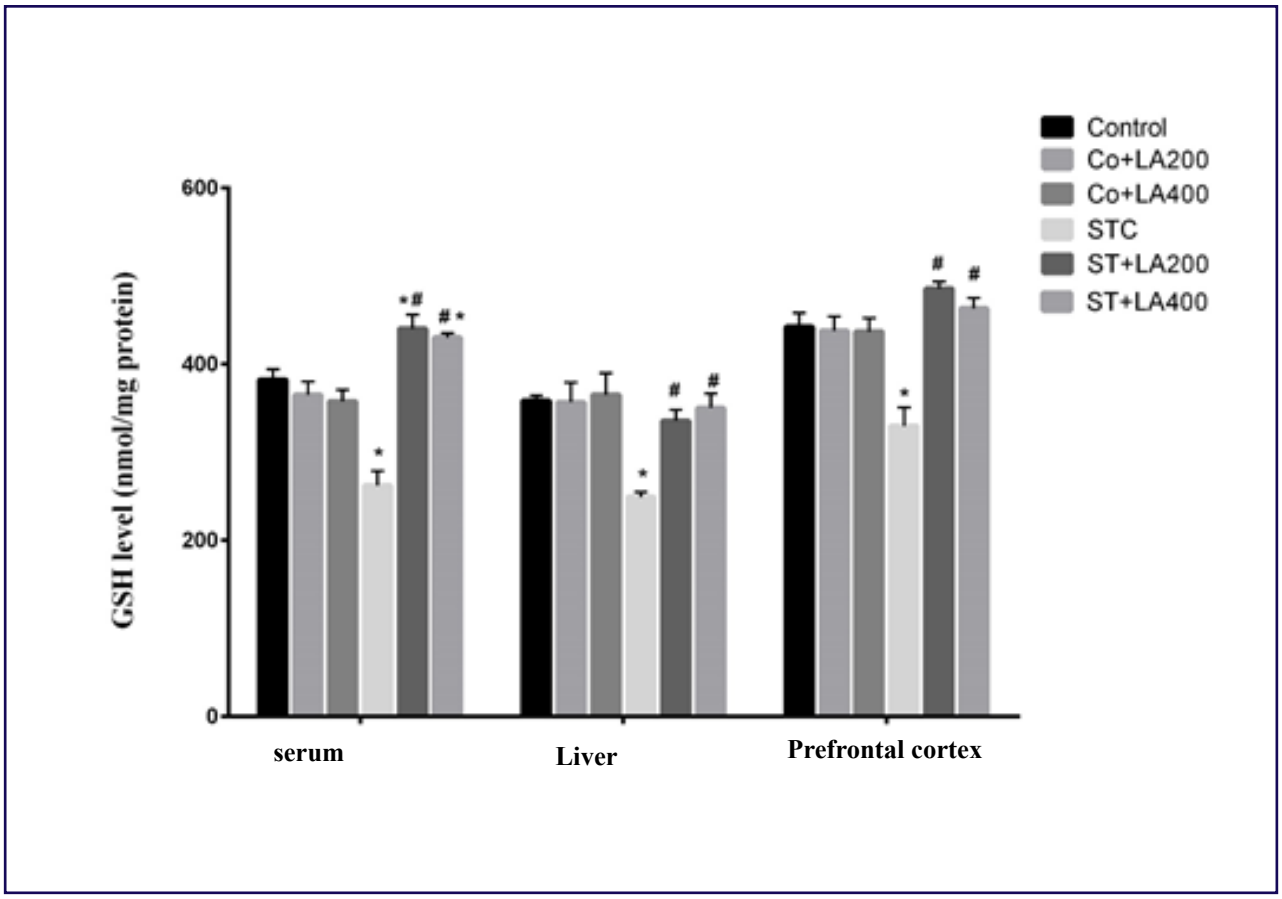

Chart 2. The effect of lavender aqueous extract on the reduced glutathione (GSH) level in the serum, liver and prefrontal cortex in a chronic mild stress model of rats. Results are showed as the means ± SEM and they were statistically examined by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test and $p<0.05$ is considered as significant. The asterisk (*) shows the remarkable differences vs. the control animals, and hash (#) indicates the meaningful differences vs. the STC group, n = 6

Chart 3 A-D illustrates the levels of enzymatic antioxidants, namely SOD, CAT, GR and Gpx in the prefrontal cortex, serum, and liver of the studied groups. Our study indicated that the antioxidant enzymes activity significantly increased in the non-stress lavender administered rats compared to the control group ($p<0.05$), in all of the three tissues. The stress group showed the lowest level of enzymes activity. Based on the results, lavender in both 200 and 400mg/kg concentrations was able to attenuate the stress induced antioxidant enzymes activity ($p<0.05$). In addition, the SOD and Gpx and GR activities in the ST+LA400 group in the prefrontal cortex were significantly higher than those of the ST+LA200 group ($p<0.01$). A significant difference was also detected in the Gpx and CAT activity in the ST-LA400 and ST-LA200 groups in the serum ($p<0.05$) and liver ($p<0.03$), respectively.

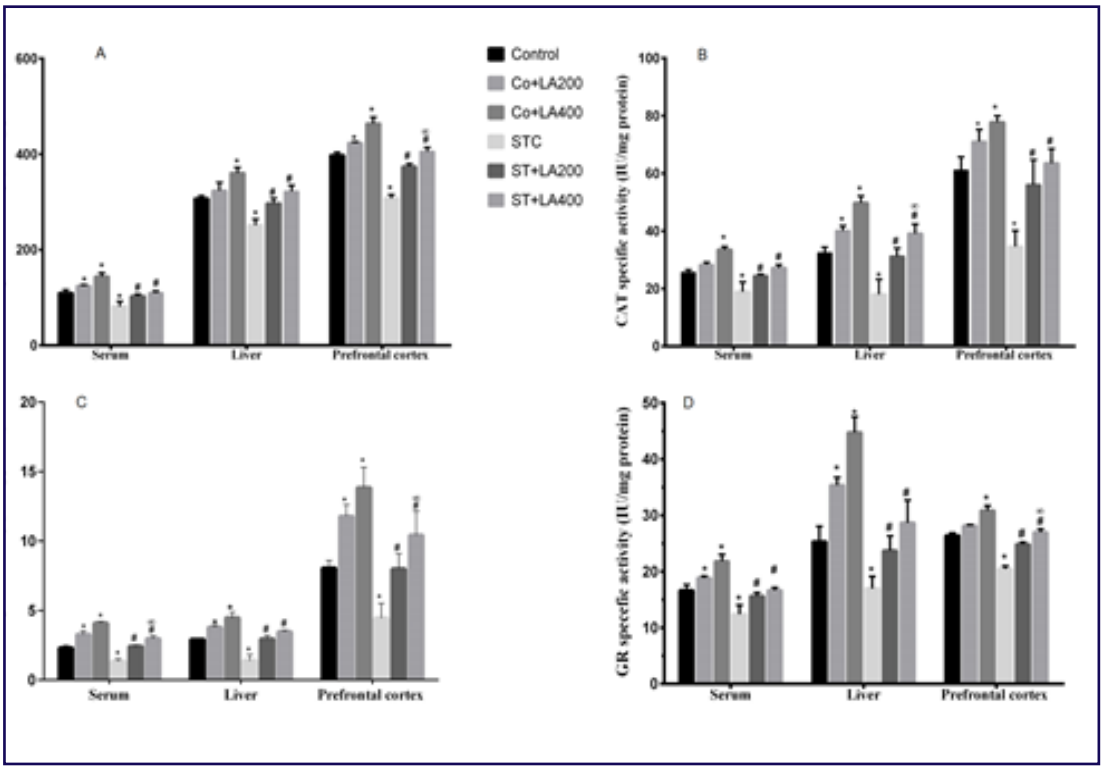

Chart3. A-D. The effect of treatment with two different doses of LAE on A, Ssuper oxida dismutase or SOD (IU/mg protein); B, Catalase or CAT (IU/mg protein); C, Glutathion peroxidase or Gpx (IU/mg protein) and D, Glutathione reductase or GR (IU/mg protein) activities in a rat model of depression. and they were statistically examined by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test and $p<0.05$ is considered as significant. The asterisk (*) shows the remarkable differences vs. the control animals, and hash (#) indicates the meaningful differences vs. the STC group, n = 6. Measurement time for SOD, Gpx and GR was 3 min, while for catalase absobancewas measured immediately after the addition of H_2O_2

Discussion

As a widely accepted theory, depression is associated with the cellular antioxidant system's deficit as well as massive production of destructive free radicals. Hence, we assumed that antioxidant property of lavender could be an effective therapeutic target to overcome stress-induced oxidative stress. Our findings indicated that chronic treatment of aqueous extract of lavender at 200 mg/kg and 400 mg/kg doses attenuated the elevated oxidative marker of MDA, and promoted antioxidant capacity through induced superoxide dismutase, glutathione reductase, glutathione peroxidase, glutathione and catalase in the serum, liver and prefrontal cortex in the rat model of chronic mild stress. Depressive disorders are known as consequential health problems with high public health burden and costs (39). So far, several medications have been introduced to be used in the treatment of depression including serotonin–noradrenergic reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake (SSRIs) (40). However, all of the available medications are far from satisfaction due to numerous side effects such as sleep disorders, intolerance to side effects, and risk of liver damage, sedation and agitation as well as poor efficacy (41, 42). Therefore, finding new, well-tolerated and more efficient antidepressants is a crucial demand. Based on the the animal model of depression was successfully produced using the chronic mild stress method which is known as a confirmed method for this purpose. "oxidative stress theory of depression", the pathological changes could occur by either overproduction of ROS or decreased antioxidant defense systems (43). A growing body of

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literature obtained from clinical and reports in the cell and animal models have provided substantial evidence indicating disturbed oxidative homeostasis lead to the pathology of stress-caused depression (43, 44). Accordingly, accumulated free radicals can lead to several damaging processes, such as neuronal damage, through lipid peroxidation of the cell membrane and DNA strand-brakes (45). Furthermore, it is reported that free radicals are able to modulate the the main neurotransmitters level involved in the neurochemistry of depression such as norepinephrine, dopamine and glutamate (46, 47). Taking all together, antioxidant compounds could be theoretically considered as new potential targets for the advancement of antidepressant therapeutics. In the present study, the animal model of depression was successfully produced using the chronic mild stress method which is known as a confirmed method for this purpose. Based on the observations, chronic mild stress caused an anxiogenic effect and depression-like behaviors in the EPM and OFT box, as well as an obvious lack of sense of pleasure tested by sucrose preferences test (Data not shown). We regarded the low level of sucrose expenditure in the stressed rats a marker of lack of sense of pleasure or anhedonia, which is known as an important sign of depression (48). Lavender is a well-known herbal plant that is widely used for its health advantages such as immunomodulatory and anti-inflammatory (29), antioxidant (28) and antidepressant properties (49). Lavender essential oil is officially confirmed by the European Medicines Agency (EMA) to be used as a temper in stress and anxiety. Although the beneficiary effects of lavender oil have been extensively studied in various models of depressive impairments, there are less data, to the best of our knowing, on molecular mechanisms the lavender aqueous extract effects. In the current study two different dosages (200 and 400 mg/kg) of LAE were used. These doses were based on our pilot examinations as well as previous studies (31, 50). Here, we revealed that chronic treatment of aqueous extract of lavender at 200 mg/kg and 400 mg/kg significantly prevented the rise in the MDA level and up-regulation of SOD, CAT, GR and Gpx activities and GSH level in the prefrontal cortex tissue. This is in agreement with the reports indicating that the lavender oil has antioxidant and anti-inflammatory effects (51). High oxygen consumption, modest antioxidant defense and lipid-rich formation have made the brain an organ vulnerable to oxidative stress (OS) (52). OS can lead to induced behavioral and cognitive decline as well as neural death and structural changes in the brain. For example, it has been shown that several pivotal sections of the brain such as hippocampus and amygdala, prefrontal cortex are the most sensitive structures of the brain in stress-induced OS undergoing neural loss and structural decline (52, 53). The prefrontal cortex alterations, such as dendritic shrinking, are strictly associated with depression symptoms since it is a region that is exactly implicated in cognition and emotion (54). Lavender essential oil is able to reverse depression behavior induced by corticosterone treatment (27) Furthermore, it is shown that in stress condition, lavender induces neural plasticity, dendritic branching and reverses the decreased number of the neurons in the hippocampus of the rats under stress (27). Our results are also in line with those of Wang et al, (54) about MDA, SOD, CAT and GSH levels in the brain tissue of lavender oil treated mice model of cerebral ischemia/ reperfusion injury. Therefore, the current study could be regarded as evidence which lavender has potential effect on the affected brain by depression-induced oxidative stress. Furthermore, our study provided evidence indicating that CMS model leads to a notable decline in SOD, CAT, GR and Gpx activities, reduced level of non-enzymatic antioxidant of the GSH level and elevated MDA level in the serum and liver tissue. These observations are consistent with several clinical studies that had shown serious liver

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damage due to long duration stressors, which are supposed to be caused by OS (43, 55). Furthermore, there is evidence indicating disturbed antioxidant system and lipid peroxidation markers in the serum, plasma, or urine of depressed patients (43). We demonstrated that administration of lavender aqueous extract (200 and 400 mg/kg) considerably raised these antioxidant enzyme activities and reduced the MDA level when compared with the control group. Although our knowledge about the effect of antidepressant compounds on antioxidant system function in the liver in animal depression models is limited, our study and a recently published report (55) could be regarded as promising results. So far, most of this type of studies have focused on the elevation of oxidative markers and oxidant system deficit on brain structures in depressive condition. However, there are some reports indicating enhanced protein and lipid peroxidation level in the brain and liver of the stressed animals, which is possibly associated with similar oxidative stress in the prefrontal cortex (35, 56, 57). The potential role of OS has been recently highlighted in the pathogenesis of depressive diseases. Then, it would be plausible to consider antioxidant compounds to be used as potential therapeutics against depressive-like symptoms. In the current study, we showed the antioxidant action of lavender aqueous extract on the liver, serum and prefrontal cortex against stress induced-oxidative status. Due to the lack of information about the composition of LAE a parallel study in our laboratory was performed and the chemical composition of LAE was determined by GC-MS technique. Our results showed that (unpublished) LAE contained seven bioactive compounds belonging to the terpens. Among them, the major ingredients were camphor (67%) linalool (16.46%). Linalool and camphor has been shown to have many biological activities, such as antidepressant, anti-inflammatory, analgesic, neurpprotective and antioxidant effects (58, 59). Published data suggest linalool attenuates oxidative stress and mitochondrial dysfunction mediated by glutamate toxicity (60). The underlying mechanism by which linalool exerts its effectiveness is via a protective impact on the mitochondrial integrity as well as ability to limit oxidative stress. Linalool reduces ROS, calcium production and lipid peroxidation levels. It also improved mitochondrial morphology, membrane potential and respiration (61). Our findings indicate that LAE protects rats from oxidative stress induced depression due the existence of these compounds and suggest LAE as a potential therapeutic agent for the management oxidative stress mediated depression.

This study suggests that the upsurge of the antioxidant defense and reduction of lipid peroxidation could be associated with the involvement of lavender aqueous extract in its antidepressant action versus stress-induced oxidative stress. The clinical value of this observation remains to be proved since there are several unrevealed aspects of molecular mechanisms of lavender effects.

Conclusion

Lavender aqueous extract applied protective effects against chronic stress-induced depression and anxiety. This can be due to the decrease in oxidative stress and increase in tricyclic antidepressant in both brains and sera of the chronic mild stress rats. Treatment of healthy rats with LAE had no adverse effects.

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Conflicts of Interest

The authors declare that there are no conflicts of interest in this work.

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Ethical Considerations

The authors of the article declared that all of animal research conducted is in accordance with in ethical considerations.

Code of Ethics

Code of this article is IR.SUMS.REC.1397.861.

Author's Contributions

Mir Behrad Aghazadeh Ghadim and Asma Neisy performed the experiments. Zahra Khoshdel proposed and designed the study. Zahra Khoshdel and Amir Mahmoodzadeh developed the data and wrote the manuscript.

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