Research Paper

Antidepressant Effect of Hydroalcoholic Extract of Quercus Brantii and Oil of Quercus Brantii on a Rat Model of Postpartum Depression

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ABSTRACT

Background and Objectives One of the most common complications after childbirth is postpartum depression (PPD), a major depressive disorder. The aim of this study was to investigate the effects of the hydroalcoholic extract and oil of Quercus brantii as an experimental model of PPD in rats.

Subjects and Methods 42 adult female Wistar rats in six groups were used in this study. All animals received daily progesterone injections at a dose of 5 mg/kg intraperitoneally for 5 consecutive days. A hydroalcoholic extract of Quercus brantii (100mg/kg) and oil (45%) were administered simultaneously with PPD modeling by progesterone withdrawal. On day 8, depressive behavior was then assessed by a forced swim test. To investigate the role of the oxidant-antioxidant system, reduced glutathione (GSH), catalase, superoxide dismutase (SOD) and malondialdehyde (MDA) have been assessed after the last injection.

Results Statistical analysis showed that progesterone induced significant immobilization in the control group receiving saline (P<0.001) and in the vehicle group receiving sesame oil (P<0.001). The administration of hydroalcoholic oak extract (100 mg/kg) shortened the immobility time compared to the control group (P<0.05). The results of this study show that depression has no effect on locomotor activity. The hydroalcoholic extract of Quercus brantii (100mg/kg) significantly improved depression, decreased MDA and increased SOD. On the other hand, Quercus brantii oil (45%) has no significant effect on depression, but lowers MDA and increases catalase.

Conclusion Q. brantii appears to be a natural source of antidepressant compounds that increase antioxidant levels, which is currently being investigated by our group.

Keywords Antioxidant, Oxidative stress, Postpartum depression, *Q. brantii*

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Introduction

Postpartum depression (PPD), described in the "*Diagnostic and Statistical Manual of Mental Disorders IV*" (DSM-IV) as a specific major depressive disorder (MDD) that occurs immediately after childbirth, has raised a major public health concern [1]. PPD, like major depression, is a disabling disorder. Crying spells, sleep and eating disorders, depressed mood, fatigue, anxiety, poor concentration and suicidal thoughts are common symptoms. PPD has been linked to antenatal depressive symptoms, young maternal age, major life events or stressors during pregnancy, history of depression, hormonal changes, low social support and smoking [2,3]. At the molecular level, PPD is characterized by abnormalities in the metabolism of neurotransmitters such as serotonin and dopamine, mitochondrial dysfunction, an imbalance of the hypothalamic-pituitary-adrenal (HPA) axis imbalance,the production of reactive oxygen species (ROS) and *malon*dialdehyde (MDA), and finally depletion of antioxidant defenses such as superoxide dismutase (SOD) and catalase [4]. ROS (superoxide anion, hydrogen peroxide, hydroxyl radical, peroxyl radical) and reactive nitrogen species (*RNS*) (nitric oxide (NO), peroxynitrite, nitroxyl anion) can cause oxidative damage to cells and organs. ROS are chemically reactive molecules that are formed as a by-product of normal cell metabolism [5]. ROS have been shown to be involved in the development of various neuropsychiatric disorders, including depression and its associated diseases, such as Alzheimer's), schizophrenia, Parkinson's, and anxiety [6]. Because it is a large consumer of oxygen and rich in oxidizable lipids, the brain is more sensitive to free radical damage than any other organ in the body, and inadequate defenses against excessive ROS can lead to neuronal dysfunction and death [7]. According to data from several studies, ROS associated with a neuroinflammatory sign promote deregulation of brain functions and abnormalities in neuronal signaling pathways and have emerged as a major cause of depressive disorders, including PPD [8]. In people with severe depression, oxidative stress leads to cell damage by reducing the volume of the hippocampus and affecting the prefrontal cortex [9, 10]. Progesterone injections are one of the methods that can be used to simulate PPD in animals and have been shown to be successful in several studies [11, 12, 13].

The drugs of first choice for PPD are selective serotonin reuptake inhibitors (SSRIs) [14]. Despite the positive effect of SSRIs on PPD and depressive symptoms, the remission rate remains low and the risk of relapse and recurrence is still considerable. The side effects of antidepressant medications are also a major concern [15]. Although, synthetic medications are widely used to treat a variety of psychiatric disorders, current therapies have limited success and a third of depressed people do not respond adequately to currently available medications or cannot tolerate pharmacological approaches [16, 17]. There is therefore a medical need for effective and less expensive alternatives to the antidepressant drugs currently available. As a result, research into herbal antidepressants , which contain a variety of pharmacologically active substances, is playing an important role in health programs around the world [18]. Research into medicinal plants, particularly with regard to psychiatric disorders, has made enormous progress over the last decade and their therapeutic potential has been investigated in a number of animal models. According to a study of depressed patients, the use of herbal medicines was more effective than conventional therapy in more than 57 percent of patients with severe depression [19,20]. Iranian medicinal herbs and derivatives have been shown to be a useful source of therapeutic agents for a variety of conditions, including psychiatric disorders such as PPD [19,21].

Quercus is a traditional herbal remedy suitable for dry and cold regions and is found in the mixed pine-oak forests of the Zagros Mountains, which cover more than half of the western forests of Iran. In general, the oak belongs to the *Fagaceae* family, specifically the Quercus genus, which includes 500 species. For almost 1000 years, this tree and its fruits, known as acorns, have been used in Europe, Asia, North Africa, the Middle East and North America. The secondary metabolites found in the fruits of *Q. brantii* include tannins, gallic acid and ellagic acid, vitamins C,

A and B, various galloyl and hexahydroxydiphenoyl derivatives, linoleic and linolenic acids, polymeric proanthocyanidins, proteins and minerals, as well as fatty acids. One of the most important biological properties of these natural chemicals is their antioxidant capacity [22]. *Q. brantii* extract has been shown to have significant hepatoprotective, anti-tumour, and anti- ageing potential, which could be due to the antioxidant capacity of its components and the influence on the expression of cytochrome P450 2E1 (*CYP2E1*) [23]. To our knowledge, there are no documented reports on the effects of the hydroalcoholic extract and oil of *Q. brantii* on PPD. Also, based on the above evidence for the relationship between oxidative stress and PPD disease and the antioxidant capacity of the oak extract and oil, the aim of the present study was to investigate the efficacy of a hydroalcoholic extract of the fruit and oil of Q. brantii in the treatment of progesterone -induced PPD in an animal model.

Materials and Methods

Extract preparation and characterization

The oak acorn (*Q. brantii*) was collected in August 2020 from the forests around the city of Khorramabad (Lorestan, Iran). The fruit was washed in distilled water before being separated from the bark and finely ground into a powder. The alcoholic extract consisted of a finely powdered sample (100 g). The extraction was carried out by maceration or soaking in 70% ethanol for 48 hours at room temperature [24]. To avoid sedimentation and to ensure efficient extraction, the mixture was stirred thoroughly. Whatman filter paper No. 1 was used to condense the extract as much as possible, and the solvent was evaporated to produce a concentrated extract, which was then dried in an incubator at 37 °C. The extract samples were stored in universal bottles and refrigerated at 4°C prior to use. The acorn oil is obtained from the company Roghankadeh, Tehran, Iran.

Animals

For this experimental study, 42 adult female Wistar rats (200–250 g) were obtained from the animal house of the Faculty of Veterinary Medicine, Ahvaz, Iran. The animals were housed in groups of six in polycarbonate cages (43.5 × 21.5 × 25.5 cm) and had

ad libitum access to standard rat chow and water in a temperature-controlled room (24±1°C) in a humidity-controlled vivarium with a 12-h light/ dark cycle. All rats were allowed to acclimate to their cage environment for at least one week prior to PPD induction. All experiments were performed in accordance with institutional guidelines for the care of animals and approved by the local ethics committee at Shahid Chamran University of Ahvaz, Ahvaz, Iran based on a guide for the care and use of laboratory animals (Code number: EE/1400.2.24. 25654/SCU.ac.ir). To exclude the confounding influence of diurnal variations in spontaneous behavior, behavioral observations were conducted in soundproof rooms at the same time of day. Each animal was tested only once.

Experimental design and components

Animals grouping

To investigate the effects of oak extract and oak oil on the antioxidant profile of depressed female rats, 42 animals were randomly divided into 6 groups (n = 7), including controls, progesterone withdrawal (PWD), and treatment (oak extract and oak oil), shown in Table 1. One dose of oak extract and oak oil was administered in each of the respective groups for eight days, and on the eighth day, open field and forced swimming tests (FST) were conducted. The injections and all behavioral experiments took place during the light cycle and were performed from 8:00 am to 2:00 pm. Before each injection, oak extract (100mg/kg, dispersed in %0.9 saline) and oak oil (45%) were shaken for 1 min [25]. All components were injected intraperitoneally (i.p.) in a volume of 0.5 cc. After the last test, the rats were decapitated under deep anesthesia, and about 5 ml of blood was quickly collected from the heart. After 15 min of centrifugation at 4000 rpm, the serum was collected in a test tube and stored at -70°C for the measurement of biochemical factors. Due to differences in the control groups, the groups were compared in pairs. The saline group (NPS) was compared with progesterone + saline (PS), the vehicle group (NPO) with progesterone + vehicle (PSO), progesterone + vehicle (PSO) with progesterone + oak oil (PPO), the progesterone + saline group (PS) with progesterone + oak extract (PE), and the progesterone + saline (PS) group with progesterone +

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vehicle group (PSO).

Induce the PPD model

The PPD was performed according to the protocol of Beckley and Finn [11]. To induce PWD, all depressed groups received daily injections of progesterone (5mg/kg) (*Iran* Hormone Company, Tehran, Iran) dissolved in sesame oil (Roghankadeh Company, Tehran, Iran) overnight at 37 °C with stirring for 5 days. After 5 days, the progesterone was withdrawn for 3 days [13]. In a preliminary study to confirm the effect of PWD, two groups that received saline solution and sesame oil instead of progesterone served as the control groups.

Open field test

Locomotor activity was assessed using open field tests (OFT) and was performed at the end of the treatment. At the beginning of the test, the rats were placed in the center of a box area (80×80×40 cm) whose inner walls were covered with a black surface. The box area was divided into 16 equal squares. The duration of observation in the open-air box was 5 min. The rats activities and changes were recorded with a video camera and analyzed later. The recorded parameter was the number of crossed squares. A rat has crossed a line when all four of its paws are within a square [26].

Force swimming test

Animals were tested for depression-like behavior in the FST, which was conducted with slight modifications of the methods described by Lucki *et al* [27]. FST was conducted 1 h after the completion of OFT. For this study, female rats were placed for 6 min in clear, transparent glass cylinders (height 60 cm, diameter 25 cm) filled to a height of 30 cm with 25 ± 2 °C warm water while a video camera recorded the mouse's behavior during the testing session for subsequent analysis. The duration of immobility (defined as a rat making no active movements except to keep the rat's nose above the water level) was recorded manually using stopwatches. Only the last 4 min of each 6 min test session were used for scoring [28].

Biochemical assays

Serum was tested for reduced glutathione (GSH), catalase, SOD and MDA using a UV/Vis spectrophotometer (Optimize, South Korea). The Ellman method was used to calculate the GSH concentration [29]. In this method, the thiols react with the Ellman reagent (DTNB) as a substrate. The yellow color was determined immediately after combining the chemicals in a spectrophotometer by measuring the absorbance of visible light at 412 nm. GSH was determined in micromolar amounts per ml (μmol/mL).

The standard method of Koroluk *et al.* [30] *was used to determine c*atalase activity. The reaction was started by adding 10 µl of the sample (blood serum) to 100 µl H_2O_2 in 0.05 mmol/L Tris-HCl buffer pH = 7 and placed in a 96-well plate for 10 min. The reaction was terminated by addition of 50 µl 4% ammonium molybdenum. The color intensity was measured at a wavelength of 410 nm in comparison to a blank sample. Catalase activity was determined at one micromole per minute (µmol/min).

SOD activity was determined according to the method described by Kono [31]. In this approach, the inhibition of nitro-tetrazolium reduction (NBT) was measured in the presence of SOD. The reaction of NBT with superoxide produces formazan red. In the sample, the enzyme superoxide dismutase combines with the superoxide to convert it into hydrogen peroxide without producing a red color. The color intensity was measured at 560 nm. In parallel, controls were performed without the homogenate. The activity was measured in units per milliliter.

The MDA content in serum was determined using the thiobarbituric acid reaction substances (TBARS) method of Placer *et al* [32]. TBARS were quantified using a spectrophotometer at 532 nm by comparing the absorbance with the standard curve of MDA equivalents formed by acid-catalyzed hydrolysis of 1,1,3,3-tetramethoxypropane. To determine the MDA content, a working solution of 15% trichloroacetic acid and 0.25 N HCl was prepared to quantify the MDA content. 250 µ serum and 500 µl working solution were combined for each sample and immersed in boiling water for 10 minutes. After cooling, the samples were centrifuged for 10 min at 3000 rpm. Finally, 200 µl of each supernatant was transferred to microplates, and the optical density (OD) of the samples was measured at 535 nm. The MDA concentration in serum was reported as

nmol/mL.

Statistical analysis

The mean of the data was compared between groups using Graph Pad InStat software (version 3.00), and statistical significance was defined as $p < 0.05$. Graphical data are expressed as mean ± SEM. Data analysis was performed using one-way analysis of variance (ANOVA) and Tukey post-hoc statistical tests were performed between multiple groups, and a student t-test was used to compare two groups.

Results

Hydro-alcoholic oak extract and oak oil in the FST of PPD

Figure 1 shows the effect of administration of hydroalcoholic oak extract (100mg/Kg) and oak oil

(45%) on FST in a progesterone-induced PPD model . Statistical analysis showed that progesterone caused significant immobilization in the control group receiving saline (P<0.001) and the vehicle group receiving sesame oil (P<0.001). The administration of hydroalcoholic oak extract (100 mg/kg) shortened the immobilization time compared to the control group (P<0.05). On the other hand, oak oil (45%) caused no significant change compared to the control group (P<0.05).

Effects of hydroalcoholic oak extract and oak oil on locomotor activity in the OFT of PPD

The results of this study show that depression has no effect on locomotor activity. There was also no significant difference in locomotor activity between hydroalcoholic oak extract (100mg/kg) and oak oil (45%) in the OFT. (Figure 2).
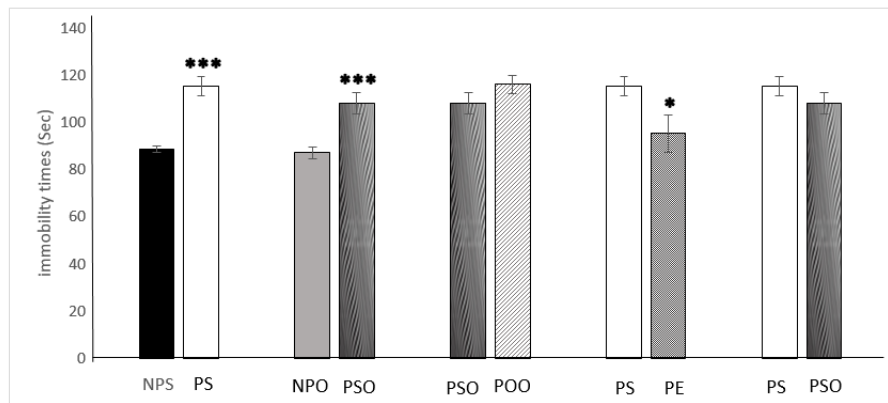

Figure 1. The effect of hydro-alcoholic oak extract (100mg/kg) and oak oil (45%) on the PPD in FST. Significant differences between groups are indicated by * *p*<0.05 and *** *p*<0.001. FST: force swimming test; NPS: no PPD + saline; NPO: no PPD + sesame oil; PPD: postpartum depression; PS: PPD + saline; PSO: PPD + sesame oil; PE: PPD + oak extract; POO: PPD + oak oil.
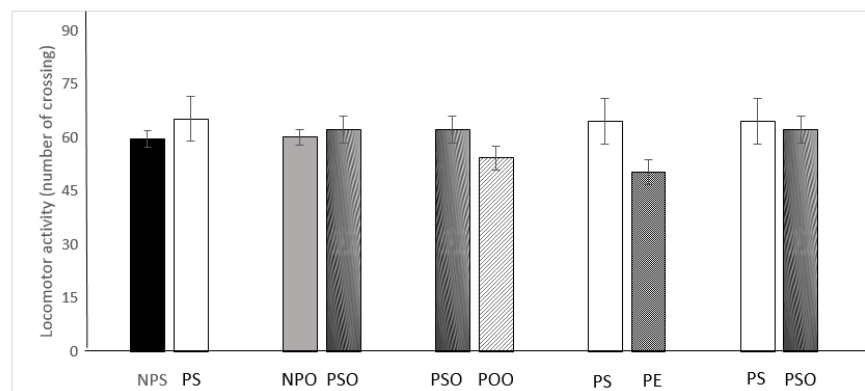

Figure 2. The effect of hydro-alcoholic oak extract (100mg/kg) and oak oil (45%) on the PPD in OFT. Significant differences between groups are indicated by * *p*<0.05 and *** *p*<0.001. NPS: no PPD + saline; NPO: no PPD + sesame oil; OFT: open field tests; PPD: postpartum depression; PS: PPD + saline; PSO: PPD + sesame oil; PE: PPD + oak extract; POO: PPD + oak oil.

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Effects of hydroalcoholic oak extract and oil on GSH levels

Statistical analysis revealed that progesterone caused a significant decrease ($p<0.05$) in the mean serum GSH level compared to the control group receiving saline, while the mean serum GSH level of the vehicle group receiving sesame oil decreased only slightly ($p<0.05$) compared to the control group. However, the hydroalcoholic oak extract (100mg/kg) and oak oil (45%) had no significant effect on GSH levels ($p<0.05$) (Figure 3).
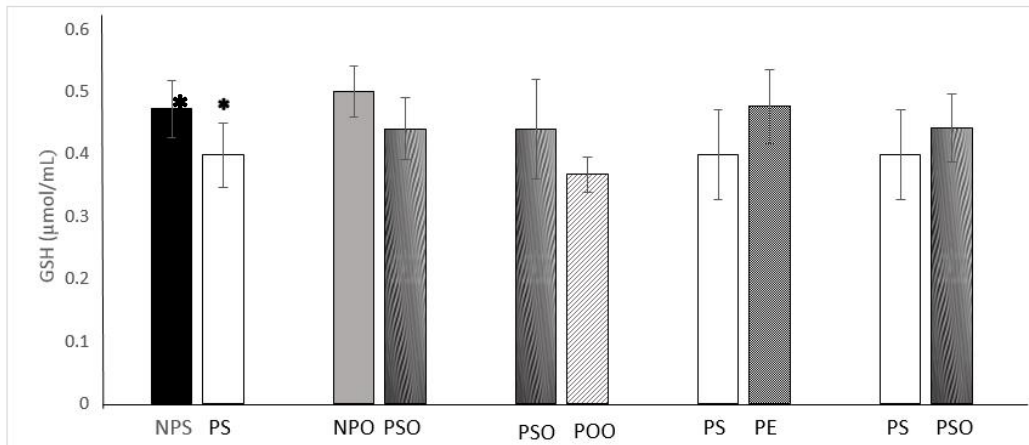

Figure 3. The effect of hydro-alcoholic oak extract (100mg/kg) and oak oil (45%) on the serum level of total GSH during the PPD. Significant differences between groups are indicated by * $p<0.05$ and *** $p<0.001$. GSH: reduced glutathione; NPS: no PPD + saline; NPO: no PPD + sesame oil; PPD: postpartum depression; PS: PPD + saline; PSO: PPD + sesame oil; PE: PPD + oak extract; POO: PPD + oak oil.

Effects of hydroalcoholic oak extract and oil on catalase levels

As shown in Figure 4,there was a significant difference ($p<0.05$) in serum catalase levels between the depressed groups without extract or oil treatment compared to the control groups without depression. However, the catalase concentration was significantly increased in the oak oil group (45%) compared to the control group ($p<0.05$). On the other hand, the hydroalcoholic oak extract (100mg/kg) had no effect on catalase levels.
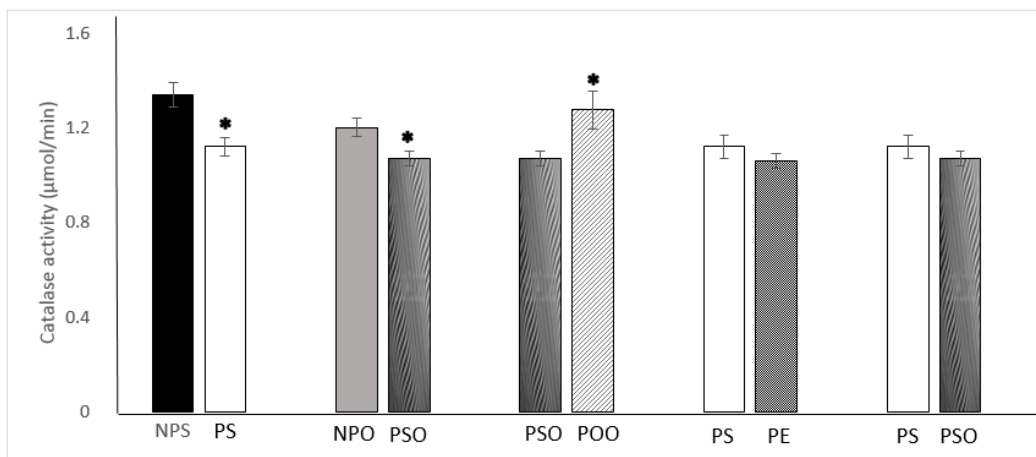

Figure 4. The effect of hydro-alcoholic oak extract (100mg/kg) and oak oil (45%) on the serum level of total catalase during the PPD. Significant differences between groups are indicated by * $p<0.05$ and *** $p<0.001$. NPS: no PPD + saline; NPO: no PPD + sesame oil; PPD: postpartum depression; PS: PPD + saline; PSO: PPD + sesame oil; PE: PPD + oak extract; POO: PPD + oak oil.

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Figure 5. The effect of hydro-alcoholic oak extract (100mg/kg) and oak oil (45%) on the serum level of total SOD during the PPD. Significant differences between groups are indicated by * $p<0.05$ and *** $p<0.001$. NPS: no PPD + saline; NPO: no PPD + sesame oil; PPD: postpartum depression; PS: PPD + saline; PSO: PPD + sesame oil; PE: PPD + oak extract; POO: PPD + oak oil.
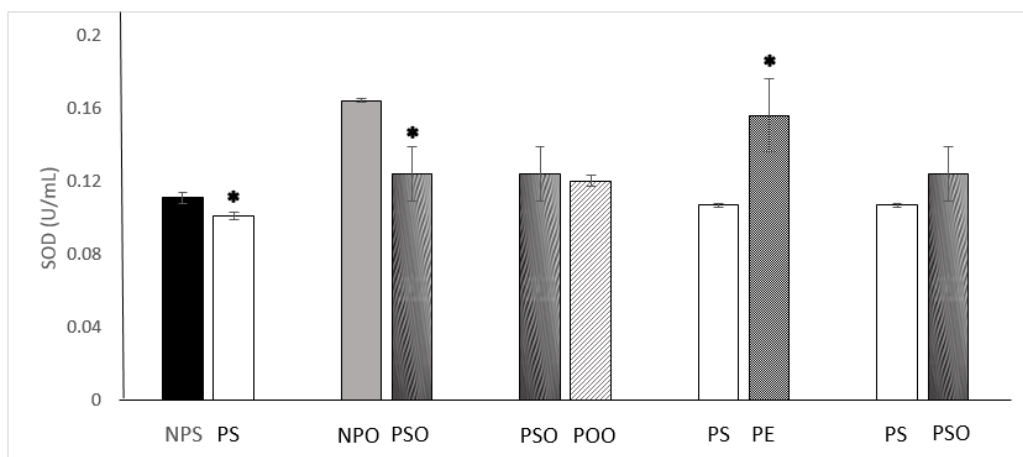

Figure 6. The effect of hydro-alcoholic oak extract (100mg/kg) and oak oil (45%) on the serum level of total MDA during the PPD. Significant differences between groups are indicated by * $p<0.05$ and *** $p<0.001$. MDA: malon-dialdehyde; NPS: no PPD + saline; NPO: no PPD + sesame oil; PPD: postpartum depression; PS: PPD + saline; PSO: PPD + sesame oil; PE: PPD + oak extract; POO: PPD + oak oil.
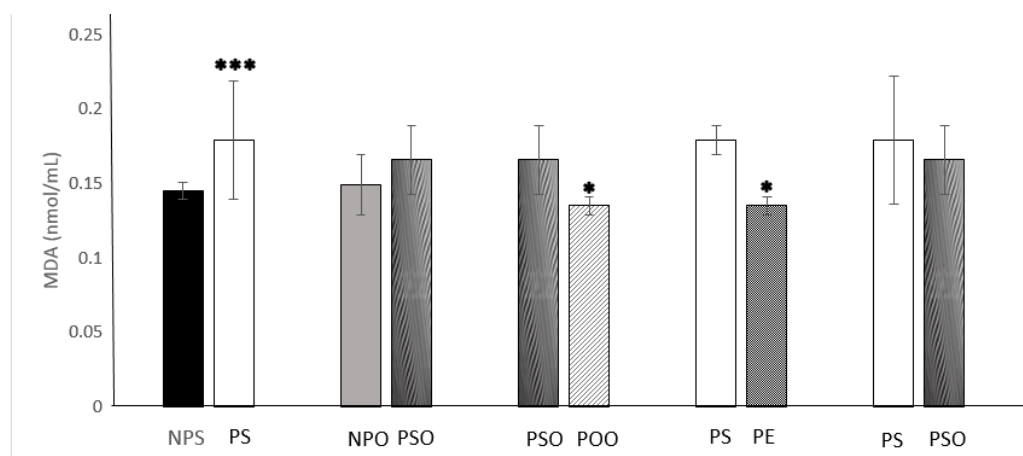
Effects of hydroalcoholic oak extract and oil on SOD levels

The results showed that serum SOD levels were significantly lower in the depressed groups compared to the control groups ($p<0.05$). However, the SOD level was significantly higher in hydroalcoholic oak extract (100mg/kg) than in the control group ($p<0.05$). In contrast, oak oil (45%), had no effect on SOD levels (Figure 5).

Effects of hydroalcoholic oak extract and oil on MDA levels

Statistical analysis showed that progesterone caused a significant (P<0.001) or insignificant ($p<0.05$) increase in the mean serum MDA level of the control group receiving saline and the vehicle group receiving sesame oil, respectively, compared to their control counterpart. Administration of hydroalcoholic oak extract (100 mg/kg) reduced the MDA level compared to the control group (P<0.05). The administration of oak oil (45%) also led to a significant reduction in MDA levels compared to the control group ($p<0.05$) (Figure 6).

Discussion

The current study, like previous reports [26,33,34], showed that chronic withdrawal of progesterone treatment can induce depression-like behavior in rats. Moreover, the antidepressant-like effects of chronic administration of the hydroalcoholic extract and oil of *Q. brantii* were investigated for the first time in a PWD model in our study, a *Q. brantii* extract

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(100mg/kg) significantly reduced immobility time in the FST after acute administration, while oak oil (45%) had no effect on immobility. A key issue in the search for new antidepressant drugs is determining the animal model that is most appropriate and reliable to adequately identify different antidepressant therapies without committing errors [35]. In this case, the FTS model developed by Porsolt *et al* [36] is widely accepted as an attempt to fulfil these requirements. Our data suggest that depression is caused by an imbalance between prooxidants and antioxidants. After an induced PPD, MDA increases while antioxidant enzymes such as GSH, catalase and SOD decrease drastically, but the hydro-alcoholic extract and oil of *Q. brantii* counteract these effects and significantly increase the level of these enzymes in some groups. Numerous studies have shown that PPD is partly caused by a decrease in the levels of the reproductive hormones estradiol and progesterone. According to several research studies, the sudden and significant fluctuations in steroid hormones associated with pregnancy lead to an excessive release of neurotransmitters in the brain, resulting in a lack of suppression of numerous depressive variables [37,26] .

In addition, new research suggests that changes in the brain 's bioenergetic network and the pathophysiology of MDD are related to changes in brain function, neuronal plasticity, and cerebral blood flow. Oxidative stress is one of the main causes of these structural and functional changes in the brain in MDD. For example, significant correlations have been found between the severity of depression and SOD/lipoperoxidation levels in erythrocytes [38]. Consistent with our findings, many studies have found that lower levels of antioxidants and higher levels of oxidative stress biomarkers, such as MDA, play a role in the development of depression [39–41]. In the meantime, there is some research indicating that there were no significant differences in MDA levels between the depressed and non-depressed groups [42,43]. In addition, many studies, as well as our results, reported that there was a significant difference in antioxidant enzymes between patients with major depression, including PPD, and non-depressed participants [44, 45]. Rybka *et al*. discovered that depression was associated with decreased activity of key antioxidant enzymes such as

SOD-1 and glutathione peroxidase-1 (GPx-1). In contrast, they discovered higher MDA and H2O2 levels as well as greater DNA damage in depressed individuals compared to control subjects [46]. Therefore, the elimination of ROS by increasing antioxidant enzymes is probably one of the most effective defenses of a living organism against disease. Acorn, a type of traditional national medicine with antioxidant properties, has been reported to have an antioxidant effect [47]. The extract and oil of Q. brantii may play a role in the prevention of chronic diseases caused by oxidative stress, as they contain antioxidant components such as gallic acid, p-coumaric acid, ellagic acid, rutin, epi-catectechin, quercetinand many unsaturated lipids [48]. In addition, the acorns of *Quercus* species are used as food and as a medicinal plant for the treatment of diarrhea, hemorrhagic and inflammatory diseases, due to their phenolic, which are believed to be related to their biological activity [49]. As far as we know, this is the first study to show that *Q. brantii* can protect against PPD. Our results showed that *Q. brantii* increases SOD activity, which was also confirmed by Dogan *et al*. and Solimanzadeh *et al*. [47, 50]. In another study that went in the same direction as our results showed, administration of *Q. brantii* extract also reduced MDA levels in mice exposed to lead (Pb), which is consistent with the results of Dogan *et al* [47]. In a recent study, one of the *Quercus* species (*Quercus ilex*) was found to be rich in phenolic-astringent compounds and fibers, exhibiting significant DPPH/ABTS free radical scavenging activity and a remarkable increase in endogenous antioxidant enzyme activities (catalase, SOD, and GPx) and a reduction in lipid peroxidation levels (2022). In some groups, the observed effects of oak oil were lower than those of the extract, which could be related to its high fat content and low dose. In this regard, no study has yet been conducted on the effects of oak oil on rats and there is very little information on this subject. Therefore, different dosages of the oil or a particular lipid may be isolated and used in future studies.

Our data suggest that the fruit extract and oil of *Q. brantii* appear to be a natural source of antidepressant-like compounds that increase antioxidant levels, which will be further investigated by our group. Previous studies have shown that this

plant extract is a natural source of phytochemicals that are valuable for human health [51, 52].

Conclusion

Our data suggest that the fruit extract and oil of Q. brantii appear to be a natural source of antidepressant-like compounds that increase antioxidant levels, which will be further investigated by our group. Previous studies have shown that this plant extract is a natural source of phytochemicals that are valuable for human health.

Conflicts of interest

The authors declare that there is no conflict of interests.

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