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Effects of Hesperidin During Pregnancy on Antidepressant-like behaviour in Postpartum Mice

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Abstract

BACKGROUND: Post-partum depression is has higher prevelance among other mental illness and herbal therapies are potential alternatives and adjuncts for its treatment. Hesperidin is the major flavonoid isolated from citrus fruits which has neuroprotective, antioxidant and antidepressant activity.

OBJECTIVES: We studied the effect of prepartum administration of Hesperidin on postpartum antidepressant-like effects in mice.

METHODS: Twelve male and 40 female mice (28-30 gr) were randomly selected and after determination of the pregnancy using vaginal plaque, allocated into 4 experimental groups. Group 1 was kept as control and groups 2-4 were i.p. injected with hesperidne (0.1, 0.5 and 1 mg/kg) on days of 5, 8, 11, 14 and 17 of pregnancy. The control group received i.p. injection of the saline on the same days. Following postpartum, forced swimming test (FST), tail suspension test (TST) and open field tests were used to evaluate depressive-like antidepressant activity of hesperidin. Also, serum Malondialdehyde (MDA), glutathione peroxidase (GPx), superoxide dismutase (SOD) and total antioxidant capacity (TAC) were determined.

RESULTS: Based on findings, administration of the different levels of the hesperidin (0.5 and 1 mg/kg) at GD 5, 8, 11, 14 and 17 significantly diminished immobility time (S) in TST and FST on postpartum mice in comparison to control group ($P \leq 0.05$). Pre-partum administration of hesperidin (0.1, 0.5 and 1 mg/kg) had no effect on OFT ($P > 0.05$). Administration of the hesperidin (0.5 and 1 mg/kg) during the GD significantly diminished MDA levels on postpartum compared to control group ($P \leq 0.05$). Also, pre-partum administration of the hesperidin (0.1, 0.5 and 1 mg/kg) significantly increased SOD and GPx levels on postpartum mice in comparison to control group ($P \leq 0.05$).

CONCLUSIONS: These results suggested pre-partum administration of hesperidin has antidepressant and antioxidant effect in postpartum mice.

KEYWORDS: Pregnancy, Hesperidin, Antidepressant, Antioxidant, Postpartum, Mice

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Introduction

Depressive disorders are the most prevalent form of mental illness worldwide. Major depression is characterized by a change in psychosocial and physical impairment mood as well as lack of interest in the surroundings (Saravi *et al*., 2016). There are growing reports on the incidence of depression in both males and females in modern society (Gu *et al*., 2014). The post-partum period represents profound physiological and emotional changes in mothers to ensure the well-being and nurturance of the offspring. However, several psychiatric disorders can develop in this phase (Perani and Slattery, 2014). Post-partum mood and anxiety disorders affect maternal and infant as well as developing psychiatric disorder in later life such as post-partum depression (PPD), post-partum anxiety and post-partum psychosis (Ming and Shinn-Yi, 2016). Several animal methods such as stress-based, high-fat diet-based and pup separation models are used to induce experimental PPD (Ming and Shinn-Yi, 2016). There are growing reports of new antidepressant agents with side effects (Alimohammadi *et al*., 2019).

Hesperidin is the major flavonoid isolated from citrus fruits (Li and Schluesener, 2017). The hesperidin molecule is composed of a glycone unit known as hesperetin and a disaccharide, rutinose (Iranshahi *et al*., 2015). Hesperidin has several biological effects including antioxidant, anti-inflammatory, antimicrobial, anti-carcinogenic and anti-allergic effects and insulin-sensitizing activity (Li and Schluesener, 2017). In addition, hesperidin neuropharmacological properties have been reported for the hesperidin (Hajialyani *et al*., 2019). It has high potential for radical scavenging and protective effects and can cross blood brain barrier (Khan and Parvez, 2015). Hesperidin promotes has neuroprotective effects by increase survival and differentiation of the neurons (Matias *et al*., 2017) which have positive effect for stroke, Huntington's, Alzheimer's and Parkinson's disease (Antunes *et al*., 2014). Several antioxidant compounds, such as flavonoids derived from natural products, have demonstrated neuroprotective activity in PPD (Antunes *et al*., 2014).

Antioxidant enzymes, such as glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD), also are important mediators in the reduction of oxidative stress (Khan *et al*. 2012). It is reported that (50 mg/kg) treatment increased GPx, SOD and CAT activity in mouse model of Parkinson's disease (Antunes *et al*., 2014). Hesperidin in the acute (1 mg/kg) and chronic (0.1, 0.3 and 1 mg/kg) levels improved tail suspension test (TST) which improved antidepressant-like effect (Donato *et al.*, 2014). Based on the aforementioned evidence, we sought to investigate effects of the Hesperidin exposure during pregnancy on antidepressant-like effects postpartum in mice.

Materials and methods

Animals

The NMRI male (n=12) and virgin female mice (n=40, age: 8–10 weeks old and 28–30 gr) were supplied from the Razi Serum and Vaccine Institute (Tehran, Iran). The animals acclimatized for 1 week before beginning the study. All experimental procedures were approved by the Animal Ethics Committee of Science and Research Branch of Islamic Azad University, Tehran, Iran (IR.IAU.SRB.REC.1398.117). follow-

ing 7 days of acclimatization, the female mice were kept with fertile male mice. Every day, the female mice were checked and presence of the vaginal plug or sperm was defined as onset of pregnancy. The pregnant mice were randomly assigned into 4 groups (n = 10 for each group) and provided *ad libitum* food and water.

Experimental procedure

In control group, pregnant mice were i.p. injected with saline containing 0.05% Tween-80 at 5, 8, 11, 14 and 17 days of gestation (GD). In groups 2, 3 and 4, mice were injected with 0.1, 0.5 and 1 mg/kg of hesperidin at same days, respectively. The dosage of the hesperidin was determined based on the previous reports (Antunes *et al*., 2014; Donato *et al*., 2014; Khan and Parvez, 2015; Pari *et al*., 2015) and our pilot study. Then after delivery, antidepressant-like effects of the hesperidin were evaluated using neurobehavioral tests that were done on female mice.

Tail suspension test (TST)

The TST is one of the most common techniques for assessing antidepressant-like activity in mice (Cryan *et al*., 2005). The TST was done in accordance to stated by Steru *et al*. (1985). Briefly, the animal was far from nearest objects and were both acoustically and visually isolated from observing or interacting each other. Then mice suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the extremity of the tail, in such a position that it cannot escape or hold on to nearby surfaces. Immobility time was monitored during a 6 minutes. Mice were considered immobile only when they had no strong body shaking and movement of the limbs as they hung passively and completely motionless.

Open field test (OFT)

The Open field test (OFT) was used to evaluate effects of hesperidin on the locomotor and exploratory activities. The OFT was done using 45×45×30 cm^3 poly wood cage. The flour of OFT cage was divided into 3×3 squares. Each animal was placed individually at the center of the apparatus and observed for 6 minutes to record the locomotion (number of segments crossed with the four paws) (Donato *et al*., 2014).

Forced Swimming Test (FST)

FST was carried out following the protocol as described previously in mice (Castagné *et al*., 2011). Each mouse was plunged into a glass cylinder (height: 25 cm; diameter: 15 cm) containing 10 cm of water (25 ± 1 °C) for 15 min (pre-test session). The immobility time for mouse was described as when it ceased struggling and remained floating motionless in the water, making only small movements necessary to keep its head above water. The total duration of immobility during the last 4 minutes of the 6 minutes testing period was measured.

Antioxidant activity

At the end of the neurobehavioral tests, blood samples were taken from each mouse and serum MDA, SOD, GPx and total antioxidant capacity (TAC) were determined using Zell Bio GmbH (Germany) assay kits.

Statistical analysis

Data was analyzed by one-way analysis of variance (ANOVA) and is presented as the mean ± SEM. For treatments found to have an effect according to the ANOVA, mean values were compared with Tukey's test. $P \leq 0.05$ was considered to indicate significant differences between the treatments.

Results

Effect of exposure to different levels of Hesperidin during pregnancy on immobil-

ity time (S) in TST on postpartum mice is presented in Figure 1. As seen, administration of the different levels of the hesperidin (0.5 and 1 mg/kg) at GD 5, 8, 11, 14 and 17 significantly decreased immobility time (s) in TST on postpartum mice compared to control group ($P \leq 0.05$).

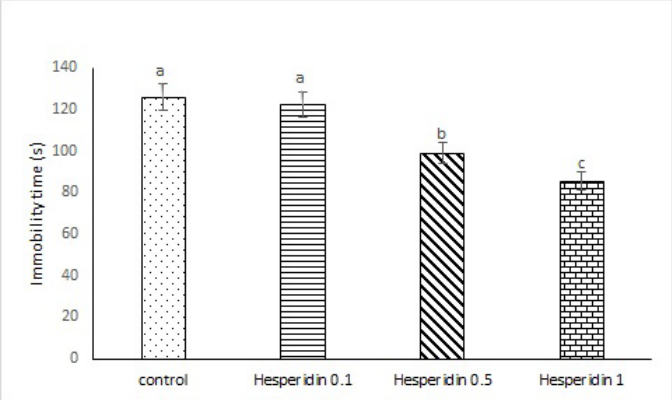

Figure 1. Effect of exposure to different levels of Hesperidin during pregnancy on immobility time (sec) in TST on postpartum mice. TST: tail suspension test. There are significant differences between groups with different superscripts (a, b and c; $P \leq 0.05$).

According to the Figure 2, administration of the hesperidin (0.5 and 1 mg/kg) at GD 5, 8, 11, 14 and 17 significantly decreased immobility time (S) in FST on postpartum mice compared to control group ($P \leq 0.05$).

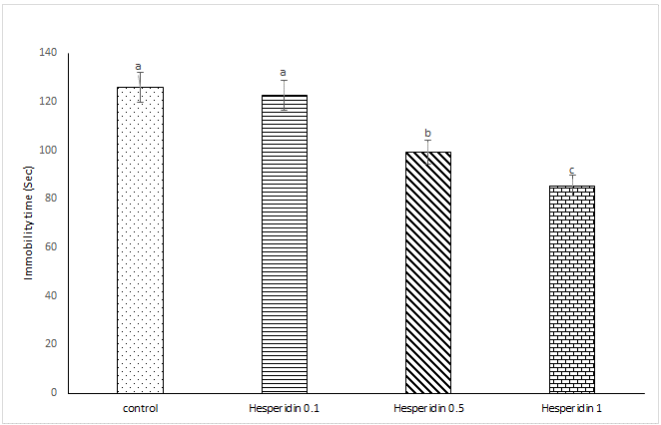

Figure 2. Effect of exposure to different levels of Hesperidin during pregnancy on immobility time (sec) in FST on postpartum mice. FST: forced swimming test. There are significant differences between groups with different superscripts (a, b and c; $P \leq 0.05$).

However, pre-partum exposure to the hesperidin (0.1, 0.5 and 1 mg/kg) had no significant effect on OFT following delivery compared to control group (P>0.05) (Figure 3).

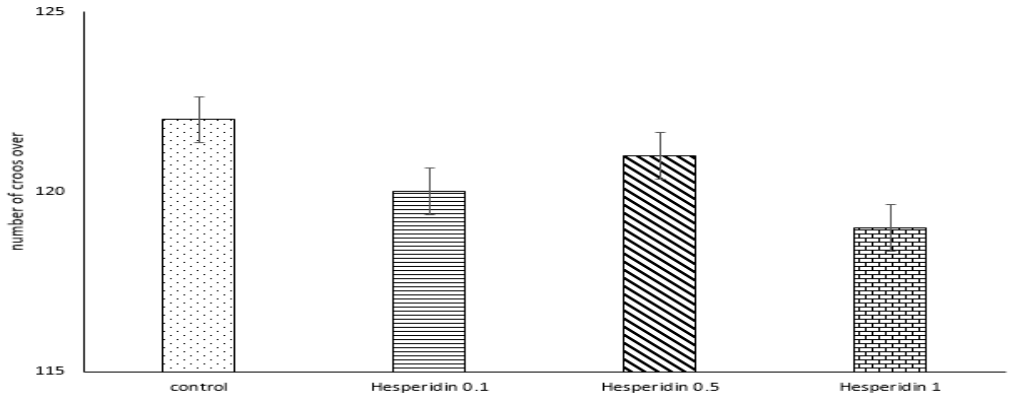

Figure 3. Effect of exposure to different levels of Hesperidin during pregnancy on immobility time (S) in OFT on postpartum mice. OFT: open field test.

As seen in Figure 4. administration of the hesperidin (0.5 and 1 mg/kg) during the GD significantly decreased MDA levels on postpartum mice compared to control group (P≤0.05). Furthermore, administration of the hesperidin (0.5 and 1 mg/kg) significantly increased GPx levels on postpartum mice compared to control group (P≤0.05) (Figure 5).

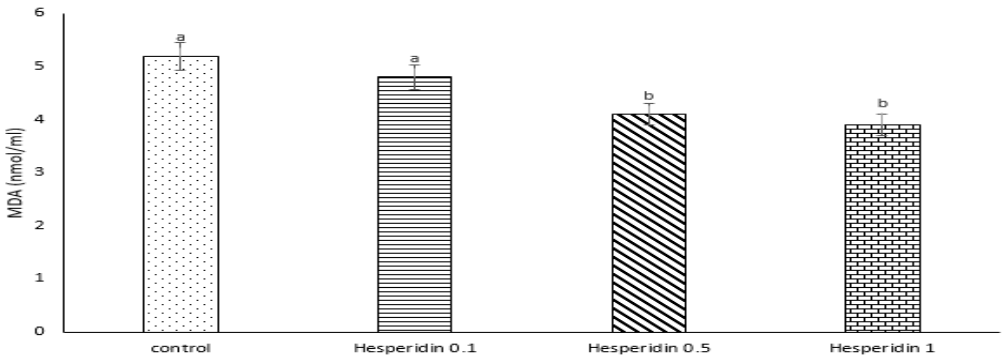

Figure 4. Effect of exposure to different levels of Hesperidin during pregnancy on postpartum serum Malondialdehyde (MDA) level in mice. There are significant differences between groups with different superscripts (a and b; $P \leq 0.05$).

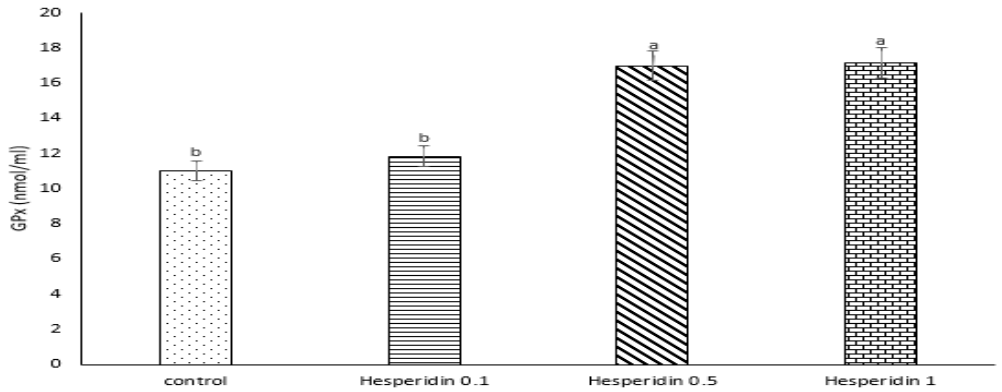

Figure 5. Effect of exposure to different levels of Hesperidin during pregnancy on postpartum serum glutathione peroxidase (GPx) level in mice. There are significant differences between groups with different superscripts (a and b; $P \leq 0.05$).

Pre-partum exposure to the hesperidin (0.1, 0.5 and 1 mg/kg) significantly increased SOD levels on postpartum mice compared to control group ($P \leq 0.05$) (Figure 6) but had no significant effect on TAC following delivery compared to control group ($P > 0.05$) (Figure 7).

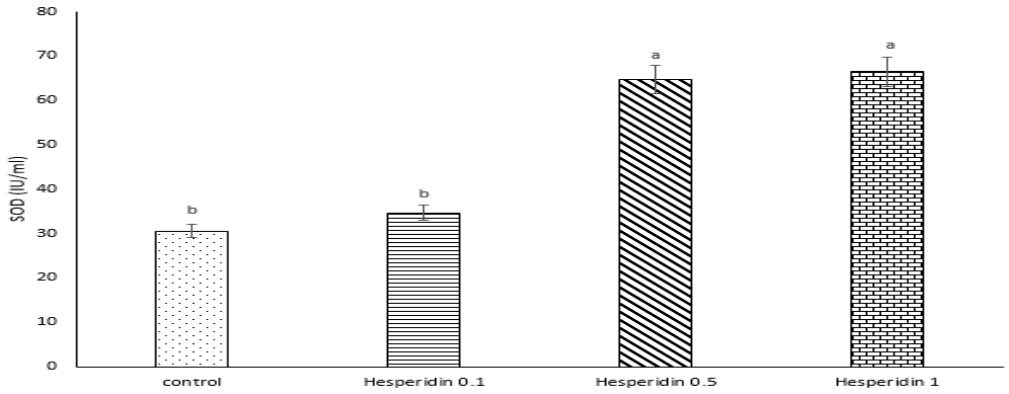

Figure 6. Effect of exposure to different levels of Hesperidin during pregnancy on postpartum serum superoxide dismutase (SOD) level in mice. There are significant differences between groups with different superscripts (a and b; $P \leq 0.05$).

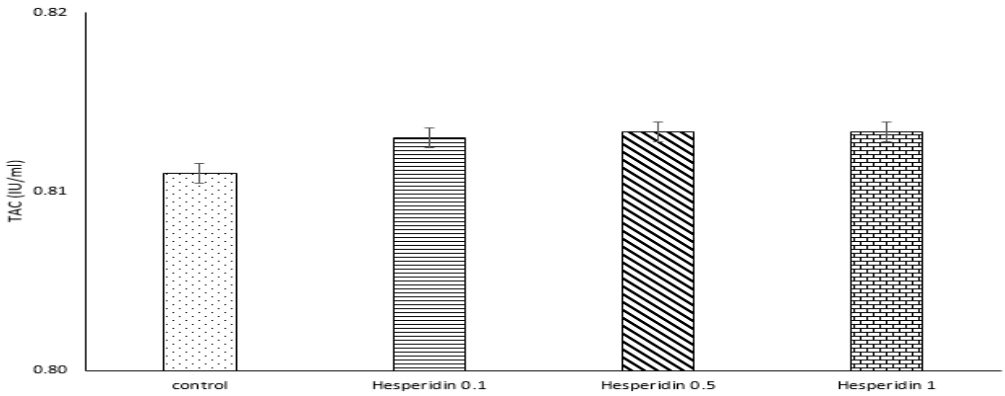

Figure 7. Effect of exposure to different levels of Hesperidin during pregnancy on postpartum serum total antioxidant capacity (TAC) in mice.

Discussion

Depression is a common, chronic, recurrent illness with severe morbidity. Although a number of research studies have been done on its physiological mechanisms, brain areas underlying this disorder are not yet well understood. Postpartum depression is a severe mood disorder which happens right away after childbirth and is observed by sadness and anxiety in mothers (O'Hara and McCabe, 2013). According to the results, administration of the different doses of hesperidin (0.5 and 1 mg/kg) at GD 5, 8, 11, 14 and 17 significantly decreased immobility time in TST and FST on postpartum mice compared to control group. Hesperidin (1mg/kg) significantly reduced immobility time in FST in mice (Filho *et al*., 2013). In a similar study, it was reported hesperidin (50 mg/kg) improved depressive-like behavior in the TST and memory in the Morris water maze test (Antunes *et al*., 2014). The antidepressant-like effect of hesperidin has been reported in FST and TST tests (Souza *et al*., 2013). Moreover, hesperidin suppressed depressive-like behaviors in TST using intra-striatal injection of 6-hydroxydopamine in Parkinson's disease (Antunes *et al*., 2014). Hesperidin

(25, 50 and 100 mg/kg) had anti-depressant effect in diabetic rats (El-Marasy *et al*., 2014), our results were in agreement with the reports.

Immobility time in FST resembles a state of despair and mental depression. Stress-induced depression like behavioral alterations are routinely determined by TST and FST in rodents. Immobility time in TST and FST reflects the behavioral despair which is similar to depression in human (Walia and Gilhotra, 2016). Differences on neurochemical pathways of the FST and TST have been reported. Despite the tests seems very similar but because of pharmacokinetic and pharmacodynamic factors, their accuracy are different (Amin *et al*., 2015). We also studied effect of the hesperidin on locomotor activity using open field test. As observed, pre-partum exposure to the hesperidin (0.1, 0.5 and 1 mg/kg) had no significant effect on OFT following delivery. It is revealed hesperidin at the levels of 0.1, 0.5 and 1 mg/kg, had no sedative effect, our finding was similar to this report.

Bioavailability is a key step in ensuring the bio efficacy of hesperidin which is affected by physiological conditions. It is selectively metabolized by both cytochrome P450 isoforms (CYP1A and CYP1B1) to eriodictyol, indicating that there is Odemethylation of hesperidin in liver. It has higher bio activity compared to the other flavonoids which can be related to the inhibition of phase II metabolism (glucuronidation and sulfation of hesperidin). The metabolites of hesperidin are detected in urine but not in feces. In oral administration, more than 40% of the radioactivity of hesperidin -3-14C was expired as carbon dioxide which indicates further bacterial degradation in the colon than blood circulation (Roohbakhsh *et al*., 2014). The ability of hesperidin to cross the blood brain barrier makes it an ideal bioactive substance for treatment of CNS disorders (Iranshahi *et al*., 2015). Hesperidin decreases risk of Parkinson's disease as well as Alzheimer's disease in flavonoid deficient patient (Antunes*et al*., 2014). The neuroprotective role of the hesperidin is mediated via anti-inflammatory and antioxidant activities (Menze *et al.*, 2012). Hesperidin (0.01, 0.3 and 1 mg/kg) has antidepressant-like effect and increased hippocampal brain-derived neurotrophic factor (BDNF) in the hippocampus of mice (Donato *et al*., 2014). It is reported that nitrate/nitrite levels decreased in the hippocampus of hesperidin-treated mice. Anti-depressant activity of the hesperidin is inhibited by pretreatment with L-arginine (processor of nitric oxide). Also, administration of the hesperidin increased the brain-derived neurotrophic factor (BDNF) level in the hippocampus of mice (Donato *et al*., 2014). Perhaps, antidepressant-like activity of the flavonoids mediates via BDNF (Hajialyani *et al*., 2019). Also, it is reported antidepressant effect of hesperidin is also dependent on nitric oxide (NO)/cGMP pathway (Donato *et al*., 2014). Hesperidin, (0.1, 0.3 and 1 mg/kg), reduced nitrate/nitrite levels in the hippocampus of mice (Donato *et al*. 2014). It is suggested plasma nitrate levels and nitric oxide synthase (NOS) expression increased in the hippocampus of depressed patients. Inhibition of NOS may decrease immobility time in the TST elicited by hesperidin (Donato *et al*., 2014). Based on the limitation of the study, we were not able to determine interaction of the hesperidin with NO pathway.

Based on the findings, pre-partum exposure to the hesperidin (0.1, 0.5 and 1 mg/

kg) significantly increased SOD and GPx levels on postpartum mice compared to control group. It is reported that hesperidin has antioxidant protection against free radicals-induced oxidative damage (Hemanth Kumar *et al*., 2017). However, Antunes *et al*. (2014) reported hesperidin (50 mg/kg) treatment attenuated the 6-OHDA-induced reduction in GPx, SOD and CAT levels in mouse model of Parkinson's disease. Also, it is reported hesperidin increased glutathione, SOD, CAT and decreased MDA and nitrite level (Roohbakhsh *et al*., 2014). Administration of hesperidin (20, 40 and 80 mg/kg) reversed the levels of serum hepatic CAT, SOD, GPx and glutathione S-transferase (GST) enzyme levels (Pari *et al*., 2015) which is similar to our result. antioxidant activity of hesperidin mediates by radical scavenging activity and ERK/Nrf2 signaling pathway as well (Elavarasan *et al*., 2012). Injection of the hesperidin (0.5 and 1 mg/kg) during the GD significantly decreased MDA levels on postpartum mice compared to control group. Hesperidin has protective effect against reactive oxygen species (ROS) production and oxidative stress. Hesperidin enhanced antioxidant enzymes CAT, SOD and GST level (Visnagri *et al*., 2014). The enzymatic antioxidants CAT, SOD, GPx and GST have crucial role on scavenging ROS. There is a correlation between depressive disorders and increased oxidative stress, neuro-inflammation and anti-oxidant defenses (Black *et al*., 2014).

Hesperidin–therapy is safe, has a non-accumulative nature with lowest adverse effect, even during the pregnancy period (Hajialyani *et al*., 2019). Hesperidin administered at doses up to 5% for 13 weeks had no mutagenic, toxic, and carcinogenic effects on mice (Garg *et al*., 2001). In the model of rat colon carcinogenesis, hesperidin decreased intestinal tumor incidents via antioxidant defense with no toxicity to the liver and colon (Aranganathan and Nalini, 2009). Hesperidin is able to decrease streptozotocin–isoproterenol-induced myocardial toxicity (Agrawal *et al*., 2014). Although hesperidin is a safe phytochemical, possible interactions of this phytochemical should be considered (Hajialyani *et al*., 2019). In view of our findings, the obtained data indicate hesperidin has protective activity against postpartum depression.

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Conflicts of interest

The authors declared that there are no conflicts of interest.

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اثرات هیسپیریدین طی آبستنی بر رفتار ضدافسردگی پس از زایمان در موش سوری

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چکیده

زمینه مطالعه: افسردگی پس از زایمان یکی از شایع‌ترین بیماری‌های روان می‌باشد و درمان گیاهی جایگزین مناسبی برای درمان آن می‌باشد. هیسپریدین مهمترین فلاوونوئید استخراج شده از مرکبات می‌باشد که اثرات محافظتی بر نورون، آنتی اکسیدانی و ضد افسردگی دارد.

هدف: مطالعه حاضر به منظور بررسی اثرات قرار گرفتن در معرض هیسپریدین در دوران آبستنی بر اثرات ضدافسردگی متعاقب زایمان در موش‌های سوری انجام گرفت.

روش کار: ۱۲ موش سوری نر و ۴۰ موش ماده بالغ (۲۸-۳۰ گرم) بطور تصادفی در کنار یکدیگر نگهداری شده و پس از تایید آبستنی بوسیله پلاک واژن، به چهار گروه تقسیم شدند. گروه اول بعنوان کنترل و گروه ۲، ۳ و ۴ به ترتیب تزریق ۰/۱، ۰/۵ و ۱ گرم بر کیلوگرم هیسپریدین را طی روزهای ۵، ۸، ۱۱، ۱۴ و ۱۷ آبستنی را بصورت تزریق داخل صفاقی دریافت کردند. به گروه کنترل نیز در همان فواصل سرم فیزیولوژی تزریق شد. پس از زایمان ارزیابی اثرات ضدافسردگی هیسپیریدین با استفاده از آزمون‌های شنای اجباری، تعلیق دم و اوپن فیلد انجام گرفت. در انتهای مطالعه، نمونه خون اخذ و مقادیر سرمی مالون دی آلدهید (MDA)، گلوتاتیون پراکسیداز(GPx) ، سوپراکسید دیسموتاز (SOD) و ظرفیت آنتی اکسیدانی تام (TAC) ارزیابی شد.

نتایـــج: باتوجه به نتایج بدست آمده تجویز هیسپریدین (۰/۱، ۰/۵ و ۱ گرم بر کیلوگرم) طی روزهای ۵، ۸، ۱۱، ۱۴ و ۱۷ آبستنی بطور معنی‌داری موجب کاهش زمان بی‌تحرکی (ثانیه) در تست‌های شنای اجباری و تعلیق دم متعاقب زایمان در مقایسه با گروه کنترل شد ($P\leq$۰/۰۵). تجویز هیسپریدین (۰/۱، ۰/۵ و ۱ گرم بر کیلوگرم) طی روزهای ۵، ۸، ۱۱، ۱۴ و ۱۷ آبستنی بطور اثر معنی‌داری در تست اپن فیلد در مقایسه با گروه کنترل نداشت($P>$۰/۰۵). تجویز هیسپریدین (۰/۱، ۰/۵ و ۱ گرم بر کیلوگرم) طی آبستنی موجب کاهش مالون دی آلدهید متعاقب زایمان در مقایسه با گروه کنترل شد ($P\leq$۰/۰۵). همچنین، تجویز هیسپریدین (۰/۱، ۰/۵ و ۱ گرم بر کیلوگرم) در دوران آبستنی موجب افزایش گلوتاتیون پراکسیداز و سوپرااکسید دیسموتاز در مقایسه با گروه کنترل شد ($P\leq$۰/۰۵).

نتیجه گیری نهایی: نتایج نشان داد که قرار گرفتن در تجویز هیسپریدین در دوران آبستنی اثرات ضدافسردگی و آنتی اکسیدانی متعاقب زایمان در موش سوری دارد.

واژه‌های کلیدی:

آبستنی، هیسپیریدین، ضدافسردگی، آنتی اکسیدان، زایمان، موش.

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