Original Article

Effects of α-pinene Administration During Pregnancy on Depressive-like Behavior Following Delivery in Mice

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ABSTRACT

Background: Parturition depression is an important physiological problem, and several attempts have been made to ascertain this physiological phenomenon. Natural monoterpenes like α-pinene have numerous beneficial properties, but no studies have been done on their antidepressant potential in postpartum animals.

Objectives: This study aimed to determine the effects of prenatal administration of α-pinene on the antidepressant-like behavior of mice following delivery.

Methods: Pregnant female mice were randomly assigned into four groups. In the control group, the animals were injected with saline on their 5, 8, 11, 14, and 17 gestation days (GD). In groups 2 to 4, pregnant female mice were injected with α-pinene (0.1, 0.5, and 1 mg/kg, respectively) at GD 5, 8, 11, 14, and 17. On day 2 postpartum, open field test (OFT), rotarod, forced swimming test (FST), and tail suspension test (TST) were used to evaluate the antidepressant activity of α-pinene in mice. Also, serum samples were taken to determine the antioxidant activity.

Results: According to the results, α-pinene (0.5 and 1 mg/kg) significantly increased activity in OFT and staying on the rotarod ($P \leq 0.05$). Also, α-pinene (0.5 and 1 mg/kg) diminished immobility time (s) in TST and FST on postpartum mice ($P \leq 0.05$). α-pinene (0.5 and 1 mg/kg) decreased malondialdehyde while increased glutathione peroxidase, superoxide dismutase, and total antioxidant status levels in postpartum mice as compared with the control group ($P \leq 0.05$).

Conclusion: It seems that prenatal administration of the α-pinene can alleviate postpartum depression via its antioxidant property in mice.

Keywords: Antidepressant, α-pinene, Mice, Pregnancy

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1. Introduction

Postpartum depression (PPD) is a subtype of major depressive disorder (MDD) that has been used to describe a wide variety of childbearing-related mood episodes which happens before and extends after the postpartum, according to the diagnostic and statistical manual of mental disorders, the fourth edition (DSM-IV), PPD leads to physiological and emotional changes in maternal organisms. PPD adversely affects mothers and infants (Liu et al., 2020). Committing infanticide and baby abuse in severe situations are frequently seen in PPD patients. Based on several studies on neurobiological events responsible for PPD, it is assumed that fluctuation of ovarian hormones, decreased brain-derived neurotrophic factor (BDNF), and immune response are the main factors for the pathophysiology of PPD (Hing et al., 2018). Even though several treatment options have been introduced for PPD, more than 30% of the patients do not respond to therapy. Potential antidepressants are the first line for treating PPD, but many have no clinical effectiveness. So, there is an urgent need for more efficacious and novel treatments (Belzung, 2014).

α-pinene ($C_{10}H_{16}$) is a natural terpenoid (Kumar et al., 2019), and its safety has been approved (Ueno et al., 2020). It has fungicidal, antibacterial, anticancer, and anti-nociceptive pharmacological properties, positively affecting the central nervous system (CNS) . It has anti-nociceptive role on pulpal pain (Rahbar et al., 2019). α-pinene decreases psychiatric-like behavior (Ueno et al., 2019); however, there is limited information about its antidepressant property. Also, the hippocampus levels of the brain-derived neurotrophic factor (BDNF) increase after α-pinene administration (Kasuya et al., 2015) in patients with epilepsy and neuroprotective activity (Ueno et al., 2020). α-pinene (2-200 mg/L) decreases serum malondialdehyde (MDA) and improves catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione reductase levels (Türkez & Aydın, 2016). MDD increases the formation of free radicals, and pretreatment with α-pineneis beneficial against this side effect (Liu et al., 2020). Also, behavioral changes are the main characteristics of MDD patients (Belzung, 2014).

Animal models have several benefits and help understand better scientific processes. Several tests have been used in an animal model of depression anxiety-like behavior, such as the forced swimming test (FST) and tail suspension test (TST). The gold standards for despair testing are the FST when the animal is placed in a water tank, and the TST, where the animal is suspended by its tail, which is most widely preferred in basic research of depression. PPD animals usually have no interest in their surroundings, and these tests are reliable for determining the antidepressant activity of new medications (Demin et al., 2019). Thus, this research investigated the antidepressant and antioxidant effects of α-pinene exposure during pregnancy in postpartum mice.

2. Materials and Methods

Study animals

Sixteen NMRI male mice caged with 40 fertile female mice were kept in laboratory conditions, with free access to chow pellet and freshwater. Female mice were examined for the presence of sperm or vaginal plug as an indication of pregnancy. Then, they were randomly assigned into four groups (n=10 in each group). In the control group, mice were injected IP with saline on the 5, 8, 11, 14, and 17 of the gestational day (GD). In groups 2 to 4, mice were injected with α-pinene (0.1, 0.5, and 1 mg/kg IP, respectively) on GD 5, 8, 11, 14, and 17. The study procedure is shown in Figure 1. Level of α-pinene was obtained according to some studies (Porres-Martínez et al., 2015; Türkez & Aydın, 2016). Following delivery, antidepressant-like effects of the α-pinene were determined.

Open field test (OFT)

The open field test (OFT) was done on day 2 postpartum in mice (Craft et al., 2010) with a 45×45×30 cm^3 wooden box. Mice were placed individually at the center of the box, and the number of crossed squares was counted during the final 4 minutes of a 6-minute period (Donato et al., 2015).

Rotarod test

The accelerated rotarod test is a standard sensory-motor test to investigate animals' motor coordination and learning skills by measuring the mouse's ability to stay and run on the accelerated rod. The rotarod test was done on day 2 postpartum at 0–20 rpm for 8 minutes (Craft et al., 2010). The time was recorded when the mouse fell off the rod or started to rotate with the rotarod without running. After an initial training trial, mice were tested for 5 trials over two days. The recovery phase between trials was 10 min. The time was recorded when the mouse fell off the rotarod (Eltokhi et al., 2021).

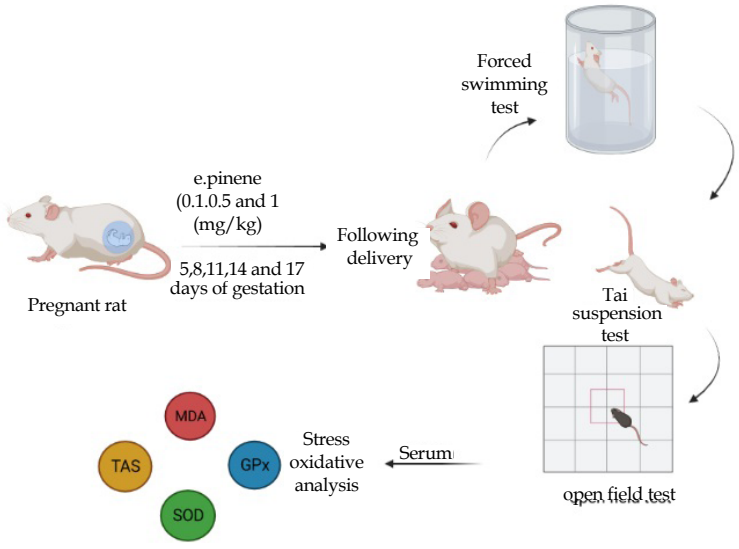

Figure 1. Flowchart of the study procedure

Tail suspension test (TST)

The TST was done on day 2 postpartum (Cryan et al., 2005) based on Steru et al. (1985) and Alimohammadi et al. (2019). Briefly, mice away from the nearest objects were suspended above the floor, and immobility time was monitored for 6 minutes.

Forced swimming test (FST)

The FST was done according to Nasehi et al. (2019). On day 2 postpartum (Craft et al., 2010), mice individually were plunged into a glass cylindrical containing water. Mouse was left in the cylinder, and the duration of immobility in the water was measured during the last 4 minutes of the 6 minutes period.

Antioxidant activity

After determining the behavioral tests, blood samples were taken, and serum MDA, SOD, GPx, and TAS were determined using commercial kits.

Statistical analysis

The obtained data were analyzed using a one-way analysis of variance (ANOVA) and presented as Mean±SE. Tukey HSD determined between-group differences, and $P<0.05$ was considered significant. All tests were performed by SPSS software, version 22 (SPSS Inc., Chicago, IL).

3. Results

According to the results, α-pinene (0.1 mg/kg) had no significant effect on the number of squares crossed in OFT compared to the control group ($P>0.05$). Administration of higher doses of α-pinene (0.5 and 1 mg/kg) during the pregnancy significantly increased the number of squares crossed in OFT on postpartum mice as compared with the control group ($P\leq0.05$) (Figure 2).

As observed, α-pinene (0.1 mg/kg) did not affect time spent on rotarod compared to the control group ($P>0.05$). Administration of the higher doses of the α-pinene (0.5 and 1 mg/kg) significantly increased the time spent on the rotarod compared with control mice ($P\leq0.05$) (Figure 3).

As shown in Figure 4, administration of the α-pinene (0.1 mg/kg) had no significant effect on immobility time compared to control mice ($P>0.05$). Higher doses of α-pinene (0.5 and 1 mg/kg) significantly decreased immobility time (s) in TST on postpartum mice ($P\leq0.05$).

As seen in Figure 5, administration of a low dose of α-pinene (0.1 mg/kg) during pregnancy had no significant effect on immobility time compared to the control group ($P>0.05$). Administration of higher doses of the α-pinene (0.5 and 1 mg/kg) significantly decreased immobility time (s) in FST on postpartum mice as compared with the control group ($P\leq0.05$).

Results for exposure to α-pinene during pregnancy on serum values of MDA, SOD, GPx, and TAS in postpar-

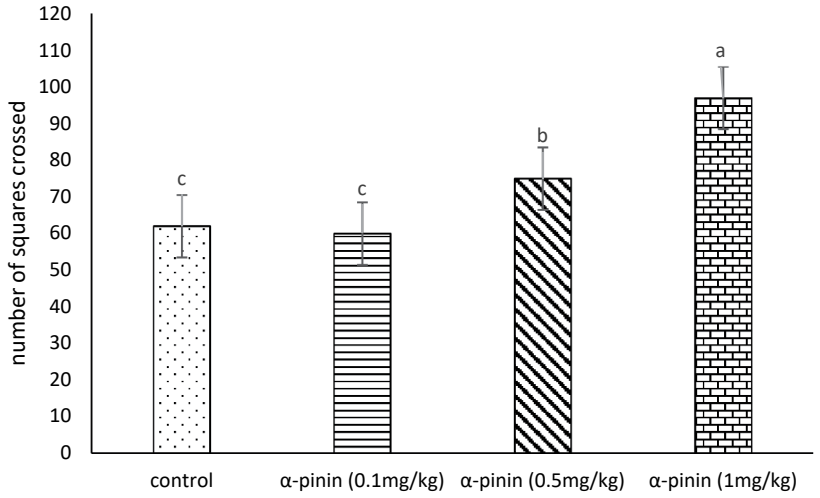

Figure 2. Effect of exposure to different doses of α-pinene during pregnancy on the number of squares crossed in the OFT on postpartum mice (n=10)

Significant differences exist between groups with different superscripts (a, b, and c, P≤0.05).

tum mice are presented in Table 1. As seen, administration of the α-pinene (0.1 mg/kg) had no significant effect on serum antioxidants in postpartum mice (P>0.05). Administration of higher doses of the α-pinene (0.5 and 1 mg/kg) significantly decreased MDA while increasing SOD, GPx, and TAS levels in postpartum mice compared with the control mice (P≤0.05).

4. Discussion

Postpartum depression is seen frequently after parturition (Liu et al., 2020, Leuner et al., 2021). In our findings, α-pinene (0.5 and 1 mg/kg) improved the number of squares crossed in OFT and spending time on the rotarod. Ueno et al. (2019) reported that pre-exposure to α-pinene did not affect the activity, but α-pinene decreased activity in the locomotor activity test. However, in the OFT, pre-exposure to α-pinene have no effect on activity in mice (Ueno et al., 2019). The differences might have been related to animal species, administering method, concentration, and time.

Based on our findings, 0.5 and 1 mg/kg of the α-pinene reduced immobility time in TST and FST in postpartum mice. Ueno et al. (2019) reported that inhalation of α-pinene decreased hyperactivity and anxiety-like behaviors and influenced the activation of astrocytes induced by dizocilpine in mice. Kong et al. (2017) found that inhalation of α-pinene attenuated depressive-like behavior using FST in rats. It is reported that α-pinene

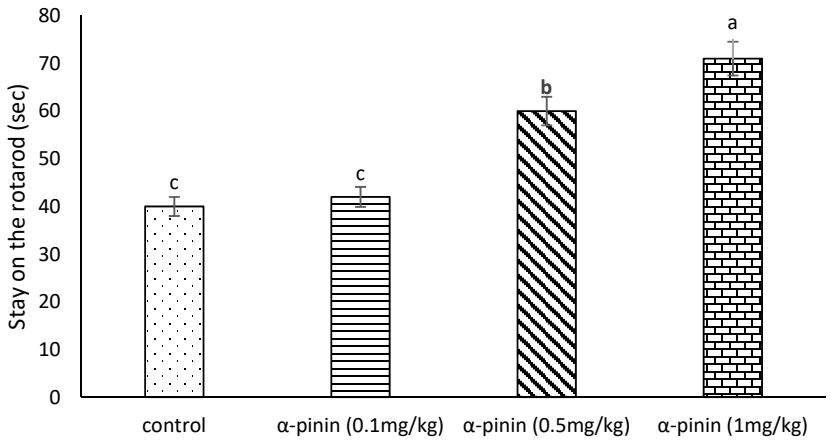

Figure 3. Effect of exposure to different doses of α-pinene during pregnancy on staying on the rotarod (s) on postpartum mice (n=10)

Significant differences exist between groups with different superscripts (a, b, and c, P≤0.05).

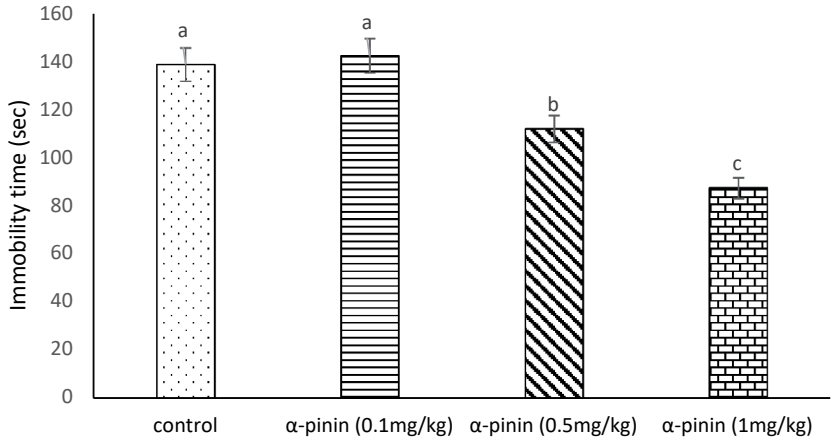

Figure 4. Effect of exposure to different doses of α-pinene during pregnancy on immobility time (s) in TST on postpartum mice (n=10)

Significant differences exist between groups with different superscripts (a, b, and c), P≤0.05.

decreased the beta-amyloid-induced depressive behavior in rats and inhibited neuronal loss (Khan-Mohammadi-Khorrami et al., 2020). Immobility time in TST and FST reminds you of despair and mental depression, similar to depression in humans (Walia & Gilhotra, 2016). However, these tests have priority over each other. Also, differences in neurochemical pathways have been reported for FST and TST (Walia & Gilhotra, 2016). For example, TST, compared to FST, does not induce hypothermia by immersion in water (Cryan et al., 2005). The current study observed a similar immobility time using 0.1 mg/kg of α-pinene (139.21 s) compared to the control group (141.31 s). Also, a significant decrease in immobility time was seen by α-pinene (0.5 and 1 mg/kg) (112.32 and 88.76 s), respectively. Interestingly, immobility time in FST decreased by 0.1 mg/kg using α-pinene (176.34 s) compared to the control group (152.11 s), but the difference was not significant. A similar procedure on reduction in immobility time was also seen between α-pinene 0.5 and 1 mg/kg (120.11 vs 102.65 s) using FST. The forced swimming test is reliable because of its sensitivity and predictive validity for determining depression in rodents (Cryan et al., 2005), while TST is also preferred (Cryan et al., 2005). Amplified immobility time is related to depressive-like behavior in these tests (Alimohammadi et al., 2019). Therefore, to evaluate the antidepressant activity in mice, both FST and TST methods were performed. OFT is a useful method to determine spontaneous animal activity and anxiety-like behavior.

For evaluating the antidepressant effect of *S. multicaulis* essential oil (containing 28.10% α-pinene and 2.80% β-pinene) using FST (Lin et al., 2015), findings revealed that it has an intense antidepressant activity.

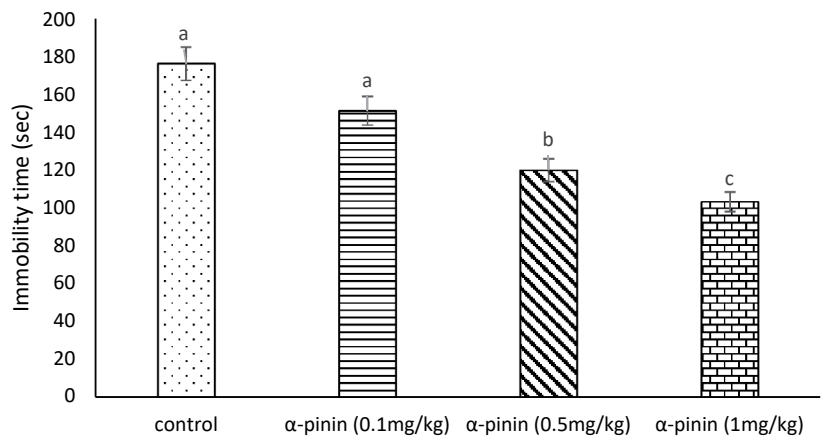

Figure 5. Effect of exposure to different doses of α-pinene during pregnancy on immobility time (s) in FST on postpartum mice (n=10)

Significant differences exist between groups with different superscripts (a, b, and c, P≤0.05).

Table 1. Effect of exposure to different doses of α-pinene during pregnancy on serum values of malondialdehyde, superoxide dismutase, glutathione peroxidase, and total antioxidant status in postpartum mice (n=10)

Group	Mean±SE			
	MDA (nmol/mL)	SOD (IU/mL)	GPx (IU/mL)	TAS (nmol/mL)
Control	15.25±0.22[a]	18.53±0.31[c]	10.22±2.24[c]	4.34±1.52[c]
α-pinene (0.1 mg/kg)	15.34±0.34[a]	18.41±0.41[c]	10.33±2.12[c]	4.36±1.54[c]
α-pinene (0.5 mg/kg)	13.03±0.41[b]	23.30±0.48[b]	11.25±2.31[b]	5.33±1.41[b]
α-pinene (1 mg/kg)	12.31±0.31[c]	28.51±0.42[a]	13.41±3.34[a]	6.35±1.35[a]

Abbreviations: MDA: Malondialdehyde; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; TAS: Total antioxidant status. [a, b, c]Significant differences between treatments (P<0.05).

These behavioral effects were similar to antidepressant drugs. Also, the administration of α-pinene decreases spontaneous activity in rats (Zamyad et al., 2016). The TST has similar limitations to the FST, including a false positive response to psychostimulants and acute drug response. The high reliability of the FST and TST has also contributed to their use, and they are both considered useful for investigating differences between strains in reactivity to stress (Slattery et al., 2012). The FST and TST do not reproduce the pathophysiology of depression. Still, they are useful in that they induce changes that are sensitive to therapeutic agents in a manner predictive of their effects in humans.

It is well known that the glutamatergic system contributes to the pathophysiology of depression. The N-methyl-D-aspartate (NMDA) receptor antagonist (MK-801) has shown an antidepressant effect in mice (Hajialyani et al., 2019). However, Ueno et al. (2019) reported MK-801 administered mice had no anti-depressive behavior. However, the current study was not done on chronic stress. α-pinene upsurges BDNF gene expression, as this factor increases survival and neurogenesis (Hajialyani et al., 2019). Observed differences might have been related to animal species, methods of administering α-pinene, and its concentration. α-pinene (2 and 4 mg/kg) decreases anxiety responses similar to diazepam in male rats by binding to the benzodiazepines position in γ-Aminobutyric acid type A ($GABA_A$) receptors (Saeedipour & Rafieirad, 2020). Essential oil of *S. miltiorrhiza* (containing 28.10% α-pinene and 2.80% β-pinene) improves intracellular chloride concentration, which is a reason for the role of the GABAergic mechanism on its anxiolytic effects (Liu et al., 2020). α-pinene increases postsynaptic Cl^- flow in $GABA_A$ receptors and hinders the activity of the NMDA receptors. The detailed mechanism of α-pinene acting on astrocytes has remained unknown, but it may affect the astrocyte NMDA receptor (Ueno et al., 2019). It is reported that the hypnotic effects of α-pinene are completely blocked by flumazenil (antagonist of the $GABA_A$ receptors). As GABA is an inhibitory neurotransmitter and $GABA_A$ receptors have a key role in minimizing neuronal activity, it seems that antidepressant activity of the α-pinene mediates via this mechanism. However, based on imitation of the current study, we could not determine the possible antidepressant activity of the α-pinene on NMDA and $GABA_A$ receptors in postpartum mice.

Nitric oxide is a major inflammatory mediator and plays a role in oxidant and depression, and α-pinene decreases nitric oxide production and inhibits interleukin-1-beta (IL-1β)-induced NF-κB (Rufino et al., 2014). α-pinene inhibited UVA-induced activation of pro-angiogenic (iNOS and VEGF), inflammatory proteins (TNF-α, IL-6, and COX-2) as well as apoptotic mediators (Bax, Bcl-2, caspase-3 and caspase 9) expression and prevented the activation of NF-κB in the mouse skin (Karthikeyan et al., 2019).

Some studies demonstrate that oxidative stress may play a role in the pathogenesis of depression. As observed, α-pinene reduced MDA while amplifying GPx, SOD, and TAS levels in postpartum mice. Similarly, Saeedipour and Rafieirad (2020) reported that α-pinene (2 and 4 mg/kg) declined MDA and increased thiol and GPx activity. Oxidative stress plays an important role in the pathogenesis of depression. The lowest antioxidant activity and highest neuro-inflammation were seen in people with depression (Moghadam, 2016). Thus, administering antioxidants is useful for treating depression (Asadi et al., 2020). Terpenes are low molecular weight compounds and high lipophilicity permeable to the blood-brain barrier (Ghosh et al., 2021). Inhaled α-pinene can cross the blood-brain barrier and have an anxiolytic effect in mice (Villareal et al., 2017). α-pinene increased

antioxidant levels and inhibited apoptosis (Porres-Martínez et al., 2015). Goudarzi & Rafieirad (2017) reported lipid peroxidation diminished following α-pinene treatment in Parkinson suffering mice. It inhibits reactive oxygen species (ROS) generation and lipid peroxidation and prevents cell damage. Antioxidants have a key role as antidepressants in treating depression (Karthikeyan et al., 2018). α-pinene decreases ROS synthesis and lipid peroxidation and increases antioxidant activity which protects cell morphology (Porres-Martínez et al., 2015). Türkez & Aydin (2016) reported α-pinene (200 mg/L) decreased cell viability but at 25 and 50 mg/L increased in TAS on human lymphocytes without mutagenic effects which that α-pinene is a source of natural antioxidant with beneficial health effects (Asadi et al., 2020).

So far, only a handful of studies have evaluated the role played by antioxidants in depressive symptoms or depression (Beydoun et al., 2013). A relationship was reported between the serum total antioxidant capacity and postpartum depression (Alamolhoda et al., 2020). MDA is the main reflecting factor during PPD. Depressive symptoms caused by stressors trigger oxidative stress, which causes reduced concentrations of antioxidants (Beydoun et al., 2013). The biological mechanism between antioxidant status and depression is that the brain is susceptible to oxidative stress due to high oxygen consumption and self-perpetuating damage from neurotoxic cellular injury. The increase in lipid peroxidation affects proteins disrupting transmembrane ion movements, cellular metabolic processes, and brain synaptic function (Beydoun et al., 2013). Also, oxidative stress leads to an autoimmune response. In severe conditions, oxidative stress decreases membrane fluidity and the inactivation of enzymes, ion channels, and receptors. As a result, alterations in neurotransmission, neuronal function, and general brain activity (Beydoun et al., 2013). Perhaps some of the observed effects of the α-pinene are mediated via these mechanisms. However, further research is suggested to determine these mechanisms' cellular and molecular accuracy.

5. Conclusion

Based on study limitations, we could not determine nitric oxide or inflammatory and apoptotic mediators' levels in postpartum mice. Also, we could not perform the histological evaluation or brain oxidation status following postpartum in mice. Determining the histological effects of the α-pinene in the brain would be helpful.

Ethical Considerations

Compliance with ethical guidelines

This study is approved by Ethic Committee of Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University (Code: IR.IAU.SRB.REC. 1399.182; 2020.02.28).

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Authors' contributions

Experimental procedur and draft the manuscript: Ali Elahiniya; Supervison: Shahin Hassanpour and Ahmad Asghari. Study design and final approval: Shahin Hassanpour; Thesis advisor: Ehsan Khaksar:

Conflict of interest

The authors declared no conflict of interest.

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مقاله پژوهشی

اثرات قرار گرفتن در معرض آلفا پینن در دوران بارداری بر رفتار ضد افسردگی متعاقب زایمان در موش

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چکیده

زمینه مطالعه: افسردگی پس از زایمان مهم ترین مشکل فیزیولوژیکی است و تلاش های زیادی برای تعیین وقایع فیزیولوژیکی دخیل در بروز آن انجام شده است. مونوترپن‌های طبیعی مانند آلفا پینن دارای فواید متعددی هستند و مطالعات کمی در خصوص اثرات ضد افسردگی آلفا پینن در افسردگی پس از زایمان انجام شده است.

هدف: این مطالعه با هدف تعیین اثرات مواجهه با آلفا پینن در دوران بارداری بر رفتار شبه ضد افسردگی پس از زایمان در موش انجام شد.

روش کار: موش‌های ماده آبسنن به طور تصادفی در چهار گروه قرار گرفتند. در گروه شاهد، به موش‌های آبستن سالین در روزهای ۵، ۸، ۱۱، ۱۴ و ۱۷ آبستنی تزریق شد. در گروه های ۲-۴، موش های ماده آبستن آلفا پینن (۰/۱، ۱/۵ و ۱ میلی‌گرم بر کیلوگرم) را در روزهای ۵، ۸، ۱۱، ۱۴ و ۱۷ آبستنی دریافت کردند. در روز دوم پس از زایمان، تست های میدان باز ، روتاورد، تست شنای اجباری و تست تعلیق دم برای ارزیابی فعالیت ضد افسردگی شبه افسردگی آلفا پینن استفاده شد. همچنین نمونه های سرمی برای تعیین فعالیت آنتی اکسیدانی گرفته شد.

نتایج: با توجه به نتایج، آلفا پینن (۰/۵ و ۱ میلی‌گرم) بطور معنی داری تعداد مربع‌های متقاطع شده در تست میدان باز و زمان ماندن در روتاورد را پس از زایمان فزایش داد ($P<0/05$). همچنین، آلفا پینن (۰/۵ و ۱ میلی گرم) به طور معنی‌داری زمان بی‌حرکتی در تست‌های شنای اجباری و تعلیق دم را متعاقب زایمان در موش‌ها کاهش داد ($P<0/05$). چنین، آلفا پینن (۰/۵ و ۱ میلی‌گرم) طور قابل توجهی مالون دی آلدئیدرا کاهش داد در حالی که سطح گلوتاتیون پراکسیداز، سوپراکسید دیسموتاز و وضعیت آنتی اکسیدانی کل را در موش های پس از زایمان در مقایسه با گروه کنترل افزایش داد ($P<0/05$).

نتیجه‌گیری نهایی: به نظر میرسد تجویز آلفا پینن در دروان آبستنی میتواند موجب تقلیل افسردگی متعاقب زایمان از طریق اثرات آنتی اکسیدانی در آن انجام شود.

کلیدواژه‌ها: آبستنی، آلفا پینن ، موش، ضد افسردگی

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