DOI: 10.22059/IJVM.2022.341647.1005263 Iranian Journal of Veterinary Medicine Original Article

Online ISSN: 2252-0554

Effects of *α*-pinene Administration Throughout Pregnancy On Depressive-like Behavior Following Delivery In Mice

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ABSTRACT

BACKGROUND: Parturition depression is important physiological problem and several attempts have been done to determine its physiological phenomenon. Natural monoterpenes like *α*-pinene have numerous beneficial activity and lack of studies have been done on its antidepressant potential in postpartum animals.

OBJECTIVES: this study aimed to determine effects of prenatal administration of *α*-pinene on antidepressant-like behavior following delivery in mice.

METHODS: Pregnant female mice were randomly assigned into four groups. In control group, animal was kept as control and injected with saline at 5, 8, 11, 14 and 17 of gestation

day (GD). In groups 2-4, female pregnant mice were injected with α-pinene (0.1, 0.5, and 1 mg/kg) at GD 5, 8, 11, 14 and 17, respectively. On day 2 postpartum, open field (OFT), rotarod, forced swimming test (FST) and tail suspension test (TST) were used to evaluate antidepressant activity of α-pinene. Also, serum samples were taken to determine anti-oxidant activity.

RESULTS: According to the results, α-pinene (0.5 and 1 mg/kg) significantly increased activity in OFT and stay on rotarod (P≤0.05). Exposure to α-pinene during pregnancy increased time spend on rotarod (P≤0.05). Also, α-pinene (0.5 and 1 mg/kg) diminished immobility time (s) in TST and FST on postpartum mice (*P*≤0.05). α-pinene (0.5 and 1 mg/kg) decreased Malondialdehyde (MDA) while increased glutathione peroxidase (GPx), superoxide dismutase (SOD) and total antioxidant status (TAS) levels in postpartum mice as compared with control group (*P*≤0.05).

CONCLUSIONS: It seems prenatal administration of the α-pinene can alleviate post-partum depression via its antioxidant property in mice.

Keywords: Antidepressant, α-pinene, Mice, Pregnancy

Introduction

Postpartum depression (PPD) is a subtype of major depressive disorder (MDD) which has been used to describe a broad variety of childbearing-related mood episodes which happens prior and extends after the postpartum, according to Diagnostic and Statistical Manual (DSM-IV). The PPD leads to physiological and emotional changes in maternal organisms. PPD has adverse effects on both mothers and their infants owing (Liu *et al.,* 2020**). In severe situations, commit infanticide and baby abuse are frequently seen in PPD patients. Despite several researches have been done on neurobiological events responsible for PPD, it is assumed fluctuation of ovarian hormones, decreased brain-derived neurotrophic factor (BDNF) and immune response are the main factors for pathophysiology of the PPD (**Hing *et al.,* 2018**). Even though several treatment options**

introduced for PPD, but more than 30 percent of the patients do not respond to therapy. On the other hand, potential antidepressants are the first line for treatment of the PPD but the vast majority have not clinical efficacy. So, there is an urgent need for more efficacious and novel-acting treatments (Belzung, 2014**).**

α-pinene ($C_{10}H_{16}$) is a nature terpenoid (Kumar *et al.,* 2019) and its safety was approved (Ueno *et al.,* 2020). α-pinene has fungicidal, antibacterial, anticancer and anti-nociceptive pharmacological properties with positive effects on the central nervous system (CNS) (Yang *et al.,* 2016). 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 limit information about its anti-depressant property. Also, hippocampus levels of the brain-derived neurotrophic factor (BDNF) increase following α-pinene administration (Kasuya *et al.,* 2015) with neuroprotective activity in patients with epilepsy (Ueno *et al.,* 2020). α-pinene at dosage of the 2-200 mg/L decreased serum malondialdehyde (MDA) and improved catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase levels (Türkez and Aydın, 2016). **MDD** increases formation of free radicals and pretreatment with α-pinene is beneficial against this side effect **(**Liu *et al.,* 2020**). Also, behavioral changes are the main characteristics of the MDD patients (**Belzung, 2014**).**

Animal models have several benefits which they may enable a better understanding of scientific processes. Several tests have been used in animal model of depression anxiety-like behavior such as FST and 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 are most widely **preferred** in basic research of depression. PPD animals are usually **lack of interest in the surroundings and these tests are reliable for determining antidepressant activity of new medications** (Demin *et al.,* 2019). **Thus, this research was done to investigate antidepressant and antioxidant effects of the α-pinene exposure during pregnancy in postpartum mice.**

Material and Methods

Animals

Sixteen NMRI male caged with fertile male forty female mice were kept at laboratory conditions with free access to chow pellet and fresh water [Ethics Committee code (IR.IAU.SRB.REC. 1399.182; 2020.02.28)]. Female mice examined for presence of the sperm or vaginal plug as indication of pregnancy. Then were randomly assigned into four groups (n = 10). In control group, mice i.p. injected with saline at 5, 8, 11, 14 and 17 of GD. In groups 2-4, mice were i.p. injected with α-pinene (0.1, 0.5, and 1 mg/kg) at GD 5, 8, 11, 14 and 17. Study procedure is shown in figure 1. Level of α-pinene was obtained according to reports (Porres-Martínez *et al.,* 2015; Yang *et al.,* 2016, Türkez and Aydın, 2016). Following delivery, **antidepressant-like effects of the α-pinene were determined.**

Open Field Test (OFT)

The OFT was done on day 2 postpartum in mice (Craft *et al.,* 2010) by a 45×45×30 cm^3 wooden box. Mice was placed individually at the center of the box and number of crossed squares were counted during at final 4 minutes of a 6 minutes' 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 through measuring the ability of the mice 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). When mice were fell off the rod or started to rotate with the rotarod without running, the time was recorded. After an initial training trial, mice were tested for 5 trials over two days. The recovery phase between trials was 10 min When mice were fell off the rotarod, the time was recorded (Eltokhi *et al.,* 2021).

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 were away from nearest objects were suspended above the floor and immobility time was monitored during a 6 minutes' period.

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 in glass cylindrical containing water. Mouse was left in the

cylinder and 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

Data were analyzed using one-way analysis of variance (ANOVA) and shown in the mean ± standard error (SE). Between group differences determined by Tukey HSD and $P< 0.05$ considered as significant differences.

Results

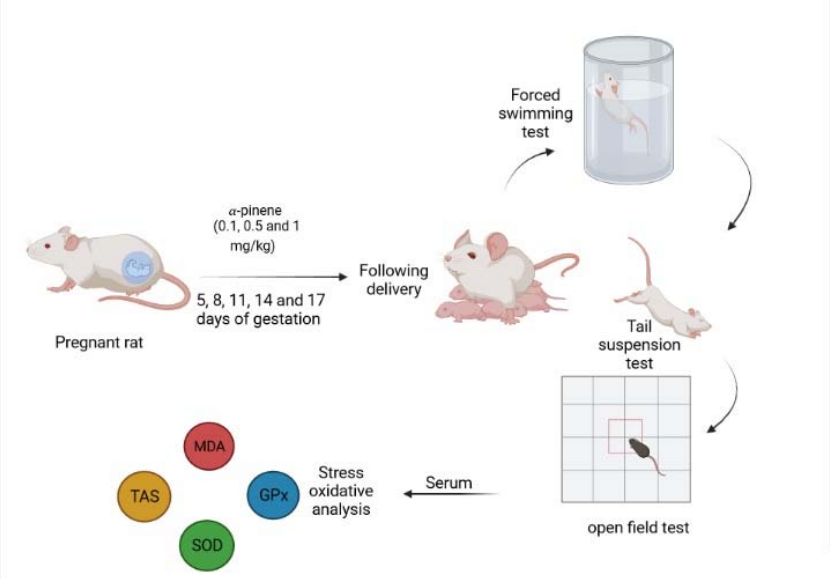

Figure 1. flow chart of study procedure

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

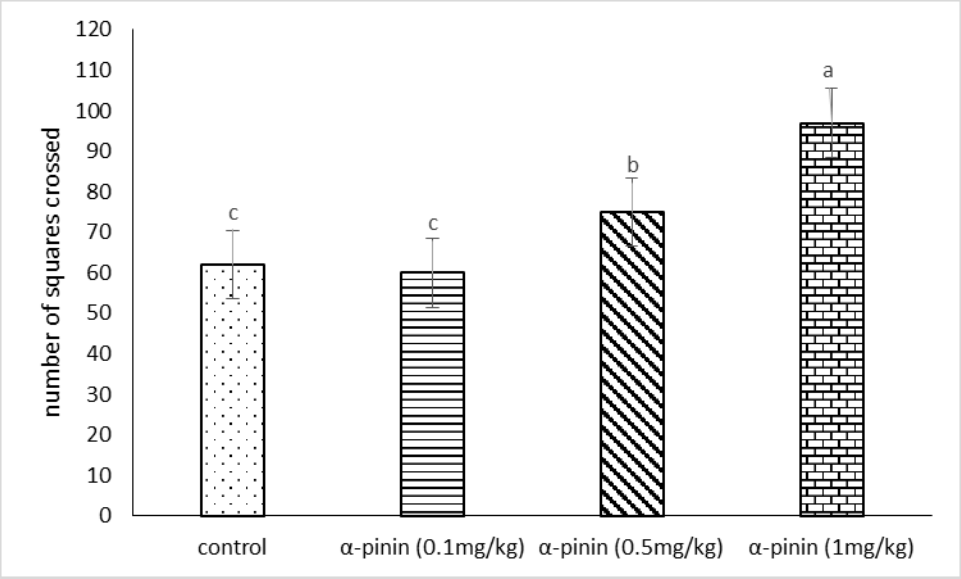

Figure 2. Effect of exposure to different levels of α-pinene during pregnancy on number of squares crossed in open field test (OFT) on postpartum mice (n=10). There are significant differences between groups with different superscripts (a, b and c; $P \leq 0.05$).

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As observed, *α*-pinene (0.1 mg/kg) had no effect on time spend on rotarod compared to control group (P>0.05). Administration of the different levels of the *α*-pinene (0.5 and 1 mg/kg) significantly increased time spend on rotarod comparing with control mice (*P*≤0.05) (figure 3).

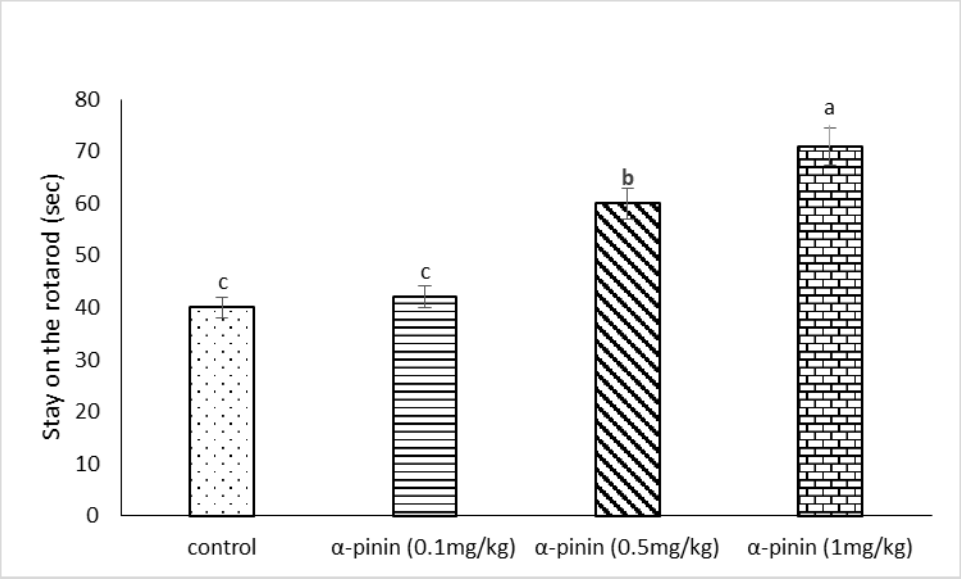

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Figure 3. Effect of exposure to different levels of α-pinene during pregnancy on stay on the rotarod (sec) on postpartum mice (n=10). There are significant differences between groups with different superscripts (a, b and c; P ≤ 0.05).

As shown in figure 4, administration of the *α*-pinene (0.1 mg/kg) had no significant effect on immobility time comparing to control mice (*P*>0.05). *α*-pinene (0.5 and 1 mg/kg) significantly decreased immobility time (S) in TST on postpartum mice (*P*≤0.05).

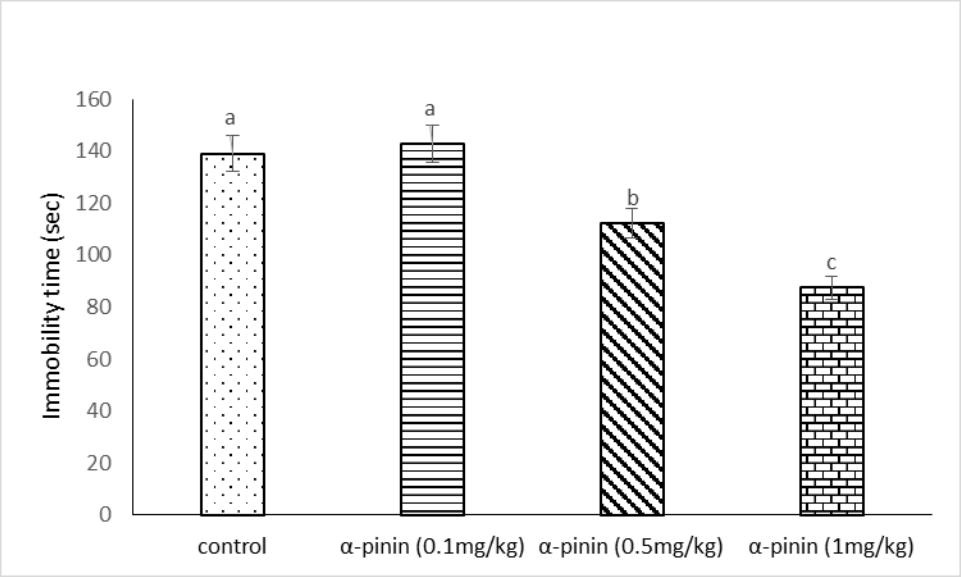

Figure 4. Effect of exposure to different levels of α-pinene during pregnancy on immobility time (sec) in tail suspension test (TST) on postpartum mice (n=10). There are significant differences between groups with different superscripts (a, b and c; P ≤ 0.05).

As seen in figure 5, administration of the *α*-pinene (0.1 mg/kg) during pregnancy no significant effect on immobility time in comparison to control group (*P*>0.05). Administration of the different levels of the *α*-pinene (0.5 and 1 mg/kg) significantly decreased immobility time (s) in FST on postpartum mice as compared with group (*P*≤0.05).

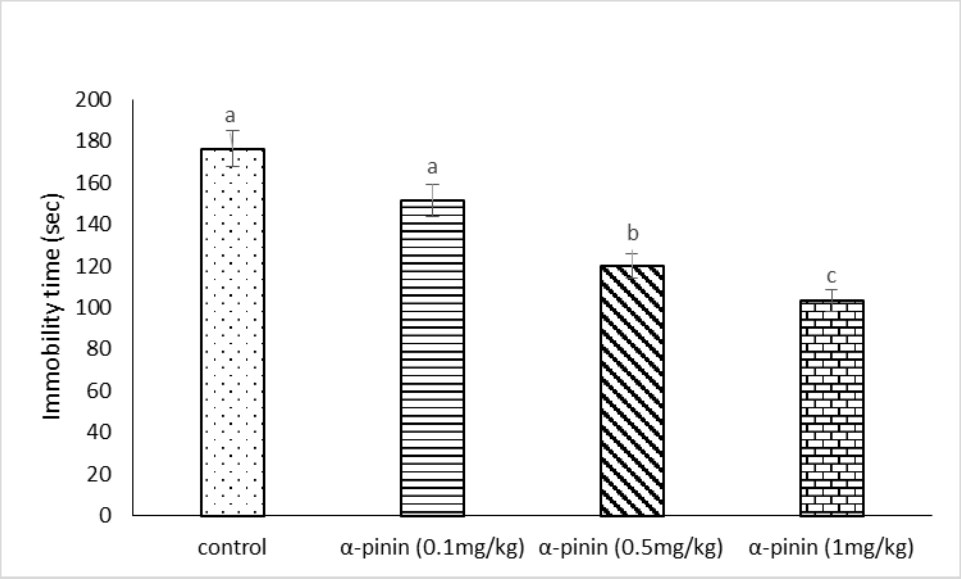

Figure 5. Effect of exposure to different levels of α-pinene during pregnancy on immobility time (sec) in forced swimming test (FST) on postpartum mice (n=10). There are significant differences between groups with different superscripts (a, b and c; $P \leq 0.05$).

Results for exposure to α-pinene during pregnancy on serum values of MDA, SOD, GPx and TAS in postpartum mice is presented in table. As seen, administration of the *α*-pinene (0.1 mg/kg) had no significant effect on serum antioxidants on postpartum mice (*P*>0.05). Administration of the different levels of the *α*-pinene (0.5 and 1 mg/kg) significantly decreased MDA while increased SOD, GPx and TAS levels in postpartum mice comparing with control mice (*P*≤0.05).

Table. Effect of exposure to different levels of α-pinene during pregnancy on serum values of Malondialdehyde, Superoxide dismutase, Glutathione peroxidase and total antioxidant status in postpartum mice (n=10).

Group	**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]

MDA: malondialdehyde, SOD: superoxide dismutase, GPx: glutathione peroxidase, TAS: total antioxidant status. Different

letters (a-c) indicate significant differences between treatments (P<0.05).

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 number of squares crossed in OFT and spending time on rotarod.** Ueno *et al.,* (2019) reported pre-exposed to ***α*-pinene had no effect on activity, but, *α*-pinene decreased activity in the locomotor activity test. However, in the OFT, pre-exposed to *α*-pinene have no effect on activity in mice (**Ueno *et al.,* 2019**). Observed dissimilarities might have related to animal species, administering method and concentration as well as the 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 inhalation of *α*-pinene decreased hyperactivity and anxiety-like behaviors and influence 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 *α*-pinene decreased the beta-amyloid-induced depressive behavior in rats and inhibited the neuronal loss (**Khan-Mohammadi-Khorrami *et al.,* 2020**). Immobility time in TST and FST remind you of a state of despair and mental depression which is similar to depression in human (**Walia and Gilhotra, 2016**). However, these tests have priority to each other. Also, differences on neurochemical pathways have been reported for FST and TST (**Walia and Gilhotra, 2016**). For example, TST compared to FST does not induce hypothermia by immersion in water (**Cryan *et al.,* 2005**). In the current study, similar immobility time was observed using *α*-pinene (0.1 mg/kg) (139.21s) compared to control group (141.31 s). Also, a significant decrease on 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 of using *α*-pinene (176.34 s) compared to control group (152.11 s), but the change was not significant. Additionally, similar procedure on reduction in immobility time was seen between *α*-pinene 0.5 and 1 mg/kg (120.11 v.s. 102.65 s) using FST.** FST is reliable method because of 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 animal spontaneous 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 it has an intense antidepressant activity. These behavioral effects were very similar to antidepressant drugs (**Bagci *et al.,* 2019**). Also, 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 but 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 glutamatergic system play role in the pathophysiology of depression. NMDA receptor antagonist (MK-801) has shown antidepressant effect in mice (Sanat *et al.,* 2008**). However,** Ueno *et al.,* (2019) **was reported MK-801 administered mice had no anti-depressive behavior. However current study was not done in the condition of chronic stress.** *α*-pinene upsurge BDNF gene expression, as these factor increases survival and neurogenesis (Hajialyani *et al.,* 2019). **Observed differences might have related to animal species, methods of administering *α*-pinene and concentration of administration. *α*-pinene (2 and 4 mg/kg) decreased anxiety responses similar to diazepam in male rats by binding to the benzodiazepines** position **in $GABA_A$ receptors (**Saeedipour and Rafieirad, **2020).** Essential oil of *S. miltiorrhiza* **(containing 28.10 % *α*-pinene and 2.80 % *β*-pinene)** improved of intracellular chloride concentration which is a reason for 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 activity of the NMDA receptors (Yang *et al.,* 2016). The detailed mechanism of α-pinene acting on astrocytes remains unknown, but it is possible that it may affect the astrocyte NMDA receptor. (Ueno *et al.,* 2019). It is reported hypnotic effects of *α*-

pinene completely blocked by flumazenil (antagonist of the $GABA_A$ receptors) (Yang *et al.,* 2016). As GABA known as inhibitory neurotransmitter and $GABA_A$ receptors have key role on minimize neuronal activity. It seems antidepressant activity of the *α*-pinene mediates via this mechanism. However, based on imitation of the current study we were not able to determine possible anti-depressant activity of the *α*-pinene on NMDA and $GABA_A$ receptors in postpartum mice.

Nitric oxide is a major inflammatory mediator and plays in oxidant and depression and *α*-pinene decreased nitric oxide production and inhibit 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 demonstrated that oxidative stress may play a role in the pathogenesis of depression. **As observed, *α*-pinene reduced MDA while amplified GPx, SOD and TAS levels in postpartum mice. Similarly, Saeedipour and Rafieirad (2020) reported *α*-pinene (2 and 4 mg/kg) declined MDA and increased thiol and GPx activity. The oxidative stress plays important role in the pathogenesis of depression. The lowest antioxidant activity and highest neuro-inflammation was seen in people with depression (**Ladan, Moghadam**, 2016). Thus, administration of the antioxidants is useful approach to treat depression (**Asadi *et al.,* 2020**). Terpenes are low molecular weight compounds and** high lipophilicity which is **permeable to the blood –brain barrier (**Ghosh *et al.,* 2021**). Inhaled *α*-pinene can across blood-brain-barrier and have anxiolytic effect in mice (**Villareal *et al.,* 2017**).** *α*-pinene increased antioxidant levels and inhibits apoptosis (Porres-Martínez *et al.,* 2015). Goudarzi and 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 damages. Antioxidants have key role as antidepressants in the treatment of depression (Karthikeyan *et al.,* 2018). *α*-pinene decrease ROS synthesis and lipid peroxidation and increase antioxidant activity which protects cell morphology (Porres-Martínez *et al.,* 2015). Türkez and Aydin (2016) reported *α*-pinene (at 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**).** To date, only a handful of studies have evaluated the role played by antioxidants in depressive symptoms or depression (Beydoun *et al.,* 2013). A relationship 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 in turn causes reduced concentrations of antioxidants (Beydoun *et al.,* 2013). The biological mechanisms between antioxidant status and depression is that 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 and cellular metabolic processes brain synaptic function (Beydoun *et al.,* 2013). Also, oxidative stress leads to autoimmune response. In severe condition, oxidative stress leads to a decrease in membrane fluidity, an inactivation of enzymes, ion channels and receptors, and as a result, alterations of neurotransmission, neuronal function and general brain activity (Beydoun *et al.,* 2013). Perhaps some of the observed effects of the α-pinene is mediated via these mechanisms. However, further researches is suggested to determine cellular and molecular accuracy of these mechanisms.

Conclusion

However, based on limitations we were not able to determine nitric oxide or inflammatory and apoptotic mediators' level in postpartum mice. Also, we were not able to determine histological evaluation or determination brain oxidation status following postpartum in mice. It would be helpful to determine histological effects of the **α-pinene in the brain.**

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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 5، 8، 11، 14 و 17 آبستنی تزریق شد. در گروه های 2-4، موش های ماده آبستن آلفا پینن (0/1، 1/5 و 1 میلی گرم بر کیلوگرم) را در روزهای 5، 8، 11، 14 و 17 آبستنی دریافت کردند. در روز دوم پس از زایمان، تست های میدان باز ، روتارود، 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 (0/5 و 1 میلی گرم) بطور معنی داری تعداد مربع‌های متقاطع شده در تست میدان باز و زمان ماندن در روتارود را پس از زایمان فزایش داد (P< 0/05). همچنین، آلفا پینن (0/5 و 1 میلی گرم) به طور معنی‌داری زمان بی‌حرکتی در تست های شنای اجباری و تعلیق دم را متعاقب زایمان در موش‌ها کاهش داد (P< 0/05). چنین، آلفا پینن (0/5 و 1 میلی گرم) 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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