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Research Article

Investigating the Effect of Hydroalcoholic Extract of Parsley Leaves (*Petroselinum crispum*) on Anxiety in Rats Treated with Lead Acetate

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Abstract

Background and aim: Heavy metals such as lead can have negative effects on the nervous system. Anxiety is one of the most common neurological disorders that can be induced under the influence of lead. The purpose of this study was to investigate the protective effect of the hydroalcoholic extract of parsley leaves (*Petroselinum crispum*; HEPL) on anxiety in rats treated with lead acetate.
Materials and Methods: Male rats were divided into 6 groups of 10. The control group did not receive drug treatment, but the sham group animals received 1 ml of distilled water as lead acetate solvent by intraperitoneal injection. The animals of the Lead group received lead acetate at a dose of 20 mg/kg and the animals of the HEPL200 group received HEPL at a dose of 200 mg/kg by intraperitoneal injection. The animals of the Lead+HEPL100 and Lead+HEPL200 groups received lead acetate with a dose of 20 mg/kg as an intraperitoneal injection 2 hours before the intraperitoneal injection of HEPL with a dose of 100 and 200 mg/kg, respectively. The study period in all groups was 21 days. At the end of the study, the open field test was used to measure anxiety behavior including the parameters of Grooming (cleaning the body, face, and legs), Rearing (standing on two rear legs), and Crossing (crossing the lines). Statistical analysis was performed using a one-way analysis of variance and the Tukey post hoc test.
Results: The results of this study showed that there was a significant decrease in the number of Grooming, Rearing, and Crossing in the Lead group compared to the control and control groups ($P<0.05$). In the Lead+HEPL200 group, a significant increase in the number of Grooming, Rearing, and Crossing was observed compared to the Lead group ($P<0.05$).
Conclusion: Lead can cause anxiety behaviors in male rats. However, the administration of HEPL can improve anxiety behaviors in male rats treated with lead acetate.

Keywords: *Lead, Hydroalcoholic extract, Parsley, Anxiety, Rat*

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Introduction

Neurological diseases and disorders are rarely unidimensional or unifactorial. Even those diseases whose etiology appears to be closely related to genetic factors are usually the product of multiple and intertwined risk factors, of which exposure to environmental chemicals may be a component (Weiss *et al.,* 2008). The public health burden of psychiatric disorders such as depression and anxiety is high, with approximately 450 million people worldwide suffering from psychiatric disorders. The term anxiety describes the experience of worry, apprehension, or nervousness associated with physical, cognitive, and behavioral symptoms. Anxiety may occasionally be experienced as part of normal life and maybe adaptive if it increases readiness for new situations. If the anxiety symptoms are persistent, excessive, or dysfunctional, it can cause neurological and psychological disorders (Gale & Millichamp, 2011). Neurotransmitters play an important role in anxiety. One of the most important neurotransmitters is gabargic neurons, which are responsible for anxiety phenomena. Oxidative stress can also be related to anxiety (Ghasemzadeh Dehkordi *et al.,* 2022). Exposure to heavy metals such as lead during pregnancy and infancy causes widespread neurological and psychological effects such as depression, anxiety, mood disorders, schizophrenia, etc (Orisakwe, 2014).

As a potent neurotoxin, lead may affect several cellular functions, including the release of neurotransmitters such as dopamine and serotonin. Lead is a systemic toxic, non-physiological, and non-biodegradable heavy metal found in the environment and used to produce lead-acid batteries, gasoline, water pipes, paint, solder, ceramic glazes, ammunition, etc (Omeiza *et al.,* 2021). Lead can enter different body tissues through dust inhalation, food consumption, and exposure to lead-containing materials (Dignam *et al.,* 2019). Despite extensive studies on the neurological consequences of lead and its compounds, such as lead acetate and lead chloride ($PbCl_2$), the nontoxic exposure threshold for lead is still unknown (Omeiza *et al.,* 2021). Lead enters the systemic circulation through the intestinal mucosa and is distributed in different tissues and organs of the body. It passes through the blood-brain barrier and accumulates in the brain tissue and causes neurological disorders (Gąssowska *et al.,* 2016; Li *et al.,* 2016). Lead can disrupt membrane ion channels and signaling molecules critical to neurotransmission, as well as inhibit endogenous antioxidants, thereby increasing the production of reactive oxygen/nitrogen species, and leading to oxidative stress (Bhat *et al.,* 2015; Ayuso & Foley, 2020).

Medicinal plants can be a sufficient source of new, safe, and effective treatments, especially since many of them show fewer side effects. Several medicinal plants have been studied for depression and anxiety disorders and have shown positive results (Es-Safi *et al.,* 2021).

Parsley (*Petroselinum crispum*) belongs to the Apiaceae family which is used in the food, pharmaceutical, perfume, and cosmetic industries (Lopez *et al.,* 1999). Parsley is scattered in all parts of Iran and is used in traditional medicine to treat many diseases (Ozsoy-Sacan *et al.,* 2006). Parsley has been used as a traditional medicine to treat hyperuricemia and gout in Iran. Phytochemical analysis of this plant has revealed the presence of several classes of flavonoids (Fejes *et al.,* 2000). Flavonols (kaempferol and quercetin) and flavones (apigenin and luteolin), which are found as glycosides in nature, are the main flavonoids in parsley (Peterson *et al.,* 2006). Kaempferol and quercetin, which belong to the flavonol group, have a wide range of biochemical and medicinal effects and are recommended as chemical preventive agents or food supplements. The dominant mechanism of their biological actions is due to antioxidant activity, enzyme inhibition, and free radical scavenging capacity. Therefore, it is hypothesized that the protective and therapeutic effects of parsley may be due to its flavonol compounds (Haidari *et al.,* 2011). Also, studies show that plants of the Apiaceae family have anti-depressant and anti-anxiety activities (Es-Safi *et al.,* 2021). This study aimed to investigate the protective effect of the hydroalcoholic extract of parsley leaves (HEPL) on anxiety in rats treated with lead acetate.

Materials and Methods

Animals

In this experimental study, 60 Wistar rats with an age range of 2.5-3 months and an approximate weight of 180±20 grams were used. The animals were obtained from the Laboratory Animal Breeding Center of the Islamic Azad University, Kazerun Branch, and were kept in polycarbonate cages with dimensions of 30×25×15 cm with a steel mesh roof. Animals were kept under standard conditions of 12 hours light/dark, temperature 22±2°C, and humidity 70%. Rat's food was obtained from Pars Animal and Poultry Company, Iran, and full access to food and water was provided throughout the study. The ethical principles of working with laboratory animals in this study were approved by the ethics committee of the Islamic Azad University of Kazerun under the number IR.IAU.KAU.REC.1400.062.

Animal grouping and study design

Sixty rats were randomly grouped into 6 equal groups after weighing. In the control group, the animals did not receive any drug treatment. In the sham group, the animals received 1 ml of distilled water daily as a lead acetate solvent by intraperitoneal injection. Lead group animals received lead acetate at a dose of 20 mg/kg and HEPL200 group animals received HEPL at a dose of 200 mg/kg intraperitoneally. Animals in the Lead+HEPL100 group received 20 mg/kg lead acetate intraperitoneally 2 hours before receiving HEPL at a dose of 100 mg/kg intraperitoneally. Lead+HEPL200 group animals received 20 mg/kg of lead acetate Sixty rats were randomly grouped into 6 equal groups after weighing. In the control group, the animals did not receive any drug treatment. In the sham group, the animals received 1 ml of distilled water daily as a lead acetate solvent by intraperitoneal injection. Lead group animals received lead acetate at a dose of 20 mg/kg and HEPL200 group animals received HEPL at a dose of 200 mg/kg intraperitoneally. Animals in the Lead+HEPL100 group received 20 mg/kg lead acetate intraperitoneally 2 hours before receiving HEPL at a dose of 100 mg/kg intraperitoneally 2 hours before intraperitoneal administration of HEPL at a dose of 200 mg/kg. The length of the study period in all groups was 21 days. At the end of the study, the open box test was used to check anxiety behaviors. The parameters used in this test included Grooming (cleaning the body, face, and legs), Rearing (standing on two rear legs), and Crossing (crossing the lines).

Preparation method of parsley leaves extract

Parsley plants were bought from farms around Kazerun City. Then, the leaves and stems of the plant were separated and dried, and powdered by scientific method. The resulting powder was placed in a percolator and 70% ethanol was added to it. The resulting mixture was collected as HEPL in a container in the form of a drop for 24 hours. After 24 hours, diluted HEPL was prepared and then dried and concentrated using a rotary machine (Ozsoy-Sacan *et al.,* 2006). The determination of the dose of HEPL for this study was based on previous studies (Takrooni *et al.,* 2019).

Behavioral study
(Open Field Test)

This test was used to measure anxiety-like behavior (Carola *et al.,* 2002). The equipment for this test was a square board with wooden walls measuring 40 x 50 x 50 cm. Each rat was individually placed in the center of one of the open sections. Then the animal started to move in the chamber and for 6 minutes their activity was checked by a video camera. The parameters of this test included the amount of Grooming (cleaning the body, face and legs), Rearing (standing on two rear legs), and Crossing (crossing the lines), which were recorded and measured. After each test, the chamber was disinfected and cleaned with ethanol.

Preparation method of lead acetate

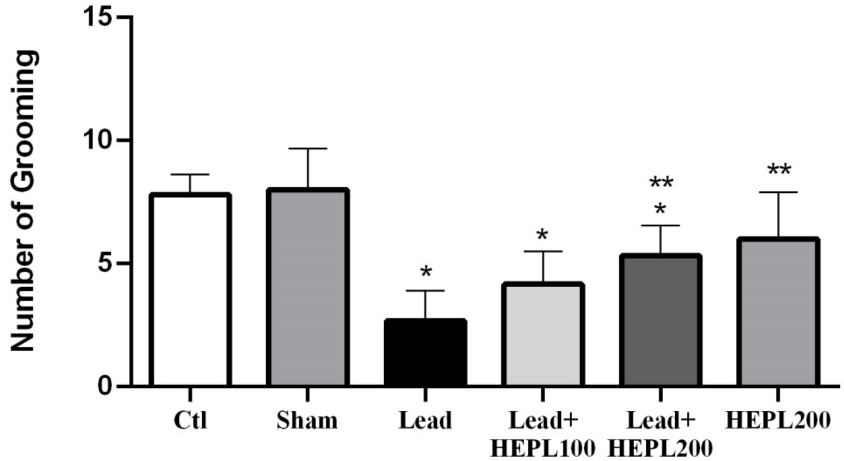
Lead acetate (Sigma-Aldrich, USA) was prepared in powder form. At first, 0.5 grams of lead acetate powder was weighed with a scale with an accuracy of 0.001. Then, 100 ml of distilled water was added to the lead acetate powder as a solvent and the required volume was prepared. The determination of lead acetate dose for this study was based on previous studies (Al-Megrin *et al.,* 2019).

Statistical Analysis

Statistical analysis of data was done using SPSS software (Version 20). One-way variance test and Tukey's post hoc test were used to compare between groups. $P<0.05$ was considered statistically significant and graphs were drawn with the help of GraphPad Prism 6 software.

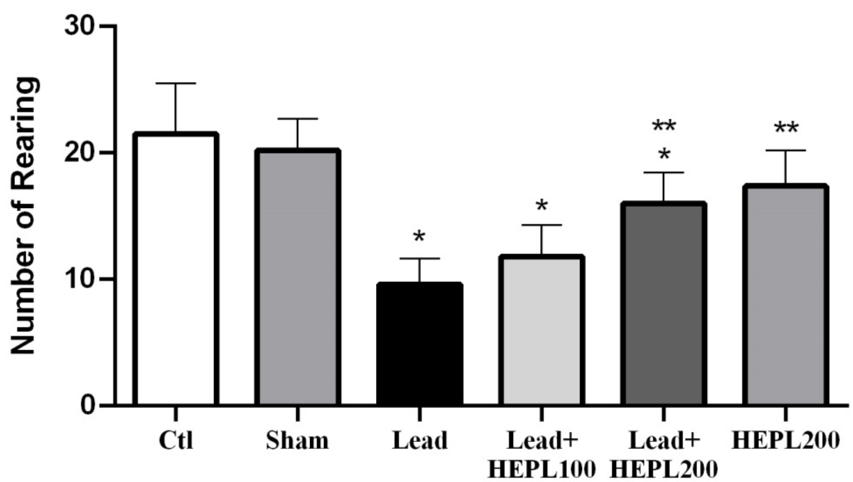
Results

Graph 1 shows the comparison of the mean and standard deviation of the amount of grooming in different groups. In the Lead, Lead+HEPL100, and Lead+HEPL200 groups, a significant decrease in the amount of grooming was observed compared to the control and sham groups ($P<0.05$). In the HEPL200 group, there was no significant difference in the amount of grooming compared to the control and sham groups (P>0.05), but it showed a significant increase compared to the Lead group (P<0.05). Also, in the Lead+HEPL200 group, a significant increase in the amount of grooming was observed compared to the Lead group (P<0.05).



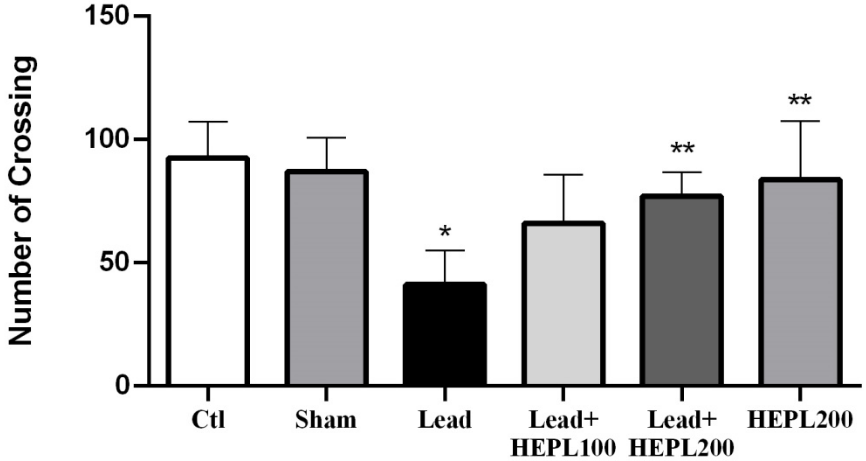
Graph 1. A comparison of the mean and standard error of the amount of grooming in different groups is shown. *: significant difference with control and sham groups (P<0.05). **: significant difference between Lead+HEPL100 and Lead+HEPL200 groups with Lead group (P<0.05). Ctl (Control), Sham, Lead, HEPL (Hydroalcoholic extract of parsley leaves).

Graph 2 shows the comparison of the mean and standard deviation of rearing in different groups. In the Lead, Lead+HEPL100, and Lead+HEPL200 groups, a significant decrease in rearing was observed compared to the control and sham groups (P<0.05). In the HEPL200 group, there was no significant difference in rearing compared to the control and sham groups (P>0.05), but it showed a significant increase compared to the Lead group (P<0.05). Also, in the Lead+HEPL200 group, a significant increase in rearing was observed compared to the Lead group (P<0.05).



Graph 2. A comparison of mean and standard error of the rearing rate in different groups is shown. *: significant difference with control and sham groups (P<0.05). **: significant difference between Lead+HEPL100 and Lead+HEPL200 groups with Lead group (P<0.05). Ctl (Control), Sham, Lead, HEPL (Hydroalcoholic extract of parsley leaves).

Graph 3 shows the comparison of the average and standard deviation of the amount of Crossing in different groups. In the Lead group, a significant decrease in the amount of crossing was observed compared to the control and sham groups ($P<0.05$). In Lead+HEPL100, Lead+HEPL200, and HEPL200 groups, there was no significant difference in the amount of crossing compared to the control and sham groups ($P>0.05$), but in the Lead+HEPL200 and HEPL200 groups, there was shown a significant increase compared to the Lead group ($P<0.05$)



Graph 3. A comparison of the mean and standard error of the amount of crossing in different groups is shown. *: significant difference with control and sham groups ($P<0.05$). **: significant difference between Lead+HEPL100 and Lead+HEPL200 groups with Lead group ($P<0.05$). Ctl (Control), Sham, Lead, HEPL (Hydroalcoholic extract of parsley leaves).

Discussion

The results of this study showed that administration of lead for 21 days can cause anxiety behaviors in male rats. Previous studies show that exposure of rats to lead during fetal, infancy, and later can increase anxiety (Bochani *et al.,* 2011). The mechanism of action of lead may involve disruption of neurochemistry such as brain monoamine neurotransmission. Lead exposure is known to disrupt catecholaminergic systems, and depression and anxiety disorders are strongly associated with disruptions in these systems. Animal studies show that chronic exposure to lead can reduce serotonergic activity in several brain regions, including the nucleus accumbens, frontal cortex, and brainstem (Bouchard *et al.,* 2009). Lead toxicity is associated with brain oxidative stress, neuroinflammation, and excitotoxicity. Currently, the interaction between these factors is considered a characteristic of structural and functional neurological disorders in the brain after exposure to lead.

The hippocampus, an important neurobiological region for cognitive processes, is believed to be central to the harmful effects of lead (McNamara & Skelton, 1993; Nehru & Sidhu, 2002). This study reports that exposure to lead impairs learning, induces anxiety, and induces depression-like symptoms in lead-exposed male Wistar rats (Gonenc *et al.,* 2005; Soleimani *et al.,* 2016). An imbalance between the production of reactive oxygen species (ROS) and the ability of antioxidant systems to easily detoxify these reactive intermediates leads to oxidative stress. High oxidative stress is involved in a wide range of neurological disorders (Gelderman *et al.,* 2007; Hwang, 2013). Lead damages cellular components by increasing oxidative stress because it directly disrupts enzyme activity, inactivates or depletes sulfhydryl pools of antioxidants, and increases free radical damage through direct ROS formation. (Ercal *et al.,* 2001; Patrick, 2006). Anxiety expression involves the coordinated activity of multiple brain pathways involving different neurotransmitters, all of which interact and are regulated by local and remote synaptic relays. The role of the inhibitory neurotransmitter GABA has long been considered central to the regulation of anxiety, and this

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neurotransmitter system is the target of drugs used to treat anxiety disorders (Lydiard, 2003). Studies show that lead can decrease GABA levels and also affect GABA receptors through channel modification (Wirbisky *et al.,* 2014).

Phenolic compounds are a very diverse group of plant secondary metabolites to protect cells against oxidative stress caused by free radical species (Costa *et al.,* 2009; Oliveira *et al.,* 2009). From a therapeutic point of view, the parsley plant shows a wide range of medicinal properties, including liver and brain protection (Farzaei *et al.,* 2013; Sęczyk *et al.,* 2016; Rahmat *et al.,* 2019). Daily feeding of pregnant rats with crude extract of parsley has been shown to protect the neonatal brain and balance the deleterious changes in behavioral status, neurotransmitters, and oxidative stress caused by exposure to lead and cadmium during pregnancy (Allam *et al.,* 2016). The effectiveness of an antioxidant can be exerted in various ways, such as scavenging free radicals, decomposing free radicals, as well as chelating metal ions (Zheng *et al.,* 2019). Studies show that the phenolic extract of parsley has antioxidant activity (Es-safi *et al.,* 2021). Recent studies also show the connection between mood disorders and oxidative stress (Nunes *et al.,* 2018; Bonifácio *et al.,* 2021) and psychological stress (Eick *et al.,* 2018; McAllister *et al.,* 2019). Therefore, this issue can open new ways to prevent or manage anxiety and depression about the potential use of antioxidants. Desrumaux et al, found that the lack of vitamin E as an antioxidant in the mouse brain increased the level of key signs of oxidative stress and anxiety-provoking behaviors (Desrumaux *et al.,* 2005). Polyphenols, including flavonoids and phenolic acids, are known for their strong antioxidant effects (Mechchate *et al.,* 2021; Fratianni *et al.,* 2019). Phytochemical screening of parsley has revealed the presence of some compounds such as flavonoids, carotenoids, ascorbic acid, and tocopherol. These components of parsley leaves destroy superoxide anions and hydroxyl radicals in laboratory conditions. Parsley juice supplementation for 50 days has been shown to partially prevent cadmium toxicity and significantly improve physical balance, motor coordination, muscle strength, and brain neurotransmitter levels in cadmium-treated infants. (Allam *et al.,* 2016).

Among other important compounds of the parsley plant is apigenin, which shows anti-anxiety activity almost without side effects (Jäger & Saaby, 2011). Using these secondary phytochemical metabolites as a way to avoid and manage anxiety and depression may be a promising strategy (Amaghnouje *et al.,* 2020). A study conducted by Akıncı et al, showed that parsley minimizes gastric damage caused by stress when taken orally by supporting the antioxidant defense system of cells, which is reflected in increasing the average level of tissue glutathione, superoxide dismutase, and catalase activities is successful (Akıncı *et al.,* 2017).

The open-box test is used to assess the animal's emotional state. Animals that are separated from their cages and placed in a different environment often show distress and anxiety by causing changes in all or some parameters such as a decrease in ambulatory activities, exploration and immobility, and an increase in grooming behavior. (Sturman *et al.,* 2018). It has been shown that parsley plant extract at a dose of 100 mg/kg can produce very significant anti-anxiety effects in rats (Es-safi *et al.,* 2021), which is consistent with the results of our study. One of the limitations of this study is the non-use of other anxiety tests such as the elevated plus maze test.

Conclusion

The results of this study showed that administration of lead at a dose of 20 mg/kg in male rats causes anxiety behaviors. However, administration of HEPL at doses of 100 and 200 mg/kg reduced anxiety behaviors, especially at a dose of 200 mg/kg in male rats treated with lead acetate. Therefore, it is suggested to consider parsley extract as a supplement for people who are exposed to lead acetate contamination.

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Conflict of interest

There is no conflict of interest between the authors.

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بررسی تاثیر عصاره هیدروالکلی برگ گیاه جعفری (*Petroselinum crispum*) بر اضطراب در موشهای صحرایی تیمار شده با استات سرب

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چکیده

زمینه و هدف: فلزات سنگین مانند سرب (Lead) می‌توانند تاثیرات منفی بر سیستم عصبی داشته باشند. اضطراب یکی از شایعترین اختلالات عصبی است که می‌تواند تحت تاثیر سرب القا شود. هدف از انجام این مطالعه بررسی تاثیر حفاظتی عصاره هیدروالکلی برگ گیاه جعفری (*Petroselinum crispum;* HEPL) بر اضطراب در موشهای صحرایی تیمار شده با استات سرب بود.

مواد و روش‌ها: موشهای صحرایی نر به ۶ گروه ۱۰ تایی تقسیم شدند. گروه کنترل تیمار دارویی دریافت نکرد اما حیوانات گروه شم ۱ میلی‌لیتر آب مقطر به عنوان حلال استات سرب به صورت تزریق درون صفاقی دریافت کردند. حیوانات گروه Lead، استات سرب را با دوز mg/kg ۲۰ و حیوانات گروه HEPL200، HEPL با دوز mg/kg ۲۰۰ به صورت تزریق درون صفاقی دریافت کردند. حیوانات گروه‌های Lead+HEPL100 و Lead+HEPL200، به ترتیب ۲ ساعت قبل از دریافت درون صفاقی HEPL با دوز ۱۰۰ و ۲۰۰ mg/kg، استات سرب با دوز mg/kg ۲۰ به صورت تزریق درون صفاقی دریافت کردند. دوره مطالعه در تمام گروه ها ۲۱ روز در نظر گرفته شد. در انتهای مطالعه از آزمون جعبه باز برای اندازه‌گیری رفتار اضطرابی شامل پارامترهای Grooming (تمیزکردن بدن، صورت و پاها)، Rearing (ایستادن روی دو پای عقبی) و Crossing (عبور از خطوط) استفاده شد. تجزیه و تحلیل آماری با استفاده از آنالیز واریانس یک طرفه و تست تعقیب Tukey انجام شد.

یافته‌ها: نتایج این مطالعه نشان داد که در گروه Lead کاهش معنادار تعداد Grooming، Rearing و Crossing در مقایسه با گروه های کنترل و شاهد مشاهده گردید ($P<0.05$). در گروه Lead+HEPL200 افزایش معنادار تعداد Grooming، Rearing و Crossing در مقایسه با گروه Lead مشاهده گردید ($P<0.05$).

نتیجه‌گیری: سرب می‌تواند موجب ایجاد رفتارهای اضطرابی در موشهای صحرایی نر شود. با این حال تجویز HEPL می‌تواند موجب بهبود رفتارهای اضطرابی در موشهای صحرایی نر تیمار شده با استات سرب شود.

واژه های کلیدی: *سرب، عصاره هیدروالکلی، جعفری، اضطراب، موش صحرایی*

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