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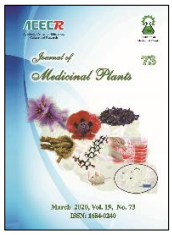

Research Article

Effects of ethanolic extract of *Artemisia persica* on scopolamine-induced cognitive impairment and anxiety in rats

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ABSTRACT

Background: *Artemisia persica* is used as an antiseptic, carminative, appetizer, antiparasitic, and antipyretic agent as well as to relieve fascial pains, and in the past, was used to relieve neuropathic pain and facilitate uterine contractions during childbirth. **Objective:** The aim of this study was to investigate the antioxidant potential and effects of *A. persica* on scopolamine-induced cognitive impairments and anxiety. **Methods:** In this experimental study, 50 male rats were randomly divided into 5 groups of 10 each, including control group, scopolamine (0.7 mg/kg, intraperitoneal injection) group, and three groups receiving scopolamine and ethanolic *Artemisia persica* extract (100, 200, and 400 mg/kg). After three weeks of treatment, behavioral tests including passive avoidance memory, plus maze test, and rotarod test were conducted. The level of malondialdehyde and the antioxidant capacity of the serum and brain in the rats were measured. **Results:** Treatment with *A. persica* extract at 100, 200, and 400 mg/kg in rats receiving scopolamine caused a significant increase in secondary latency in shuttle Box test ($P < 0.01$). Treatment of rats receiving scopolamine with *A. persica* extract at 100, 200, and 400 mg/kg significantly decreased the time elapsed in closed arms and significantly increased the time elapsed in the open arms in plus maze test ($P < 0.05$). **Conclusion:** The results of this study indicate that *A. persica* can act as a potent neuropharmacologic agent against cognitive impairment by modulating cholinergic activity and neuritis in the rat hippocampus.

1. Introduction

Alzheimer's disease (AD) is the most common neurological disorder and accounts for about two thirds of all dementia cases. AD is associated with cognitive and behavioral disorders. Non-cognitive symptoms such as distress, aggression, depression, anxiety and insanity are seen in most patients with AD [1].

Abbreviations: AD, Alzheimer disease; AChE, Acetylcholinesterase; SOD, Superoxide dismutase; GPx, Glutathione peroxidase; CAT, Catalase; ChAT, Choline acetyltransferase; BDNF, brain-derived neurotrophic factor

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The neurochemical analyses of brain tissues in AD patients have shown a significant decrease in the cortical cholinergic neurons, as well as cholinergic defects in the cortex and the hippocampus [2].

Acetylcholinesterase (AChE) is a goal in the treatment of AD, and inhibiting the activity of this enzyme to maintain the level of AChE in neuronal synapses has positive effects in AD patients. Evidence suggests that AChE inhibitors reduce the excess metabolism of synaptic ACh, and high levels of ACh in the synaptic cleft of post-synaptic movements. Memory deficits caused by cholinergic deficiency are associated with increased oxidative stress following scopolamine treatment [3].

However, a strong correlation was observed between scopolamine-induced memory deficits and oxidative stress in the hippocampus in a rat model of scopolamine-induced cognitive impairments. Reduced activity of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) in the early stages of AD has been reported [5, 6]. Scopolamine is a muscarinic receptor antagonist, which causes transient memory deficit and induces a pattern similar to that of AD in animals [7].

Due to the high prevalence of central nervous system disorders, including AD, and the lack of definite treatment for these diseases, as well as the side effects due to chemical drugs and their inappropriate use, studies are being conducted with the aim of finding compounds with appropriate efficacy [8].

Dermaneh Irani, botanically called *Artemisia persica*, is one of the most valuable medicinal plants. *A. persica* is herbaceous, perennial, and self growing plant of the *Cichorium* family, that reaches a height of 90-120 cm, and grows in snowy highlands of Iran. Its compounds include essential oils, minerals, resins, santonin, volatile fatty acids, and artemisinin. *A. persica* is used as an antiseptic, carminative, appetizer, antiparasitic, and antipyretic agent as well as to relieve fascial pains, and in the past, was used to relieve neuropathic pain and facilitate uterine contractions during childbirth [9].

In vitro studies have shown antioxidant [10] anticancer [11], anti-bacterial, antifungal [12], antiviral [13] and antimalarial [14] effects of this plant.

Although the protective effects of *A. persica* on the nervous system have not yet been investigated, the protective effects of other plants of the *Artemisia* genus on the nervous system have been shown, for example, the activity of monoamine oxidase inhibitor in the rat brain by *Artemisia vulgaris* [15], the protective effects of *Artemisia absinthium* against global brain ischemia [16], the protective effects of *Artemisia asiatica* against the damage to PC12 by the amyloid plaque [17], and the benzodiazepine-like activity of the *Artemisia herba-alba* flavonoids on the GABA receptors [18].

Although the identified compounds from *A. persica* had significant activity in AD, there is no study clarifying the possible cognitive-enhancing and antioxidant potentials of the extract from *A. persica* in a rat model of scopolamine. Therefore, we investigated the possible memory-enhancing effects of the extract from *A. persica* in memory-impaired rats and its possible mechanism on the levels of biochemical parameters in the rat hippocampus of the scopolamine model.

2. Materials and Methods

2.1. Preparation of Artemisia persica Extract

Dried *A. persica* was purchased from the groceries of the Izeh city, and after being identified as the plant of interest by a botanist, was registered at the Herbarium of Islamic Azad

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University, Izeh Branch (herbarium number: 566). The dried leaves were pulverized and then placed in 70% ethanol.

The glass flask containing the plant was placed on a magnetic shaker and then left at room temperature for 72 hours. The contents were then filtered and the solution was kept at 37 ºC to allow water and alcohol to evaporate so that the extract was dried then kept at -20 ºC until use (yielded 32%). *A. persica* extract was dissolved in saline.

2.2. Evaluation of in vitro antioxidant activity of Artemisia persica

DPPH radical scavenging activity: Briefly, 1 mL of 0.1 mM DPPH solution (prepared in 95% ethanol) was added to 1 mL of extract at different concentrations (50-300 µg/mL) and incubated for 15 min in the darkness at room temperature, and then the absorbance was read at 517 nm against blank sample. The blank sample was prepared using distilled water instead of the extract. DPPH radical scavenging activity was calculated using the following formula:

$$\text{DPPH radical scavenging activity (\%)} = [(A_{blank} - A_{sample}) / A_{blank}] \times 100$$

IC_{50} value obtained by plotting a graph of concentration (X-axis) against the percentage of inhibition (Y-axis) [19].

2.3. Grouping and treatment of rats

Male rats were kept under the same conditions (21 ± 2 ºC, 12 hour light/12 hour darkness cycle, and free access to the same water and food).

The male Wistar rats were randomly assigned into 5 groups of 10 each. The control group was injected with normal saline (1 mg/kg) for 21 days.

The scopolamine group received scopolamine at 0.7 mg/kg for 21 days.

The experimental groups received scopolamine and then the *A. persica* extract at 100, 200 and 400 mg/kg through intraperitoneal injection for 21 days.

After the treatment period was completed, behavioral tests were conducted. Then, the samples of blood and brain tissue were collected as the rats were under deep anesthesia, and then were prepared for later examinations.

2.3.1. Passive avoidance memory

Passive avoidance memory was measured by shuttle box. This apparatus has a bright chamber connected to a dark chamber by a guillotine door. Electric shocks are exerted to a conductive metal grid on the floor of the apparatus by a separate stimulus. This test was performed on each rat for four consecutive days. On the first two days, rats were individually allowed to freely explore the apparatus for 5 min. On the third day, an acquisition test was conducted. Rats were left in the bright chamber and, after 2-minute acclimatization, the guillotine door was opened and after the rat entry into the dark chamber, it was closed and an electrical shock (2 mA/second) was exerted to rat and the latency to enter the dark chamber was recorded as initial latency. Twenty-four hours later, each rat was placed in the bright chamber and latency to enter the dark chamber was measured as secondary latency (up to 60 seconds) [20].

2.3.2. Rotarod performance test

The ability to maintain balance and motor resistance was investigated using rotarod. This apparatus has a rod that rotates at a speed of 0-40 rpm. The apparatus also has a belt and the speed of the rod can be adjusted by changing the belt position. First, the animal was placed on the rotating rod of the apparatus and trained to walk on it according to the main protocol (10 rpm and

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7 rpm^2 acceleration). Thirty min later, the rat was again placed on the rod and the time to maintain balance and resist rod movement was recorded. The maximum time for each animal in this test was considered to be 300 sec [20].

2.3.3. Elevated plus maze (EPM) test

An apparatus called elevated plus maze was used to measure anxiety. This apparatus has two opposite open arms, two opposite closed arms, and a central sheath elevated 50 cm above the floor. This test was performed in a relatively dark, silent chamber, and each animal was placed gently in the center of the device facing the open arm and allowed to explore for 5 min. The number of entries and time spent in each arm were recorded [20].

2.4. Measuring serum MDA level

Briefly, 0.5g of thiobarbituric acid was mixed with 80ml of acetic acid 20% and the pH of the resulting mixture set at 3.5 by adding sodium hydroxide and its volume diluted with 100 ml acetic acid 20%. 100µl of serum sample was mixed with 100µl of SDS solution 1.8% and 2.5ml of stock solution. Samples were placed in water bath for 1 hour, and then cooled and centrifuged at 4000 rpm. The optical absorbance of the supernatant was read at 523-nm wavelength [21].

2.5. Measuring brain MDA level

One g of brain tissue was homogenized in cooled KCl 2.5% at 1:10 (weight-volume) and incubated in a metabolic incubator shaker at 37 ± 1 ºC for 60 min. Then, 1 ml of tetrachloroacetic acid 5 % and 1 ml thiobarbituric acid 67 % were added and finely mixed. The solution of each vial was centrifuged at 2000 rpm for 15 min. Then, the supernatant was transferred to another tube and placed in water bath. After 10 minutes, test tubes were cooled and optical absorbance read at 535-nm wavelength [21].

2.6. Measuring serum and brain ferric reducing ability of plasma (FRAP)

Three solutions consisting of **1:** a buffer (1.55 ml of sodium acetate and 8ml of concentrated acetic acid diluted with distilled water to a final volume of 500 ml), **2:** iron chloride solution [270 mg of iron (III) chloride diluted with distilled water to a final volume of 50 ml], and **3:** triazine solution (47 mg of triazine dissolved in 40ml of 40 mM hydrochloric acid) were used to measure the antioxidant capacity in serum and brain. Stock solution was prepared by adding 10ml of the solution 1, one ml of the solution 2, and one ml of the solution 3. Twenty five µl of serum or brain homogenate was added to 1.5 ml of stock solution and the resulting solution left at 37 ºC for 10 minutes. Optical absorbance was then read at 593 nm wavelength [21].

2.7. Statistical analysis

Data were analyzed using SPSS version 20. Analysis of Variance (ANOVA) followed by Tukey test used to identify statistical differences between means. All data were presented as mean ± SD and P value less than 0.05 was considered statistically significant.

3. Results

In the present study antioxidant activity of *Artemisia persica* extract was evaluated and the results showed that *Artemisia persica* has a strong removing activity against DPPH-free radicals (IC_{50} = 98.80 µg/ml).

The results on the duration of the initial and secondary latency in the passive avoidance memory test in the studied groups are illustrated in Fig. 1.

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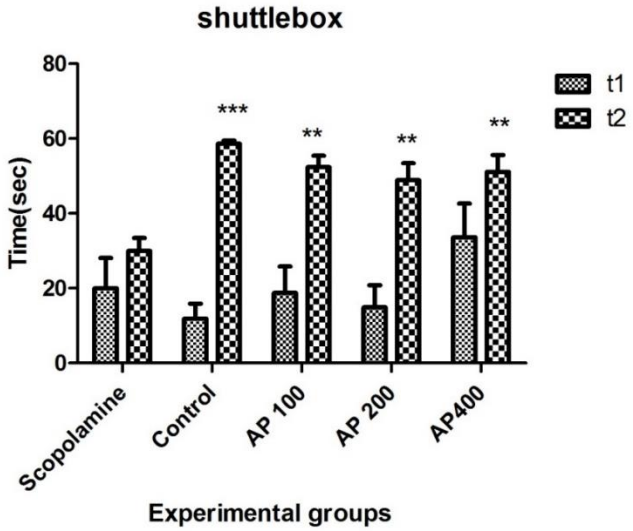

Fig. 1. Comparison of the duration of the primary (t1) and secondary (t2) latency in the passive avoidance memory test between studied groups; *** significant difference (P < 0.001); ** significant difference (P < 0.01); AP: *Artemisia persica*

Table 1. Comparison of the mean (± standard deviation) duration of balance maintenance in Rotarod test between studied groups

Experimental groups	Time on rotarod
scopolamine	24.88 ± 13.24
control	50.75 ± 25.18
Scopolamine + AP100	18.71 ± 9.3
Scopolamine + AP200	53.43 ± 50.67
Scopolamine + AP400	51.14 ± 35.01

According to the results, there was no significant difference in the primary latency to enter the dark chamber between the studied groups (F = 1.398). Secondary latency duration was significantly lower in the scopolamine receiving group (F = 8.103) than in the control group (P < 0.001). Treatment with *A. persica* extract at 100, 200 and 400 mg/kg significantly increased the latency duration in the rats given scopolamine (P < 0.01).

The results regarding the duration of balance maintenance in the Rotarod test in the studied groups are shown in Table 1. According to the results, there was no significant difference between the studied groups (F = 2.226) (P > 0.05).

As illustrated in Fig. 2, scopolamine treatment in rats caused a significant increase in the time elapsed in the closed arms (F = 5.118) and a significant decrease in the time elapsed in the open arms (F = 31.91) of the elevated plus-maze device. Treatment with *A. persica*extract at 200 and 400 mg/kg of in the scopolamine receiving rats caused a significant decrease in elapsed time in closed arms and a significant increase in elapsed time in open arms in the elevated plus-maze (P< 0.05).

According to the Table 2, scopolamine treatment significantly increased MDA levels in the serum (F = 10.44) and brain (F = 12.73) tissue in the rats (P < 0.01). The treatment with the *A. persica* extract at the three doses did not cause a significant decrease in the serum and brain MDA levels compared to the scopolamine receiving group.

According to the results of Table 3, the antioxidant capacity of the brain (F = 35.75) and serum (F = 13.89) significantly decreased in the rats treated with scopolamine. The treatment with the *A. persica* extract at the three doses did not cause a significant increase in the antioxidant capacity of the serum and brain tissues compared to the group treated with scopolamine.

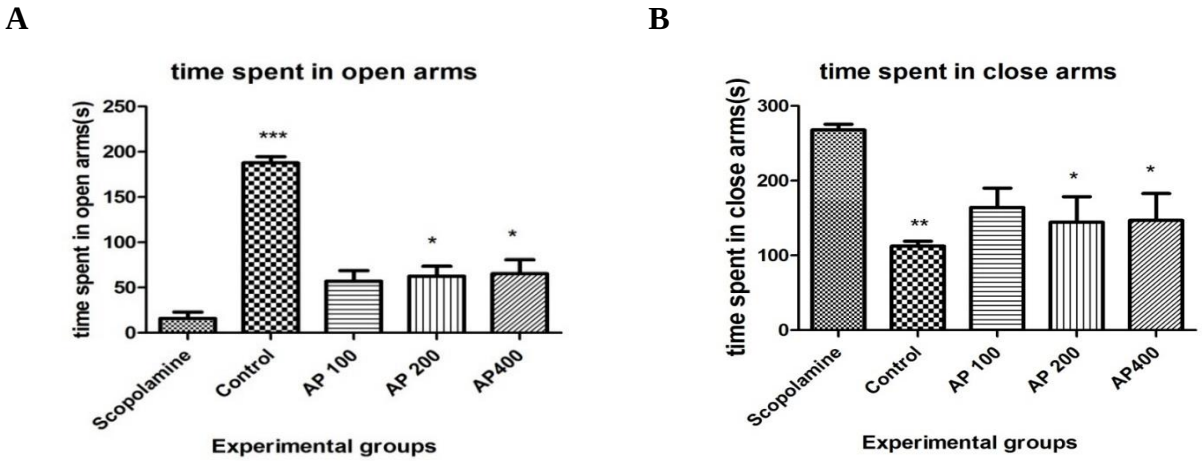

Fig. 2. Comparison of the time elapsed in the open (A) and closed (B) arms in the elevated plus-maze device between studied groups; *** significant difference (P < 0.001);** significant difference (P < 0.01), * significant difference (P < 0.05). AP: *Artemisiapersica*

Table 2. Comparison of the mean (± standard deviation) values of brain and serum malondialdehyde levels between studied groups

Experimental groups	MDA	
	Serum	Brain
Scopolamine	362.1 ± 95.14	244.4 ± 57.96
Control	241.6 ± 27.51**	148.3 ± 33.55**
Scopolamine + AP100	339.7 ± 34.90	243.3 ± 29.31
Scopolamine + AP200	292.1 ± 68.46	220.9 ± 56.22
Scopolamine + AP400	439.4 ± 54.04	302.5 ± 35.05

** Significant difference (P < 0.01)

Table 3. Comparison of mean (± standard deviation) values of antioxidant capacity of brain and serum between studied groups

Experimental groups	Antioxidant capacity	
	Serum	Brain
Scopolamine	166.1 ± 47.34	241.5 ± 16.23
Control	453.1 ± 142.9***	364.3 ± 34.30***
Scopolamine + AP100	163.7 ± 69.14	232.9 ± 17.5
Scopolamine + AP200	256.4 ± 89.77	265 ± 61.68
Scopolamine+ AP400	203.3 ± 34.66	147.6 ± 34.55

*** Significant difference (P < 0.001)

4. Discussion

In this study, the neuroprotective effects of ethanol extract of *A. persica* on scopolamine-induced learning and memory disorders were investigated. Treatment of rats with successive injections of scopolamine for 21 days resulted in a significant decrease in the secondary latency in the passive avoidance memory test. Scopolamine treatment also improved the anxiety behaviors in the plus maze test. *A. persica* extract significantly improved memory and anxiety in animals receiving scopolamine. Studies have shown that memory disorders caused by injection of scopolamine are associated with damage to cholinergic neurons and decreased levels of acetylcholine in the brain tissue.

A possible mechanism by which *A. persica* extract can improve memory and learning disorders may be increase in the sensitivity of cholinergic receptors in the brain or a decrease in AChE activity. The memory formed in the hippocampus is dependent on an increase in the level of extracellular acetylcholine (ACh). In addition, synaptic cholinergic transmission is impaired by the overexpression of acetylcholinesterase and decreased acetylcholine levels [22].

Studies have shown that *Artemisia* has potent anti-acetylcholinesterase properties *in vitro* [23]. *A. persica* has also been reported to increase the level of memory and learning through nicotinic and muscarinic receptors in human cortical tissue [24].

Studies have also shown that daily injection of scopolamine in rats with memory and learning impairment reduces the activities of choline acetyltransferase (ChAT) and brain-derived neurotrophic factor (BDNF) in the hippocampus [25]. BDNF is a protein that plays an important role in neuroprotection, neurogenicity, and synaptic plasticity, as well as in motor learning [26].

The level of this factor serves as a predictor of the development of neurodegenerative diseases, including AD [27].

Studies have shown that the ethanol extract of Artemisia increases the level of BDNF in the brain [28]. It seems that this plant can improve cognitive and behavioral disorders by affecting the factors that are effective on neurogenicity and synaptic plasticity.

Scopolamine impairs memory and learning by increasing oxidative stress in the entire brain tissue, as well as in specific structures related to memory and learning. Scopolamine also eliminates the metabolism of low molecular weight antioxidants, especially glutathione, and exacerbates the lipid peroxidation in the brain tissue, which makes the brain susceptible to ROS-induced damage due to the high concentrations of unsaturated fatty acids with high oxidizing properties, such as arachidonic acid and docosanoic acid [21].

In the present study, injection of scopolamine caused a significant reduction in the antioxidant capacity of brain and serum and a significant increase in MDA level that is a lipid peroxidation marker. In the study of Rashidch*et al*. (2010), the antioxidant effects and phenolic and flavonoid contents of the methanol extract of *Artemisia persica* were evaluated. The antioxidant activity of the extract in inhibiting DPPH free radicals was also determined.

In addition, the activity of the plant extract in inhibiting the oxidation of sunflower oil was determined by free fatty acid tests and lipid peroxidation marker. The results of these experiments showed that the plant extract had a strong antioxidant activity. The phenolic and flavonoid contents of the extract of the plant were 407 and 308 mg/g, respectively [29].

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The results of antioxidant tests on the *A. persica* extract in this study confirmed that the plant had a high antioxidant property. The results regarding serum and brain tissue antioxidant capacity indicated that the extract did not have a significant effect on oxidative stress parameters of the serum and brain tissues and cognitive impairments might be improved through other mechanisms.

5. Conclusion

A. persica is found only in Iran and is used for a wide spectrum of purposes in traditional medicine. However, few studies have been conducted on neuroprotective effects of the plant in animal models as well as in clinical trials. There is very limited information on the plant's active ingredients and the mechanism of its neuroprotective effects, necessitating further research on this subject. A possible mechanism by which *A. persica* extract can improve memory and learning disorders may be increase in the sensitivity of cholinergic receptors in the brain or a decrease in AChE activity.

Author contributions

Zahra Rabei conceived and extracted the data, revised the paper, Mahbubeh Setorki designed the study, analyzed the data and wrote the manuscript. Reyhaneh Joudaki performed all testes.

Conflict of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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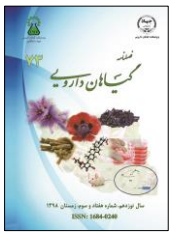

مقاله تحقیقاتی

بررسی اثرات عصاره اتانولی درمنه‌ی ایرانی (*Artemisa persica*) بر اختلالات شناختی و اضطراب ناشی از اسکوپولامین در موش‌های صحرایی

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اطلاعات مقاله

گل‌واژگان:
Artemisa persica
حافظه‌ی احترازی
اضطراب

چکیده

مقدمه: درمنه ایرانی به عنوان ضدعفونی‌کننده، بادشکن، اشتها آور، ضد انگل آسکاریس، تب‌بر و مسکن دردهای احشایی استفاده می‌شود و در گذشته برای تسکین دردهای عصبی و به عنوان تسهیل کننده انقباضات رحم در هنگام زایمان استفاده می‌کردند. در مطالعات آزمایشگاهی اثرات آنتی‌اکسیدانی، ضدسرطانی، ضدباکتریایی، ضدقارچی، ضدویروسی و ضدمالاریایی این گیاه نشان داده شده است. **هدف:** مطالعه حاضر با هدف بررسی پتانسیل آنتی‌اکسیدانی و اثرات گیاه درمنه‌ی ایرانی بر اختلالات شناختی و اضطراب ناشی از اسکوپولامین انجام شد. **روش بررسی:** در مطالعه تجربی حاضر، ۵۰ موش صحرایی به صورت تصادفی به ۵ گروه ۱۰ تایی شامل گروه کنترل، گروه دریافت‌کننده اسکوپولامین (۰/۷ میلی‌گرم بر کیلوگرم، تزریق داخل صفاقی) و گروه‌های دریافت‌کننده اسکوپولامین به همراه عصاره اتانولی گیاه درمنه در غلظت‌های ۱۰۰، ۲۰۰ و ۴۰۰ میلی‌گرم بر کیلوگرم قرار گرفتند. پس از تیمار به مدت سه هفته، آزمون‌های رفتاری شامل آزمون حافظه احترازی غیرفعال و آزمون پلاس میز و روتارود انجام شد. میزان مالون‌دی‌آلدهید و پتانسیل آنتی‌اکسیدانی سرم و مغز موش‌ها نیز تعیین شد. **نتایج:** تیمار موش‌های دریافت‌کننده اسکوپولامین توسط عصاره درمنه‌ی ایرانی در غلظت‌های ۱۰۰، ۲۰۰ و ۴۰۰ میلی‌گرم بر کیلوگرم سبب افزایش معنی‌دار زمان تأخیر ثانویه در تست شاتل باکس شد ($P<0/01$). تیمار موش‌های دریافت‌کننده اسکوپولامین توسط غلظت‌های ۲۰۰ و ۴۰۰ میلی‌گرم بر کیلوگرم عصاره درمنه‌ی ایرانی با کاهش معنی‌دار مدت زمان سپری شده در بازوهای بسته و افزایش معنی‌دار مدت زمان سپری شده در بازوهای باز دستگاه پلاس میز همراه بود ($P< 0/05$). **نتیجه‌گیری:** نتایج این مطالعه نشان می‌دهد که گیاه درمنه ایرانی می‌تواند به عنوان یک عامل نوروفارماکولوژیک قوی در برابر اختلالات شناختی از طریق تعدیل فعالیت کولینرژیک و التهاب عصبی در هیپوکامپ موش صحرایی باشد.

مخففها: Alzheimer disease (AD); Acetylcholinesterase (AChE); Superoxide dismutase (SOD); Glutathione peroxidase (GPx); Catalase (CAT); Choline acetyltransferase (ChAT); brain-derived neurotrophic factor (BDNF)

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