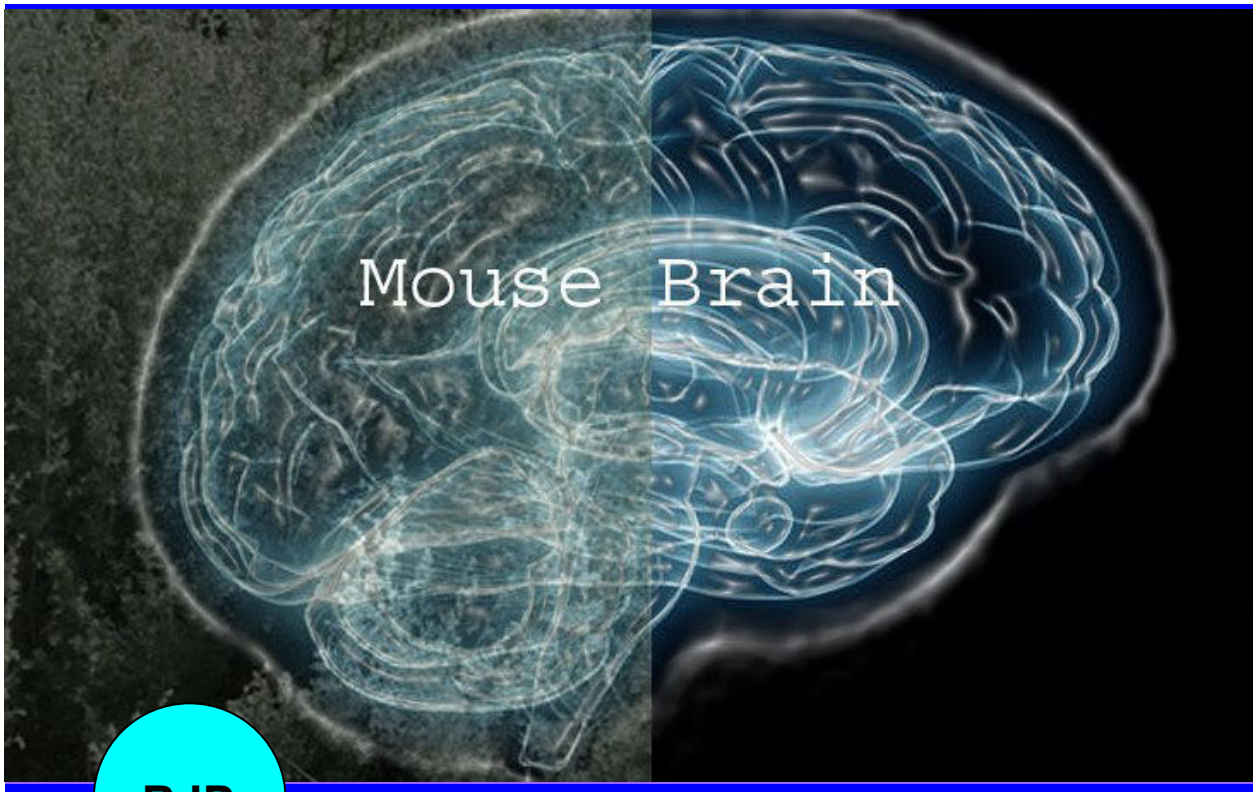

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Effect of *Artemisia persica* on seizure severity and memory and learning disorders in pentylenetetrazole-kindled mice

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Abstract

The purpose of this study was to investigate the effect of hydroalcoholic extract of *Artemisia persica* (100, 200 and 400 mg/kg) on pentylenetetrazole-induced seizure and memory impairment. Sixty mice were assigned to seven groups. Pentylenetetrazole (35 mg/kg) was injected at 48 hours intervals for 9 days, and at 60 mg/kg on day 10 to induce seizure model. Different doses of *A. persica* extract were injected daily 30 min before pentylenetetrazole injection. Exposure of mice to extract significantly reduced the frequency of repeated spinning and jumping and tonic seizures in seizure model. In addition, the extract significantly reduced the increased levels of malondialdehyde in serum and brain. The extract significantly increased the serum and brain anti-oxidant capacity but had no significant effect on nitric oxide. The extract (100 mg/kg) significantly improved pentylenetetrazole-induced memory impairment. The hydro-alcoholic extract of *A. persica* has a protective effect against pentylenetrazole-induced seizure.

Introduction

Epilepsy is a common neurological disorder characterized by unexpected and periodic seizures. The seizure is a transient behavioral change due to the rhythmic and simultaneous discharge of a group of neurons in the central nervous system (Thurman et al., 2011).

The frequent incidence of epileptic seizures significantly reduces learning and memory levels in patients with a history of seizures (Ho et al., 2015). Neuronal degeneration of the brain, especially in the CA1 region of the hippocampus, and the change in the function of the variable synapses that store the information, is considered a possible explanation for the learning disorder following kindling (Schouten et al., 2002).

The main point in the treatment of seizures and epilepsy is the need for long-term, continuous, and multi-drug treatment, which can lead to the development of various side effects. Hence, it will be essential to pay attention to traditional medicine and herbal medicines to achieve low-risk drugs with minimal side effects (Rostampour et al., 2014). The plants such as *Aitchisonia rosea* (Rasool et al., 2015), *Bacopa monnieri* (Paulose et al., 2008), *Cannabis sativa* (Leite and Carlini, 1973), *Cyperus articulates* (Bakanova and Leutskií, *2971), Sechium edule* (Mumtaz et al., 2012), *Silybum marianum* (Waqar et al., 2016) and *Zizyphus jujube* (Puhaja et al., 2011) showed antiepileptic effect.

Artemisia, belonging to the Anthemidae and the Asteraceae (chicory) family, is a large and diverse genus of medicinal plants. One of the main compounds of the plant is artemisinin. Artemisinin and its semi-synthetic derivatives are a group of medicines used to treat malaria. In addition, it has anti-inflammatory (Yu et al., 2012; Aldieri et al., 2003), anticholinergic (Hara et al., 2007), anti-oxidative stress and neuroprotective

(Wan et al., 2017), and sedative (Amos et al., 2003) effects in animal models.

Artemisia persica is one of the most valuable medicinal plants of the *Artemisia* genus. In traditional medicine, It has been used as an antiseptic, carminative, appetizing, antiparasitic, and antipyretic agent, as well as a reliever of fascial and neuropathic pains and facilitator of uterine contractions at delivery (Siadat and Direkvand-Moghadam, 2017). *In vitro* studies have indicated its anti-oxidant (Ahmadvand et al., 2014), anti-cancer (Taghizadeh et al., 2011), antibacterial, antifungal (Ramezani et al., 2004), and antiviral (Karamoddini et al., 2011) effects.

Although the neuroprotective effect of *A. persica* effect has not yet been studied, it seems that plant extract can show protective effects against pentylenetetrazole-induced seizure due to the presence of high amounts of artemisinin, and therefore the present study was conducted to investigate this possibility.

Materials and Methods

Preparation of extract

A. persica was purchased from a local market of Shahrekord, Iran and identified by an herbalist. A reference sample was kept in the Herbarium of Shahrekord University of Medical Science with voucher herbarium (specimen No. 549). The extraction was conducted by a maceration method. The dried plant sample was pulverized by an electric mill and then mixed with 70% ethanol at 1:5 sample/solvent ratio. After 72 hours, the solution was filtered through Whatman filter paper (No. 1) and the filtrate evaporated under vacuum at 40° C to dryness. Finally, the resulting solution was completely dried under 37 ± 1°C.

DPPH radical scavenging activity

Different concentrations of extract were prepared in distilled water and 1 mL of resulting solutions were mixed with 1 mL of 0.1 mM DPPH solution (prepared in 95% ethanol) and allowed to stand for 15 min at room temperature. Then, the absorbance of the samples was recorded at 517 nm using a spectrophotometer. The control was prepared using 1 mL of distilled water instead of the sample. The percentage of DPPH radicals scavenging activity was determined using the following formula:

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

IC_{50} value obtained by plotting a graph of concentration (X-axis) versus percentage of inhibition (Y-axis) (Fathi et al., 2015).

Fe^{2+} chelating activity

First, 1 mL of extract solution at different concentrations was mixed with 3.7 mL of distilled water. Then, 0.1 mL of 2 mM $FeCl_2$ and 0.2 mL of 5. mM ferrozine were added to the mixture. After 20 min, the optical absorbance was read at 562 nm. For the control sample, distilled water was used instead of the sample. Fe^{2+} chelating activity was calculated using the following formula:

$$Fe^{2+} \text{ chelating activity } (\%) = [(A_{control} - A_{sample})/A_{control}] \times 100$$

IC_{50} value was calculated from the plot of the chelating activity against the sample concentrations (Fathi et al., 2015).

ABTS radical scavenging activity

ABTS working solution was prepared by reacting ABTS (7.4 mM, 10 mL) with potassium persulfate (2.6 mM, 10 mL) for 12 hours at room temperature in the dark. Before the experiment, freshly prepared ABTS solution was diluted with methanol to reach an absorbance of 1.1 ± 0.02 at 734 nm. Then, 150 µL of the protein hydrolysate at different concentrations was added to 2850 µL of ABTS solution, and after incubation ambient temperature for 12 hours, the optical absorbance was recorded. The control sample was prepared using 150 µL of distilled water instead of the sample. ABTS scavenging activity was determined using the following formula:

$$\text{ABTS scavenging activity } (\%) = [(A_{control} - A_{sample}) / A_{control}] \times 100$$

IC_{50} value was determined from the plot of the scavenging activity against the sample concentrations (Fathi et al., 2015).

Hydroxyl radical scavenging activity

First, 1,10-phenanthroline solution (1.865 mM, 1 mL) and the extract (2 mL) were added into a test tube and mixed well. Then, 1 mL of the $FeSO_4$ solution (1.865 mM) was added to the mixture. The reaction was started by adding 1 mL of H_2O_2 (3% v/v) and after 60 min of incubation in a 37°C water bath, the absorbance was recorded at 536 nm. The solution containing extract without hydrogen peroxide was considered as blank and the solution without extract was considered negative control. Hydroxyl radical scavenging activity was determined using the following formula:

$$\text{Hydroxyl radical scavenging activity } (\%) = [(As-An)/(Ab-An)] \times 100$$

where As is the absorbance of the sample, An is the absorbance of the negative control and Ab is the absorbance of the blank

IC_{50} value was determined from the plot of the scavenging activity against the sample concentration (Fathi et al., 2015).

Laboratory animals and grouping

Male mice weighing 25-30 g were housed under standard conditions (21 ± 2°C and 12 hours light/darkness

Box 1: Shuttle Box Test

Principle

The shuttle box was used to measure the passive avoidance memory

Requirements

Computer; Mouse; Shuttle box (Borj-Sanat Azma, Iran); Software; Stimulator (ST-5500)

Component

This apparatus has a bright chamber (20 x 20 x 30 cm) connected to a dark chamber (20 x 20 x 30 cm) by a guillotine door (10 cm). Electric shocks (50 Hz, 1 mA for 1 sec) are exerted to a conductive metal grid on the floor of the apparatus by a separate stimulus. A door at the top allows an easy access of the rat to inside the box. The cage contains a general sound generator and a visual stimulus (light) for each compartment.

Procedure

Day 1

Each mouse was allowed to freely explore the apparatus for 5 min

Day 2

Each mouse was allowed to freely explore the apparatus for 5 min

Day 3

An acquisition test was conducted.

Step 1: Mice were left in the bright chamber and, after 2 min acclimatization

Step 2: The guillotine door was opened and after the mouse entry into the dark chamber

Step 3: An electrical shock was exerted on the mouse such that it just paddled.

Step 4: The latency to enter the dark chamber was recorded as initial latency

Step 5: Twenty-four hours later, each mice was placed in the bright chamber and latency to enter the dark chamber was measured as secondary latency (up to 60 sec)

Comment: If the mouse did not enter the dark compartment within 2 min, successful acquisition of passive avoidance response would be recorded

Advantage

The shuttle box can be easily set up and dismantled.

References

Kwon et al., 2010; Khalili et al., 2009; Hosseinzadeh and Sadeghnia, 2013

cycle) with free access to the same water and food.

The animals were randomly divided into seven groups of 10 each. The control group received normal saline by intraperitoneal injection for 10 days. The pentylenetetrazole group received pentylenetetrazole by intraperi-toneal injection at 48 hours intervals for 10 days. Intervention groups received pentylenetetrazole at 48 hours intervals and the *A. persica* extract at 100, 200 and 400 mg/kg doses daily by intraperitoneal injection 30 min before pentylenetetrazole injection. The positive control group received pentylenetetrazole at 48 hours intervals and 400 mg/kg of the *A. persica* extract daily, and on day 10, 2 mg/kg of diazepam by intraperitoneal injection 30 min before pentylenetetrazole injection.

The flumazenil group received pentylenetetrazole at 48 hours intervals and 400 mg/kg of the *A. persica* extract daily, and on day 10, 2 mg/kg of flumazenil by intra-peritoneal injection 30 min before pentylene-tetrazole injection. To induce epilepsy, 35 mg/kg of pentylene-tetrazole was intraperitoneally injected at 48 hours intervals for 9 days. On day 10, 60 mg/kg of pentylene-tetrazole was injected. Injections were performed for 10 days, and the severity and rate of seizure were recorded on the 10th day 30 min after injection for 30 min (Ho et al., 2015). Then, the shuttle box test was performed and finally, their blood samples were collected as they were under deep anesthesia and their brains were removed and kept at -80°C for biochemical tests.

Measurement of lipid peroxide levels

Two hundred microliter of tissue homogenate/serum was mixed with 1.5 mL of 20% acetic acid, 1.5 mL of 0.8% thiobarbituric acid and 200 µL of 8.1% sodium dodecyl sulfate. The mixture was mixed with 700 µL of distilled water and heated in a boiling water bath for 60 min. After cooling under tap water, distilled water (1 mL) and *n*-butanol/pyridine solution (5 mL) were added to the reaction mixtures and shaken vigorously. Then, the resulting solutions were centrifuged at 4,000 rpm for 10 min and the optical absorbance of the supernatant at 532 nm was recorded. Lipid peroxide levels were determined using standard calibration curve and expressed as a micromol of malondialdehyde (Namıduru et al., 2011).

Measurement of total anti-oxidant capacity

The anti-oxidant capacity of serum and tissue homo-genate was measured using ferric reducing anti-oxidant power (FRAP) assay. The working FRAP reagent was prepared by mixing acetate buffer (10 mL, 0.25 M, pH= 3.6), 2 TPTZ (5 mL, 10 mM, prepared in 40 mM HCl) and $FeCl_3.6H2O$ (2.5 mL, 20 mM). Twenty five micro-liter of tissue homogenate/serum was added to 1.5 mL of working FRAP solution and left at 37°C for 10 min. After incubation, the optical absorbance at 593 nm was recorded using a spectrophotometer (Namıduru et al., 2011).

Measurement of nitric oxide (NO) levels

The NO is a diatomic free radical with extremely short physiological half-life. In biological system, it is rapidly oxidized to stable end products such as nitrates (NO^{3-})

and nitrite (NO^{2-}). Therefore, the total nitrite content in serum and tissue homogenate was measured as the index of NO production. Briefly, 300 µL of serum or tissue homogenate was mixed with 600 µL of 75 mM $ZnSO_4$ solution and centrifuged at 1,000 x g for 5 min at room temperature. The resulted supernatant was incubated with copper cadmium granules in a glycine-NaOH buffer in order to convert nitrate to nitrite. Total nitrite level was measured by Griess reaction. One milliliter of the sample was mixed with Griess solution (1 mL of 0.5% sulfanilamide and 0.05% n-naphthalene diamine hydrochloride), and after 30 min of incubation in the dark, the absorbance at 545 nm was recorded (Namıduru et al., 2011).

Data analysis

Data analysis was performed using the SPSS version 16. One-way ANOVA was used to investigate the significance of the difference between the groups. Tukey's test was used to compare the mean values. Data were recorded as mean ± standard error of measurement, and $p<0.05$ was considered significance level.

Results

In this study, the anti-oxidant activity of *A. persica* extract was evaluated *in vitro* by using five anti-oxidant tests. The results of this study showed that *A. persica* extract had strong DPPH free radicals (IC_{50}=80.98 µg/mL) scavenging activity, moderate ABTS (IC_{50}=29.55 µg/mL) and hydroxyl (IC_{50}=600.09 µg/mL) free radicals scavenging activity, relatively good iron ion chelating activity (IC_{50}=89.53 µg/mL), and strong ferric ion reducing activity (optical absorbance at 700 nm= 0.705).

Seizure latency is illustrated in Figure 1 and the frequencies of repeated spinning and jumping, tonic seizures, total body seizures, rearing, and head seizures in Figure 2A and D. According to the results, seizure latency in the groups receiving the *A. persica* extract and the group receiving 400 mg/kg of this extract and flumazenil was not significantly different compared to that in the pentylenetetrazole group, but seizure latency was significantly higher in the group receiving 400 mg/kg of the *A. persica* extract and diazepam than in the pentylenetetrazole group ($p<0.001$, Figure 1).

The frequencies of repeated jumping and spinning and tonic seizures were significantly lower in mice receiving 400 mg/kg of the extract and diazepam than in the group given pentylenetetrazole ($p<0.05$, $p<0.05$, and $p<0.01$). The frequency of repeated jumping and spinning was not significantly different between mice receiving 400 mg/kg of the *A. persica* extract and flumazenil, and the pentylenetetrazole group (Figure 2A,B). In addition, different doses of the *A. persica* extract caused a slight and *in*significant decrease in the

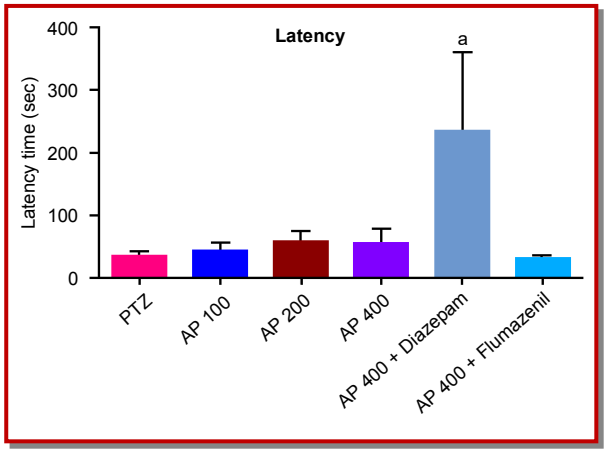

Figure 1: Comparison of seizure latency between studied groups; *significant difference compared to pentylenetetrazole (PTX) group ($^a p<0.001$); AP= *A. persica*

frequencies of seizures of the entire body and head (Figure 2C,D).

Based on the results (Figure 3A,B), in the pentylenetetrazole receiving mice, the initial latency to enter the dark chamber significantly increased, and the secondary latency to enter the dark chamber significantly decreased compared to the control group ($p<0.05$). *A. persica* extract (100 and 200 mg/kg) treatment significantly reduced the initial latency duration in the pentylenetetrazole receiving mice ($p<0.05$, Figure 3A). In the group receiving *A. persica* extract at 100 mg/kg and the group receiving *A. persica* extract at 400 mg/kg and diazepam, the secondary latency significantly increased compared to the pentylenetetrazole group ($p<0.05$ and <0.01, respectively, Figure 3B).

The successive administration of pentylenetetrazole caused a significant decrease in serum and brain anti-oxidant capacity in the mice ($p<0.01$ and <0.001, respectively).

Treatment of pentylenetetrazole receiving mice with *A. persica* extract at 100, 200, and 400 mg/kg caused a significant increase in serum and brain anti-oxidant capacity compared to the pentylenetetrazole group ($p<0.001$, Figure 4A,B).

As Figure 5A and B illustrate, serum and brain MDA levels increase significantly in the pentylenetetrazole receiving mice compared to the control group ($p<0.001$), and treatment with 100, 200, and 400 mg/kg of the *A. persica* extract significantly decreased the MDA levels in the brain and serum ($p<0.01$ and <0.001, respectively).

Serum nitric oxide levels in the pentylenetetrazole receiving mice increased slightly and insignificantly, and treatment with the extract at different doses reduced its levels; however, no significant difference was observed between the studied groups (Figure 6).

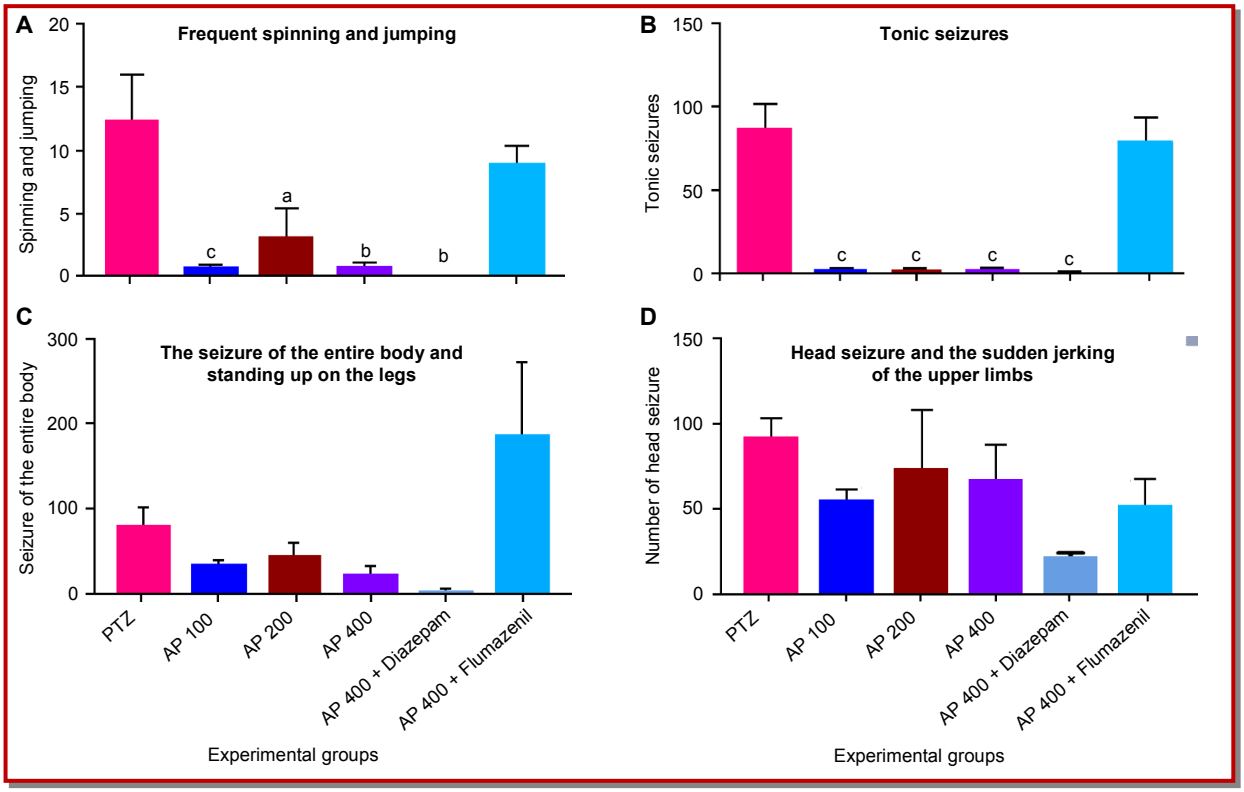

Figure 2: Comparison of the frequencies of repeated spinning and jumping (A), tonic seizures (B), seizures of the whole body, and rearing (C) as well as the frequency of head seizures (D) between groups; *significant difference compared to pentylenetetrazole group ([a]p<0.05, [b]p<0.01 and [c]p<0.001); AP = *A. persica*

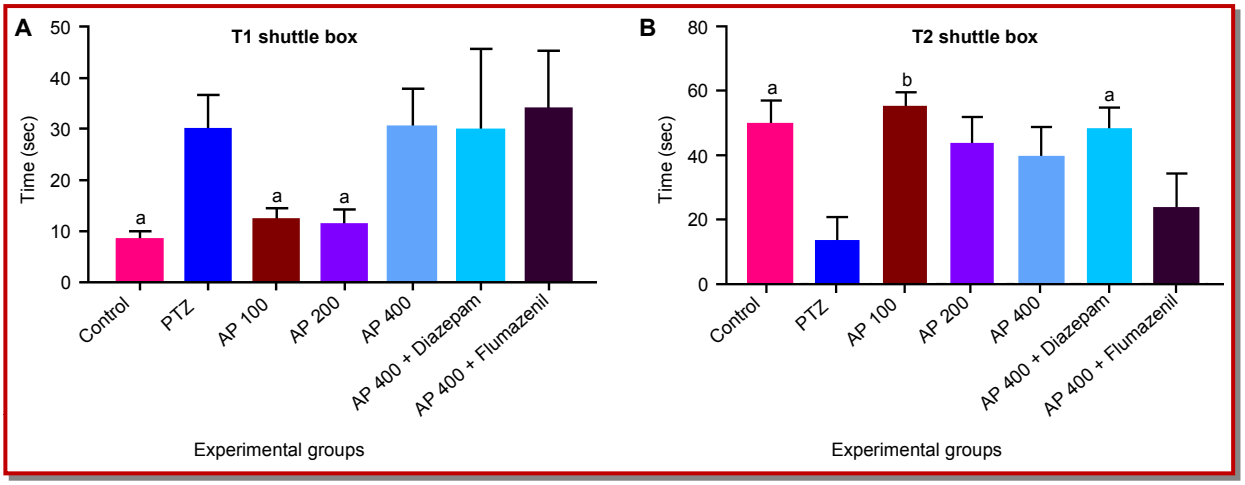

Figure 3: Comparison of initial (A) and secondary (B) latency in passive avoidance memory test between groups; *significant difference compared to pentylenetetrazole group ([a]p<0.05, [b]p<0.01 and [c]p<0.001); AP = *A. persica*

Discussion

It was observed that treatment with different doses of *A. persica* extract did not have any significant effect on the onset of seizure, but significantly decreased the frequencies of repeated jumping and spinning and tonic seizures. In addition, different doses of *A. persica* extract caused a slight and insignificant decrease in the frequencies of seizures of the entire body and head. The effect of 400 mg/kg of *A. persica* extract against tonic seizures and frequency of pentylenetetrazole-induced jumping and spinning was significantly inhibited by flumazenil.

In addition, diazepam treatment in mice receiving 400 mg/kg of *A. persica* extract enhanced the anticonvulsant effects of the extract, so that the seizure started within a shorter duration in the group receiving diazepam and

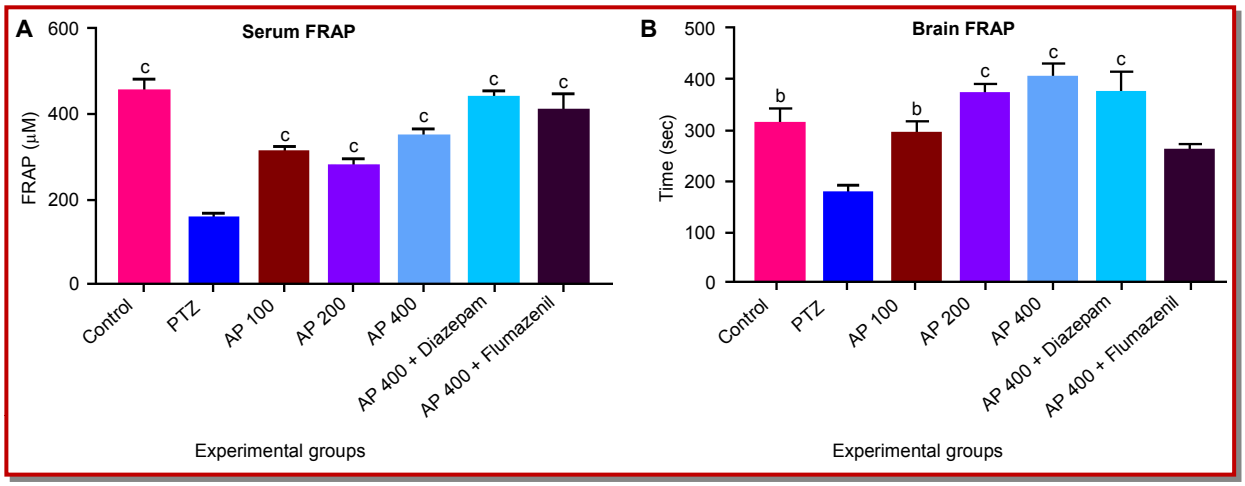

Figure 4: Comparison of total serum (A) and brain (B) anti-oxidant capacity between groups; *significant difference compared to pentylenetetrazole group ([a]p<0.05, [b]p<0.01 and [c]p<0.001); AP = *A. persica*

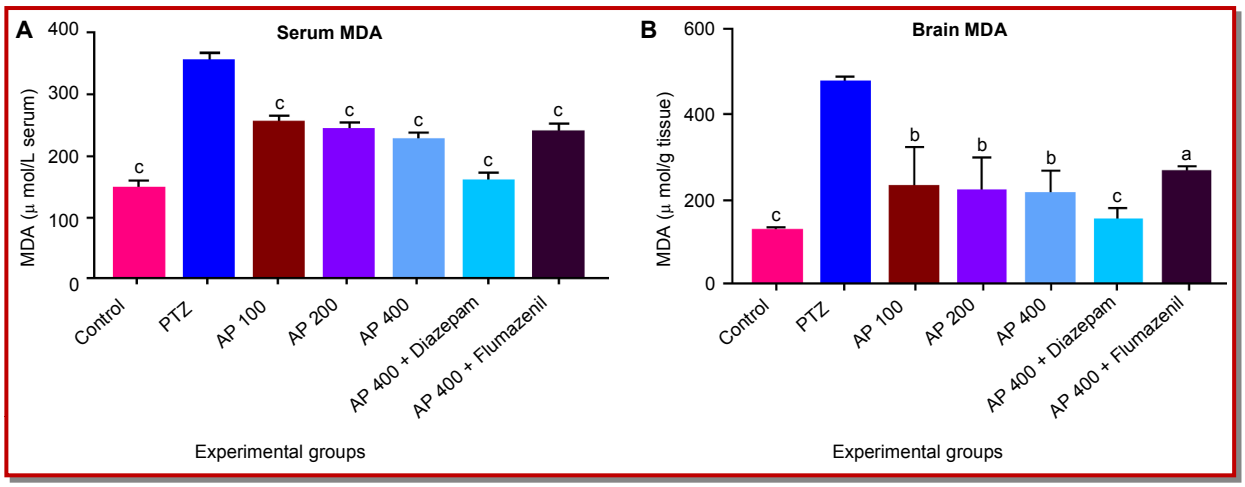

Figure 5: Comparison of serum (A) and brain (B) malondialdehyde levels between groups; *significant difference compared to pentylenetetrazole group ([a]p<0.05, [b]p<0.01 and [c]p<0.001); AP = *A. persica*

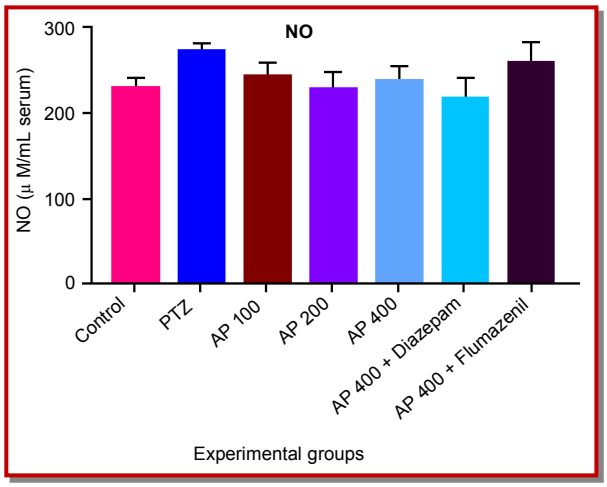

Figure 6: Comparison of serum (A) and brain (B) nitric oxide levels between groups

400 mg/kg of the extract than in the other groups.

Epilepsy is the result of long-term plasticity changes in the brain, which affects the release of neurotransmitters, the characteristics of receptors and channels, the organization of synapses, and the activity of astrocytes (Sierra-Paredes et al., 2007).

Evidence suggests that changes in GABAergic and glutaminergic synaptic transmission leads to the onset, exacerbation, and continuation of seizures. Epilepsy may occur in the case of an increase in the activity of stimulant neurotransmitters (glutamate) or a decrease in the activity of inhibitory neurotransmitters gamma-aminobutyric acid (GABA) (Bradford, 1995).

Therefore, drugs that increase the synaptic levels of GABA by inhibiting GABA catabolism or increasing GABA reabsorption, such as barbiturates and benzo-

diazepines, are considered effective anti-seizure drugs (Bradford, 1995). GABA synthesis inhibitors such as 4-deoxypyridoxine, isoniazid, thiosemicarbazide, and L-allylglycine can also cause seizure (Gale, 1992).

Diazepam is a benzodiazepine-receptor agonist that exerts sedative and anticonvulsant effects by influencing the receptors of gamma-aminobutyric acid and ultimately chlorine ion entry into neurons. Flumazenil is also a potent benzodiazepine-receptor antagonist that effectively inhibits the activity of GABA and benzodiazepine on the benzodiazepine receptors (Hosseinzadeh and Sadeghnia, 2007).

In the present study, the boosting effects of diazepam and the inhibitory effects of flumazenil on anticonvulsant activity of the *A. persica* extract, confirmed the plant's exerting activity through benzodiazepine receptors. In our study, successive pentylenetetrazole injections caused a significant reduction in anti-oxidant capacity and a significant increase in lipid peroxidation in the brain and serum samples of the mice. Pentylenetetrazole injections also caused a minor and insignificant increase in serum nitric oxide levels. Studies have shown that seizure is associated with the hemostatic balance of anti-oxidants and oxidants, which plays an important role in brain damage and death of neurons due to seizure (Gupta et al., 2003).

Epileptic seizures produce free radicals and reactive oxygen species, followed by oxidative damage to proteins, lipids, and DNA of neurons. High levels of superoxide production by mitochondria, deactivation of iron- and sulfur-dependent enzymes, such as aconitase, and iron-induced toxicity play a role in oxidative damage to neurons following seizure (Kim, 2004).

It has been observed that lipid peroxidation and erythrocyte hemolysis percentage increase in patients with epilepsy compared to healthy subjects. The levels of glutathione reductase and vitamins C, E, and A are lower in the erythrocytes of the patients with epilepsy than in those of healthy subjects (Hamed et al., 2004). Animal studies have shown that the pentylenetetrazole kindling causes a significant increase in the oxidative stress parameters including MDA, nitric oxide, and xanthine oxidase as well as a significant reduction in anti-oxidant activity (Ilhan et al., 2015). In this regard, it has been observed that anti-oxidant compounds show significant protective effects against damage due to seizure by modulating oxidative stress and enhancing anti-oxidant defense (Merritt and Foster, 1942; Ogunmekan and Hwang, 1989). In the present study, *A. persica* extract showed significant anti-oxidant activity in inhibiting hydroxyl, DPPH, and ABTS free radicals as well as in chelating and reducing iron ions. In addition, *A. persica* extract treatment increased the anti-oxidant capacity and decreased the lipid peroxidation in the brain and serum samples of pentylenetetrazole-kindled mice, and partially reduced their nitric oxide production. So far, anti-oxidant and anti-oxidative stress effects of *A. persica* extract have not been evaluated *in vivo*, but *in vitro* studies have indicated significant anti-oxidant effects of the extract (Ahmadvand et al., 2014; Rashidch et al., 2010).

As already mentioned, one of the main compounds of the extracts of Artemisia genus plants, including *A. persica*, is artemisinin (Siadat and Direkvand-Moghadam, 2017). It has been observed that artemisinin pretreatment of the PC12 cells significantly reduces hydrogen peroxide-induced apoptosis by reducing the production of reactive oxygen species in the cell, preventing the reduction of mitochondrial membrane potential, reducing abnormal changes in nucleus morphology, and decreasing caspase and lactate dehydrogenase activity (Wan et al., 2017). Laboratory studies have shown that seizure induction in rodents leads to a significant increase in inflammatory mediators in the regions involved in seizure, and anti-inflammatory drugs have been found to reduce the severity of certain types of seizures in animal models (Vezzani, 2005). Inflammatory processes often begin before the onset of seizure and play an etiopathogenic role in spontaneous seizures (Vezzani et al., 2011; Vezzani and Granata, 2005).

In studies on animal model, immediately after induction of seizure by electrical or chemical stimuli, a rapid inflammatory response begins in the glial cells. Overexpression of inflammatory cytokines such as TNF-α and IL-6 in astrocytes can reduce seizure threshold and spontaneous seizure frequency (Vezzani et al., 2011a). Inflammatory cytokines, such as IL-1β, induce stimulatory activity, reduce the production and release of GABA, and exacerbate the flow of calcium by activating the IL-1R and TLR4 receptors, followed by the IL-1R/TLR signaling pathway (Kalueff et al., 2004).

In this regard, treatment with anti-inflammatory drugs (dexamethasone) was able to reduce the severity of epileptic seizures in patients with acute and treatment-resistant epilepsy (Marchi et al., 2011). So far, the anti-inflammatory effects of *A. persica* extract have not been investigated, but other species of Artemisia have been observed to have significant anti-inflammatory activity (De Magalhães et al., 2012; Yin et al., 2008).

Artemisinin, which is present in the plants of this genus, has also shown significant anti-inflammatory activity in cell culture medium and animal models (Yu et al., 2012; Wang et al., 2008). A study shows that artemisinin significantly reduced the production of the TNF-α, IL-6 pro-inflammatory cytokines and nitric oxide by using the lipopolysaccharide-treated RAW264.7 cells (Yu et al., 2012).

In another study, artemisinin showed inhibitory effects on the NF-kB and inhibited the synthesis of nitric oxide in the cytokine-stimulated A67 stromal cells. Resear-

chers have argued that artemisinin is also able to improve neurological complications and malaria-induced inflammation in addition to eliminating the cause of malaria (Aldieri et al., 2003).

According to the above-mentioned, it seems that the protective effect of *A. persica* extract against pentylenetetrazole-induced seizures is related to its anti-inflammatory activity. However, it is necessary to confirm this assumption by investigating the levels of inflammatory mediators and their gene expression. In the present study, it was observed that different concentrations of *A. persica* extract partially improved passive avoidance memory deficits in pentylenetetrazole-kindled mice, which was statistically significant when the extract was injected at 100 mg/kg. *A. persica* extract seems to improve memory by reducing the severity of seizures and preventing oxidative damage to neurons.

Conclusion

The hydroalcoholic extract of *A. persica* has a protective effect against pentylenetetrazole-induced seizure, which is probably due to the effect of its benzodiazepine recep-tors and anti-oxidant activity.

Conflict of Interest

The authors declare that there is no conflict of interest.

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