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Original Article

Efficacy of hydroalcoholic *Petroselinum crispum* L. leaf extract on pentylenetetrazole-induced seizure in rats

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Abstract

Background and aims: Epilepsy is a disorder of the central nervous system that manifests with sudden, transient, recurrent and unpredictable seizures of sensory-motor, autonomic origin. Drugs used to treat the disorder may cause numerous side effects and treatment response may be unsatisfactory. The purpose of the present study was to investigate the *in vitro* effects of hydroalcoholic *Petroselinum crispum* L. leaf extract on pentylenetetrazole (PTZ)-induced seizure in rats.

Methods: In this experimental study, 60 male rats were randomly divided into 6 groups of 10 each. Control group received normal saline. Model group received PTZ at 90 mg/kg intraperitoneally. Intervention groups received *P. crispum* extract at concentrations of 100, 150 and 200 mg/kg 30 minutes before PTZ administration. Positive control group received 40 mg/kg phenobarbital 30 minutes before PTZ injection. Then, seizure threshold was recorded. In addition, serum and brain antioxidant capacity and malondialdehyde (MDA) levels were measured.

Results: Treatment of mice given PTZ with different concentrations of *P. crispum* extract caused a significant increase in seizure threshold ($P<0.05$). In mice receiving PTZ, a significant increase in serum and brain MDA levels was observed ($P<0.05$) but no significant change in antioxidant capacity was noticed. Treatment of mice given PTZ with different concentrations of the extract led to a significant increase in brain and serum antioxidant capacity and a significant decrease in brain and serum MDA levels ($P<0.05$).

Conclusion: *P. crispum* shows protective efficacy against PTZ-induced seizures, which may be due to its antioxidant effects.

Keywords: *Petroselinum crispum* L., Seizure, Epilepsy

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Introduction

Epilepsy refers to a set of chronic long-term medical neurological disorders characterized by seizure attacks. The attacks may be very mild and may even be left undiagnosed, or may be prolonged with severe tremors. In epilepsy, seizures occur frequently and due to no apparent reason, while attacks that occur due to known reasons should not be considered as seizure attacks (1).

In most cases, the cause of seizure is unknown, but in some people epilepsy may be caused due to certain reasons such as brain damage, brain cancer, drug and alcohol abuse. Epileptic seizures occur due to excessive and abnormal cellular activity of the cortical or membrane nerve in the brain. The diagnosis usually involves removing all conditions that may cause similar symptoms, such as syncope, and examining whether there was any other instantaneous cause. Epilepsy can also be confirmed by electroencephalography. Epilepsy is an untreatable disease, but seizures can be controlled with medication in up to 70% of the patients. If the attacks do not respond to drugs, surgery, nerve stimulation and dietary changes may be considered. Not all epilepsy syndromes are lifelong, and most people recover to the extent that they no longer need medication (2).

Generalized seizures are of six types: tonic, tonic-clonic epilepsy, tonic, clonic, muscle tension, anxiety, and seizures. All these attacks involve loss of consciousness and usually occur without warning. Stretching-elastic attacks are accompanied by stiffening and then stretching of the limbs and simultaneous arching of the back, which lasts 10-30 seconds (stretching phase). Then a coordinated vibration of the limbs occurs (elastic phase). Stretching attacks cause uniform muscle contractions. In elastic attacks, uniform vibration of the limbs occurs. Muscle attacks include muscle cramps in some or all areas.

Anxiety attacks can be subtle and involve only a slight twitching of the head or blinking of the eyes. The person does not fall and returns to normal posture after the completion of the period. Weak seizures include loss of muscle activity for more than one second, occurring on both sides of the body (3).

Parsley (*Petroselinum crispum* L.) is a member of the Apiaceae family. *P. crispum* is a biennial plant that reaches a height of 0.3-1 meter, has a straight spindle-shaped

or swollen root (depending on different breeds) and is yellowish. The plant both grows wild and is cultivated in some regions. Its leaves, transparent to dark green, have rhombic or triangular cuts with subdivisions. *P. crispum* is a rich source of vitamins A, C and K. In addition, the plant is a good nutritional source of iron and folic acid. *P. crispum* contains two main types of ingredients that have made this vegetable critically important for human health

The two classes are volatile oils and flavonoids. Essential oils of *P. crispum* are the most important compounds of the plant that are also called plant extracts. Main compounds in this class include myristicin, limonene, alpha-thujene, and eugenol (4). Flavonoids are the second most important compounds of the plant. Important compounds in this class found in *P. crispum* include apiin, apigenin, crisoeriol, and luteolin (5). Thanks to medicinal compounds in *P. crispum*, the plant produces modulating effects against serum cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein in diabetic rats. It also reduces oxidative stress markers and improves heart function in diabetic rats (6). *P. crispum* extract and its flavonoids, including kaempferol and quercetin, decrease oxidative stress markers and serum uric acid level in hyperuricemic mice (7).

Studies have also shown that the extract reduces histopathological changes in the liver, kidneys and pancreas in rats receiving sodium valproate. The neuroprotective effects of the plant have also been investigated in a number of studies and it has been observed that the plant extract relieves pain at both phases of formalin test and also mitigates abdominal contractions in the abdominal contraction test (8).

Today, despite many advances in the treatment of seizure, millions of people around the world still suffer from uncontrollable epilepsy that is resistant to common anticonvulsant drugs, as one per three patients does not respond well to these drugs. In addition, about one-third of patients who recover from epilepsy experience recurrence after medication discontinuation. The toxicity-related complications of conventional antiepileptic drugs have led to their limited use and failure to achieve desirable therapeutic effects.

Therefore, it seems necessary to seek out effective drugs with fewer side effects to treat the disorder. The need to give further attention to traditional medicine and herbal medicines with the aim of achieving low-risk medicines with minimal side effects has recently been intensified. We therefore decided to investigate the antiepileptic and anti-seizure effects of *P. crispum* extract in a rat model of pentylenetetrazole (PTZ)-induced seizure.

Materials and Methods

Procurement and maintenance of animals

The experimental animals were male rats aged 6-8 weeks and weighing 190-220 g that were procured from the Laboratory Animal Breeding and Maintenance Center. Then they were kept under suitable temperature (21 ± 2 °C) and a 12:12-hour light:dark cycle. All rats were provided free access to the same water and food, and 5 days before the test, they were trained daily between 10 and 9 a.m. to adapt to the test conditions and minimize their stress.

Preparation of Petroselinum crispum extract

In the present experimental study, after *P. crispum* samples were purchased from local stores in Shahrekord, its genus and species were identified by a botanist at the Medical Plants Research Center of Shahrekord University of Medical Sciences and one sample was stored in the Herbarium Unit (Herbarium No: 375).

Extraction was performed using maceration. For this purpose, fresh *P. crispum* leaves were shade dried and then ground. The resulting powder was mixed with 70% alcohol in a ratio of 1 to 5 (plant powder/alcohol) and left at room temperature for 72 hours. The extract was then filtered through filter paper and the resulting solution was concentrated by a rotary apparatus. The resulting solution was dried in an oven at 37 °C and stored at -20°C until the experiment (9).

Evaluation of anticonvulsant effects of extract

Control group (n = 10) was intraperitoneally injected with normal saline as the solvent of the studied drugs.

PTZ group (n = 10) received PTZ at a concentration of 90 mg/kg intraperitoneally (10). PTZ + extract groups were given hydroalcoholic *P. crispum* leaf extract at 100, 150 and 200 mg/kg separately through intraperitoneal injection about 30 minutes before PTZ administration (9).

Measurement of total antioxidant capacity (TAC)

The TAC of serum and brain tissue homogenate was determined by the ferric reducing antioxidant power (FRAP) assay. To this end, the FRAP solution was prepared by adding 2.5 mL 0.25 mM acetate buffer (pH 3), 2.5 mL 10 mM TPTZ prepared in 40 mM hydrochloric acid and 2.5 mL 20 mM iron chloride, 6-hydrate. Twenty-five microliters of serum sample or tissue homogenate was mixed with 1.5 mL of FRAP working solution, and 10 minutes later the absorbance was read at 593 nm wavelength by spectrophotometer at 37°C (11).

Measurement of malondialdehyde (MDA) level

To measure MDA level, 200 µL of serum/brain tissue homogenate was mixed with 1.5 ml acetic acid 20%, 1.5 ml thiobarbituric acid 0.8%, and 200 µL sodium dodecyl sulfate solution 8.1%.

The samples were left in boiling water for 60 minutes and then cooled, and then 1 ml distilled water and 5 mL n-butanol-pyridine water were added and the resulting solution was stirred. The mixture was then centrifuged at 4000 rpm for 10 minutes and the optical absorbance of the supernatant was recorded at 523-nm wavelength (11).

Data analysis

Data were analyzed using SPSS version 16. First, the normality of data distribution was investigated using the Kolmogorov-Smirnov test and then the homogeneity of the variances using Levene's test. Then one-way analysis of variance (ANOVA) was used to examine the significance of differences between the treatments and Tukey's test to compare the mean values. Data were recorded as mean ± SEM and $P < 0.05$ was considered significance level.

Results

In the present experimental study, aimed to investigate the effect of hydroalcoholic *P. crispum* leaf extract on PTZ-induced seizures, 60 male rats were randomly divided into six groups of 10 each consisting of controls, PTZ receiving group, PTZ + extract (100, 150 and 200 mg/kg) receiving groups, and PTZ + phenobarbital (40 mg/kg) receiving group.

Treatment of mice receiving PTZ with *P. crispum* extract (at different concentrations) caused a significant increase in seizure threshold ($P < 0.05$). In the mice of this group, a significant increase in serum and brain MDA levels was observed ($P < 0.05$) but no significant change in antioxidant capacity was noticed.

Treatment of mice receiving PTZ with different concentrations of extract led to a significant increase in brain and serum antioxidant capacity and a significant decrease in brain and serum MDA levels ($P < 0.05$).

The group receiving PTZ was significantly different to the PTZ + phenobarbital ($P = 0.00$), PTZ + extract (150 mg/kg) ($P = 0.00$), and PTZ + extract (200 mg/kg) ($P = 0.00$) groups. The group that received PTZ + extract (100 mg/kg) showed a significant difference to the PTZ + phenobarbital ($P = 0.009$), PTZ + extract (150 mg/kg) ($P = 0.041$), and PTZ + extract (200 mg/kg) ($P = 0.001$) groups, but no significant difference to the PTZ group ($P > 0.05$) Figure 1.

In addition, the PTZ + extract (150 mg/kg), PTZ + extract (200 mg/kg), and PTZ + phenobarbital groups were not significantly different ($P > 0.05$). The seizure threshold was significantly longer in the PTZ + extract (150 mg/kg), PTZ + extract (200 mg/kg), and PTZ + phenobarbital groups than in the PTZ and PTZ + extract (100 mg/kg) groups.

The group that received PTZ + extract (100 mg/kg) was significantly different to the PTZ ($P = 0.000$), PTZ + extract (200 mg/kg) ($P = 0.000$), and PTZ + phenobarbital ($P = 0.028$) groups. The group that received PTZ + extract (150 mg/kg) was significantly different to the PTZ ($P = 0.000$) and PTZ + phenobarbital ($P = 0.000$) groups. The group that received PTZ + extract (200 mg/kg) showed significant difference to the control ($P = 0.001$), PTZ ($P = 0.000$), PTZ + extract (100 mg/kg) ($P = 0.001$), and PTZ + phenobarbital ($P = 0.000$) groups (Figure 2).

The mean brain MDA level was lowest in the PTZ + extract (200 mg/kg) group followed by the corresponding amounts in the PTZ + extract (100 and 150 mg/kg), control, PTZ + phenobarbital, and PTZ groups. The PTZ + extract (150 mg/kg) group was not significantly different to the PTZ + extract (100 and 200 mg/kg) groups ($P < 0.05$).

The group that received PTZ + extract (100 mg/kg) showed significant difference to the control ($P = 0.000$), PTZ ($P = 0.000$), PTZ + extract (150 mg/kg) ($P = 0.051$), PTZ + extract (200 mg/kg) ($P = 0.000$) and PTZ + phenobarbital ($P = 0.000$) groups.

The group that received PTZ + extract (1500 mg/kg) showed significant difference to the control ($P = 0.000$), PTZ ($P = 0.000$), extract (100 mg/kg) ($P = 0.051$), PTZ + extract (200 mg/kg) ($P = 0.020$) and PTZ + phenobarbital ($P = 0.000$) groups.

The group that received PTZ + extract (200 mg/kg) showed significant difference to the control ($P = 0.000$), PTZ ($P = 0.000$), PTZ + extract (100 mg/kg) ($P = 0.001$), PTZ + extract (150 mg/kg) ($P = 0.020$) and PTZ + phenobarbital ($P = 0.000$) groups(Figure 3).

The mean brain FRAP was highest in the PTZ + extract (200 mg/kg) followed by the corresponding amounts in the PTZ + extract (100 and 150 mg/kg), control, PTZ + phenobarbital, and PTZ groups. The control group was not significantly different to the PTZ + phenobarbital group in this regard ($P < 0.05$).

The group that received PTZ + extract (100 mg/kg) showed significant difference to the PTZ ($P = 0.036$), PTZ + extract (150 mg/kg) ($P = 0.000$), and PTZ + extract (200 mg/kg) ($P = 0.000$) groups (Figure 4).

The group that received PTZ + extract (150 mg/kg) showed significant difference to the control ($P = 0.000$), PTZ ($P = 0.000$), extract (100 mg/kg) ($P = 0.000$), and PTZ + phenobarbital ($P = 0.000$) groups. The group that received PTZ + extract (200 mg/kg) showed significant difference to the control ($P = 0.000$), PTZ ($P = 0.000$), PTZ + extract (100 mg/kg) ($P = 0.001$), and PTZ + phenobarbital ($P = 0.000$) groups.

The mean serum FRAP was highest in the PTZ + extract (200 mg/kg) followed by the corresponding amounts in the PTZ + extract (100 and 150 mg/kg), control and PTZ + phenobarbital, and PTZ groups. The phenobarbital,

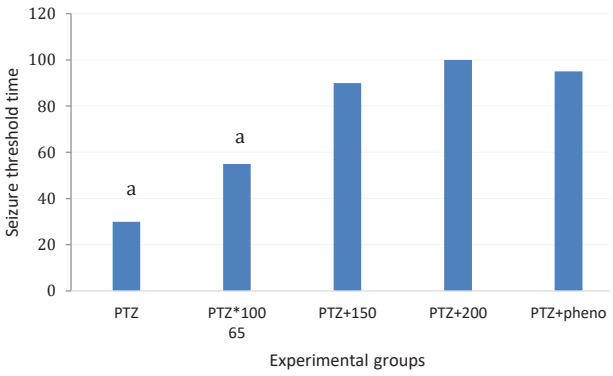

Figure 1. Comparison of seizure threshold in studied groups.
[a] Significant differences to the pentylenetetrazol (PTZ), PTZ + hydroalcoholic *Petroselinum crispum* L. leaf extract (extract, 200 mg/kg), and PTZ + phenobarbital ($P < 0.05$) groups.

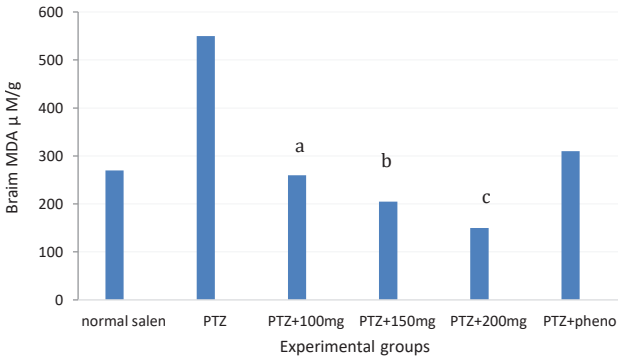

Figure 2. Comparison of mean brain malondialdehyde levels in studied groups.
[a] Significant difference to the pentylenetetrazol (PTZ), PTZ + hydroalcoholic *Petroselinum crispum* L. leaf extract (extract, 200 mg/kg), and PTZ + phenobarbital ($p < 0.05$) groups;
[b] Significant difference to the control, PTZ, PTZ + extract (200 mg/kg), and PTZ + phenobarbital ($P < 0.01$) groups; and
[c] Significant difference to the control, PTZ, PTZ + extract (100 mg/kg), PTZ + extract (150 mg/kg), and PTZ + phenobarbital ($P < 0.01$) groups.

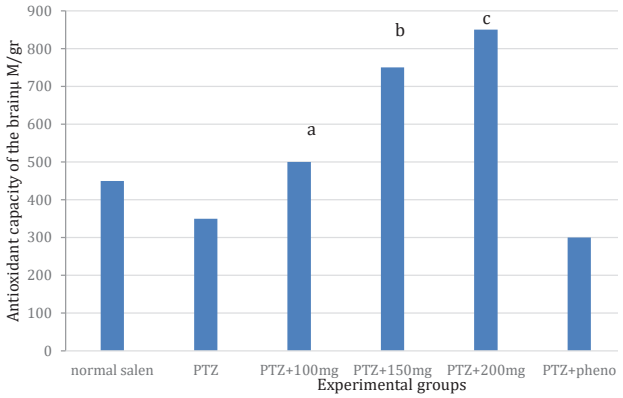

Figure 3. Comparison of mean brain antioxidant capacity in studied groups.
[a] Significant difference to the control, pentylenetetrazol (PTZ), PTZ + hydroalcoholic *Petroselinum crispum* L. leaf extract (extract, 150 mg/kg), PTZ + extract (200 mg/kg), and PTZ + phenobarbital ($P < 0.001$) groups;
[b] Significant difference to the control, PTZ, PTZ + extract (100 mg/kg), PTZ + extract (200 mg/kg), and PTZ + phenobarbital ($P < 0.001$) groups; and
[c] Significant difference to the control, PTZ, PTZ + extract (100 mg/kg), PTZ + extract (150 mg/kg), and PTZ + phenobarbital ($P < 0.001$) groups.

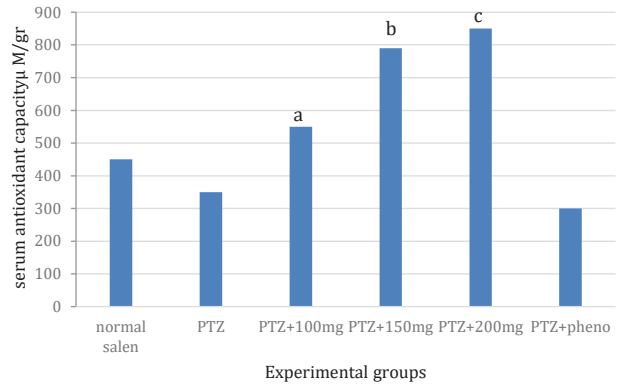

Figure 4. Comparison of serum antioxidant capacity in studied groups.
[a] Significant difference to the pentylenetetrazol (PTZ), PTZ + hydroalcoholic *Petroselinum crispum* L. leaf extract (extract, 150 mg/kg), PTZ + extract (200 mg/kg), and PTZ + phenobarbital ($P < 0.001$) groups;
[b] Significant difference to the control, PTZ, PTZ + extract (100 and 200 mg/kg), and PTZ + phenobarbital ($P < 0.001$) groups; and
[c] Significant differences to the control, PTZ, PTZ + extract (100 and 150 mg/kg), and PTZ + phenobarbital ($P < 0.001$) groups.

control, PTZ, and PTZ + extract (100 mg/kg) groups were not significantly different in this regard ($P < 0.05$).

Discussion

The aim of this study was to investigate the protective effects of *P. crispum* extract against PTZ-induced seizure. We observed that treatment of mice receiving PTZ with 100, 150 and 200 mg/kg of the extract caused a significant increase in seizure threshold. *P. crispum* extract treatment also caused a significant reduction in lipid peroxidation and a significant increase in serum and brain antioxidant capacity in PTZ-receiving mice. The pathological mechanism of epilepsy is extremely complex and many factors are involved in developing the disease, including imbalance in the level of excitability and inhibition of cortical activity, impaired neurotransmitter secretion, structural disorders, ion channel function, decreased endogenous neuropeptides and metabolic brain disease (1,12).

It seems that the compounds in parsley extract with modulation of glutamate and gamma-aminobutyric acid (GABA) and glutamate neurotransmitters have caused anticonvulsant effects in the present study. In a 2004 study by Losi et al, it was observed that apigenin showed protective effects against glutamate-induced toxicity in the cortical cell line (13).

Apigenin also significantly reduces the amplitude and frequency of postsynaptic excitation currents. The results of this study indicate the antagonistic effects of apigenin on NMDA receptors (13). Studies have shown that luteolin inhibits calcium uptake from voltage-dependent calcium channels, causing of rat cortical synaptosomes (14).

Laboratory studies have also shown that the combination of apigenin 7-O-glucoside with inhibition of NMDA receptors reduces intracellular calcium, followed by the release of glutamate and neuropeptides, and inhibits the postsynaptic stimulatory activity of glutamate neurons (15).

In the present study, a significant increase in MDA level, as a marker of lipid peroxidation, was observed in the brain and serum of mice receiving PTZ. Subsequent treatment of mice receiving PTZ with *P. crispum* extract at different concentrations not only reduced lipid peroxidation in the brain and serum, but also significantly increased their antioxidant capacity.

The protective effects of *P. crispum* extract on oxidative stress in the brain and other vital organs due to toxic compounds have been demonstrated in several studies. In one study, the extract showed inhibitory effects against lipid peroxidation induced by free radicals in brain homogenate (16).

Ethanol extract of *P. crispum* leaves in mice receiving digalactose significantly reduced lipid peroxidation and increased the activity of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) (10).

The plant extract has also been shown to have protective effects on oxidative stress in brain tissue due to cadmium (17). In addition, different concentrations of aqueous extract of parsley reduced the peroxidation of nerve cells

in the experimental model of Parkinson's induction with 6-hydroxy dopamine in male rats (9).

Studies have reported that apigenin, which is also present in *P. crispum* extract, produces protective effects by counteracting oxidative stress against kainic acid-induced seizures in vivo and in vitro. Treatment of seizure mice with apigenin at concentrations of 25 and 50 mg/kg significantly reduced seizure severity and caused a significant increase in seizure threshold Apigenin also inhibited cytotoxicity induced by kainic acid in neuronal culture media. Researchers have reported that apigenin protects neurons against kainic acid-induced cytotoxicity by decreasing the production of oxygen free radicals and increasing the reduced levels of glutathione (18). Apigenin has also been shown to have inhibitory effects against oxidative stress and apoptosis caused by subarachnoid hemorrhage in rats (19). In another study, luteolin, another compound in the plant extract, could inhibit oxidative stress markers in the brains of mice exposed to heroin (20). and sodium nitroprusside (21). Laboratory studies show that induction of seizures in rodents causes a significant increase in inflammatory mediators in areas affected by seizures, and anti-inflammatory drugs can reduce the severity of some types of seizures in animal models (22). Inflammatory processes often begin before the onset of seizures and play an etiopathogenic role in the development of spontaneous seizures (23). In studies of animal models, a rapid inflammatory response was observed to begin in the glia immediately after induction of seizures by electrical or chemical stimuli. High expression of inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 (IL-6) in astrocytes reduces seizure threshold and spontaneous seizure frequency (24). Inflammatory cytokines such as IL-1 beta induce stimulating activity, reduce GABA production and release, and intensify inward movement of calcium by activating IL-1R and TLR4 receptors and then the IL-1R/TLR signaling pathway (25). Research evidence shows that flavonoids can reduce seizure severity in animal models by reducing the levels of inflammatory mediators (26). Due to the anti-inflammatory effects of *P. crispum* extract (27) and its active ingredients including apigenin (28), luteolin (29,30), apigenin glycoside (31) and coumarin (32), anti-inflammatory activity can be supposed to be one of the mechanisms involved in producing the anti-inflammatory effects of the extract, however, this argument needs to be further examined.

Conclusion

In the present study, *P. crispum* extract showed protective effects against PTZ-induced seizures in rats possibly due to reduced lipid peroxidation and strengthening of the antioxidant defense system, followed by reduced nerve cell damage and apoptosis. The anticonvulsant effects of *P. crispum* extract seem to be related to its active ingredients including apigenin, apiin and luteolin.

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Authors' contribution

NJ, ER, ZF: Data acquisition, analysis, and interpretation, and draft writing. NJ and ZF: Study designing, and critical revision of the manuscript for important intellectual content. NJ: Study designing, data analysis and interpretation, and supervision. All authors wrote the draft of the manuscript and approved the final manuscript.

Conflict of interests

The authors declared that there is no conflict of interests.

Ethical Approval

The ethics approval was obtained from Shahrekord University of Medical Sciences (with the ethical code of IR.SKUMS.REC.1396.76).

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