

The Effect of Hydroalcoholic *Anethum graveolens* Extract on Hippocampal Markers of Inflammation and Oxidative Stress in a Rat model of Temporal lobe Epilepsy

Sara Amirian¹, Tourandokht Baluchnejadmojarad², Mehrdad Roghani^{3*}

1. School of Medicine, Shahed University, Tehran, Iran

2. Department of Physiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran

3. Neurophysiology Research Center, Shahed University, Tehran, Iran

Abstract

Background and Objective: Temporal lobe epilepsy (TLE) is a neurological disease with no effective treatment and is the most common form of focal epilepsy in adults and is usually resistant to conventional drug treatments. Enhanced oxidative stress and inflammation are important markers of TLE as a result of limbic system involvement. The aim of the present study was to investigate the effect of *Anethum graveolens* (Dill) with known antiepileptic properties on hippocampal markers of oxidative and inflammatory events in kainate rat model of TLE.

Materials and Methods: In this experimental study, 32 male Wistar rats were randomly divided into 4 groups: Sham, sham receiving Dill extract, epileptic, and epileptic receiving Dill extract. Kainic acid was used to induce epileptic seizures in animals. Dill extract at 400 mg/kg was injected intraperitoneally daily, starting one week before surgery and ending one hour before surgery. In the first twenty-four hours after surgery, seizure behavior was recorded and scored based on Racine classification. At the end of the study, oxidative and inflammatory markers were measured in the hippocampal tissue.

Results: The results of this study showed that kainic acid injection significantly increases seizure severity and hippocampal malondialdehyde (MDA), nitrite, tumor necrosis factor α (TNF α) and cyclooxygenase-2 (COX-2) and decreased catalase activity and pretreatment with Dill extract in the epileptic group significantly reduced seizure behavior and hippocampal MDA, TNF α , and COX-2 and improved catalase activity.

Conclusion: Pretreatment with Dill extract reduces seizure intensity and lowers hippocampal oxidative stress and inflammation in the kainate epileptic rats.

Keywords: Temporal Lobe Epilepsy, Kainate, *Anethum graveolens*, Cyclooxygenase-2, Inflammation, Oxidative Stress

1. Introduction

Epilepsy is regarded as one of the most common neurological problems in the world. Epilepsy dates back to the Stone Age. It was well known in ancient civilizations. It is a chronic disorder characterized by recurrent seizures. During epileptic seizures, there is a sudden and severe discharge of the nervous system caused by the abnormal and simultaneous discharge of brain neurons, which leads to sensory disturbances, loss of consciousness, mental disorders, and convulsive movements (1). Factors that intensify neuronal excitation and increase neuronal depolarization include oxygen deficiency, oxidative and inflammatory changes, blood glucose deficiency, blood alkalosis, fluid retention in the body, lack of sleep, and some medications (2-4). Kainic acid (KA) is L-glutamate analogue and a powerful agonist of KA receptors. It was first extracted from a red algae, i.e. *Digenea simplex*. KA exposure could induce robust depolarizations and with eventual cell death which is also observed in TLE (5). After KA injection, hippocampal levels of reactive oxygen species (ROS) and malondialdehyde (MDA) increase and levels of antioxidants such as superoxide dismutase (SOD), heme oxygenase (HO) and glutathione (GSH) decrease. Inflammation is another important pathogenic factor in the epileptogenesis event. Activation of NF- κ B signaling and release of tumor necrosis factor α (TNF- α) leads to cell death and neuronal rearrangement (6-8).

Despite the presentation of a multitude of drugs with different forms of action for controlling epilepsy, however, 20–30% of people are still not responding to these drugs. Thus, exploring new drugs with less side effects is of high clinical significance. Presently, some studies have focused on analyzing the efficacy of herbal medicines for epilepsy management (9, 10).

A. graveolens (Dill in the plant family Apiaceae) is an aromatic medicinal plant which is cultivated worldwide. The Dill seeds have intense fragrance and are routinely used as a spice to flavor the food products (11). Both the leaves and fruits of this plant have therapeutic properties such as antioxidant, anti-inflammatory, antinociceptive, anti-microbial, anti-parasitic, and even diuretic effects (12). This herb is also effective for controlling irritable

bowel syndrome, hyperlipidemia, diabetes, and so forth (13, 14). Furthermore, Dill products can also improve cognitive function in animal models (15, 16). Additionally, Dill extract could exert protective role against nicotine-provoked neurotoxicity through alleviating oxidative and inflammatory events and reducing behavioral changes in mice (17). Meanwhile, drinking of the essential oil of Dill containing carvone and limonene can be considered as a promising strategy for protecting the tissues against cadmium-instigated oxidative damage (18). Of relevance to this study, hydroalcoholic Dill extract can attenuate dentate gyrus neurodegeneration in the epileptic mice (19) besides its attenuation of pentylenetetrazol-induced seizures in adult mice (20). Thus, this study was done to evaluate the effect of hydroalcoholic *A. graveolens* extract on hippocampal markers of oxidative stress and inflammation in the kainate rat model of TLE.

2. Materials and Methods

In this study, 32 male Wistar rats weighing 190–220 g were used and the animals were randomly divided into 4 groups. All animals were housed at 21–23°C in groups of 3 to 4 per cage. The animals had free access to tap water and rat food for 3 weeks. In addition, the study was conducted according to the protocols and guidelines recommended by the National Institutes of Health for the Care and Use of Laboratory Animals. The animals were randomly divided into the following groups: Sham group, Sham receiving hydroalcoholic Dill extract which was injected intraperitoneally at a dose of 400 mg/kg daily from one week before surgery till one hour before surgery, Epilepsy, and Epilepsy treated by Dill hydroalcoholic extract at a dose of 400 mg/kg. For inducing epileptic seizures, kainic acid (Sigma, USA) was used at a dose of 0.8 μ g per rat dissolved in normal saline solution and injected into the CA3 region of the right hippocampus with anteroposterior coordinate: - 4.1 mm, lateral: 4 mm, and ventral 4.2 mm below the skull surface using a Hamilton syringe (injection volume was equal to 5 μ l). For stereotaxic surgery, rats were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (8 mg/kg).

In the first 24 hours after surgery, rats were evaluated for seizure behavior based on the Racine classification (scored from zero to five) at four-hour intervals using a behavior recording camera and data transfer to a computer. In this regard, a score of zero was considered for no response, a

score of one was for mounting, blinking, or mild facial clonus, a score of two was for head shaking or multiple clonus in the head area, a score of three was for myoclonic jerks in the forelimbs, a score of four was for clonic seizures in the forelimbs and rising on two legs, and a score of five was for clonic and generalized seizures in the body and loss of balance. At the end of the work (seven days after the surgery), hippocampal oxidative and inflammatory markers were measured.

2.1. Biochemical assessment

To prepare 2.5% hippocampal tissue homogenate, we added hippocampal blocks to 150 mM Tris-HCl lysing solution. This was done and then we mixed the resulting mixture using a homogenizer. We transferred the resulting suspension to a refrigerated centrifuge while maintaining the cold chain and centrifuged at 5000 rpm for 10 minutes. Then, we separated the resulting supernatant from the sediments using a sampler and transferred it into a microtube.

2.1.1. MDA assay

MDA is an indicator of lipid peroxidation. It is also classified as a family of oxidative stress indicators. For MDA assay, a dedicated MDA assay kit from Sigma Aldrich, USA was used. This kit is based on the reaction with thiobarbituric acid (TBA). After reacting with thiobarbituric acid at boiling temperature, malondialdehyde produces a pink color that can be examined in a spectrophotometer with a maximum light absorption at a wavelength of 532 nm. Finally, we studied the obtained absorbances based on a standard curve drawn based on tetraethoxypropane dilutions.

2.1.2. Nitrite assay

Nitrite is a side metabolite resulting from nitric oxide metabolism. The Griess method was used to measure nitrite levels. To perform this method, we took 50 μ l of the tissue homogenate supernatant and mixed it with 50 μ l of Griess reagent under acidic conditions. This reagent contains n-naphthylethylenediamine and sulfanilamide. Then, we rested it for 10 minutes at room temperature and finally read its optical absorption at a wavelength of 540 nm. Then we compared it with known concentrations of sodium nitrate.

2.1.3. Catalase activity assay

This enzyme is one of the main enzymes that

neutralize hydrogen peroxide. Therefore, it is considered an antioxidant enzyme. In this study, a specific catalase activity assay kit from Kiazist Company, made in Iran, was used to measure catalase. In this experiment, catalase has peroxidase activity in the presence of methanol and stops in the presence of its inhibitor, and the formaldehyde produced from it reacts with Purpald and produces a purple color, which ultimately absorbs light at a wavelength of 540 nm. Finally, we added the periodate solution in the kit and read it after 5 minutes at a wavelength of 550 nm and studied the absorbances with the formula in the kit.

2.1.4. TNFa and COX-2 assay

We used specific Elisa antibodies (Santa Cruz, USA) for these parameters and optical density was obtained at 450 nm.

2.2. Statistical analysis

Statistically, all results were expressed as mean \pm standard error of the mean (SEM). After determining the distribution of data using the Kolmogorov-Smirnov test, one-way parametric ANOVA was used to analyze the behavioral and biochemical parameters. In all studies, $p < 0.05$ was considered as the significant level.

3. Results

3.1. Findings on oxidative factors and antioxidants

Figure 1 shows the results of hippocampal tissue malondialdehyde level, as an indicator of lipid peroxidation, in the different groups. In this regard, there was no significant difference in the sham group receiving *A. graveolens* extract at a dose of 400 mg/kg compared to the sham group. In the kainate group, a significant and obvious increase in malondialdehyde was obtained compared to the sham group ($p < 0.001$), and the same significant increase in malondialdehyde was also obtained to a lesser extent in the kainate group treated with the extract at a dose of 400 mg/kg compared to the sham group ($p < 0.05$). On the other hand, the hippocampal MDA level in the kainate group receiving *A. graveolens* extract had a significant decrease compared to the kainate group ($p < 0.05$).

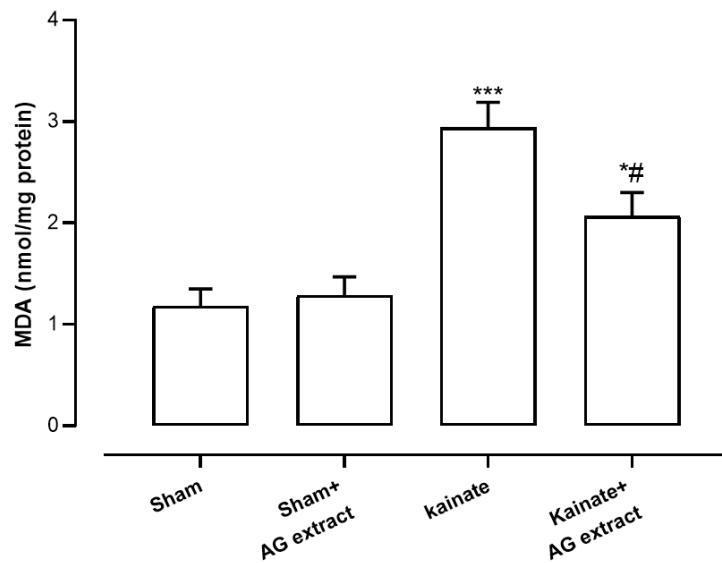


Fig. 1. This figure shows hippocampal MDA level as an indicator of lipid peroxidation in different groups under study. *A. graveolens* (AG) extract was given at a dose of 400 mg/kg. * $p<0.05$, *** $p<0.001$ (compared with the sham group), # $p<0.05$ (compared with the kainate group).

Figure 2 shows the results of hippocampal nitrite level, as an indicator of nitric oxide (NO) metabolism in the different groups. In this regard, there was no significant difference in the sham group receiving *A. graveolens* (AG) extract at a dose of 400 mg/kg compared to the sham group. In the kainate group, a significant increase in nitrite was obtained compared to the sham group

($p<0.05$) and no such increase was noted in the kainate group treated with the extract at a dose of 400 mg/kg compared to the sham group ($p>0.05$). On the other hand, the hippocampal nitrite level in the kainate group receiving *A. graveolens* extract had no significant decrease as compared to the kainate group ($p>0.05$).

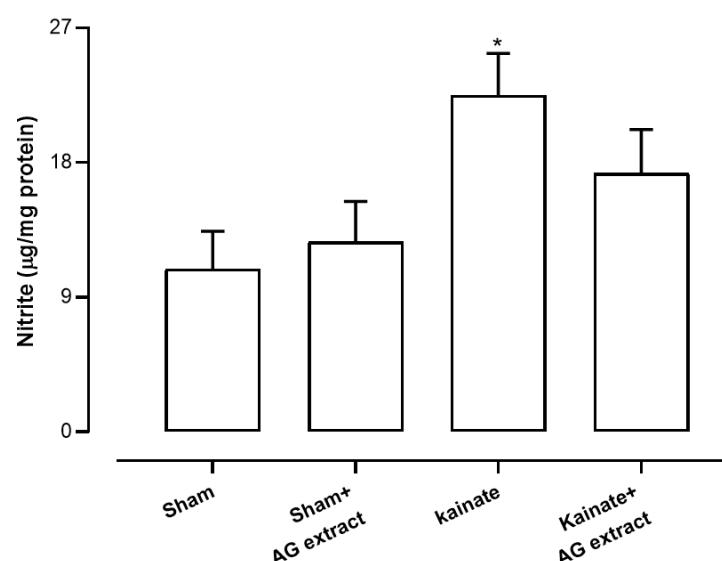


Fig. 2. This figure shows hippocampal nitrite level as an indicator of nitric oxide (NO) production and metabolism in different groups. *A. graveolens* (AG) extract was given at a dose of 400 mg/kg. * $p<0.05$ (compared with the sham group)

Figure 3 shows the results of hippocampal activity of catalase as an indicator of defense against hydrogen peroxide in the different groups. In this regard, there was no significant difference in the sham group receiving *A. graveolens* extract at a dose of 400 mg/kg compared to the sham group. In the kainate group, a significant reduction of catalase activity was obtained compared to the

sham group ($p<0.01$) and no such decrease was noted in the kainate group treated with the extract at a dose of 400 mg/kg compared to the sham group ($p>0.05$). On the other hand, the hippocampal catalase activity in the kainate group receiving *A. graveolens* extract had a significant increase as compared to the kainate group ($p<0.05$).

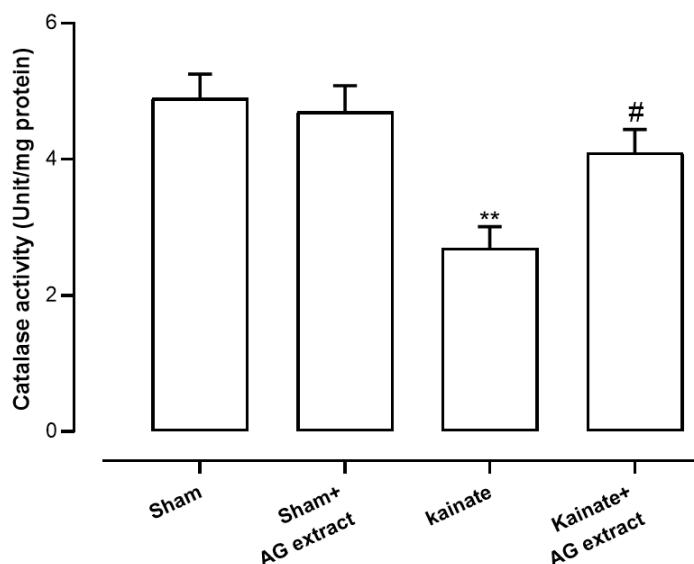


Fig. 3. This figure shows hippocampal activity of catalase as an indicator of defense against hydrogen peroxide in different groups. *A. graveolens* (AG) extract was given at a dose of 400 mg/kg. ** $p<0.01$ (compared with the sham group), # $p<0.05$ (versus the kainate group)

3.2. Finding on inflammatory factors

By measuring the hippocampal level of cyclooxygenase-2 (COX-2) by sandwich ELISA method, it was determined that the level of this enzyme in the sham group pretreated with hydroalcoholic extract of Dill seeds at a dose of 400 mg/kg did not show a significant decrease compared to the sham group, in the kainate group treated with kainic acid, a significant increase in

the level of this enzyme was observed compared to the sham group ($p<0.01$), and pretreatment of the kainate group with hydroalcoholic extract of Dill seeds caused a smaller increase in this parameter compared to the sham group ($p<0.05$). Also, pretreatment of the kainate group with hydroalcoholic extract of Dill seeds caused a significant decrease in cyclooxygenase 2 compared to the kainate group ($p<0.05$) (Figure 4).

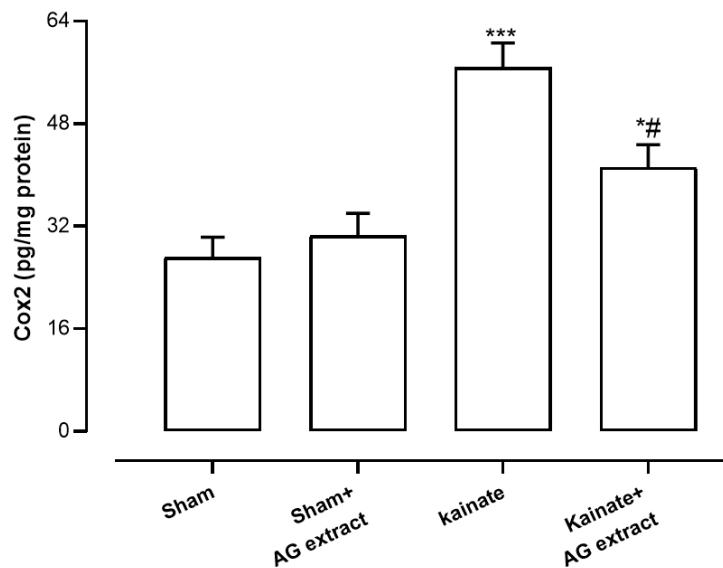


Fig. 4. This figure shows hippocampal level of COX-2 as an indicator of inflammation in different groups. *A. graveolens* (AG) extract was given at a dose of 400 mg/kg. * p<0.05, *** p<0.001 (compared with the sham group); # p<0.05 (versus the kainate group)

By measuring the hippocampal level of the inflammatory index TNF α by the sandwich ELISA method, it was determined that the level of this factor in the sham group pretreated with 400 mg/kg Dill seed hydroalcoholic extract compared to the sham group had a slight and non-significant increase in the kainate group treated with kainic acid, a significant increase in the level of this factor compared to the sham group was observed

(p<0.001), and pretreatment of the kainate group with Dill seed hydroalcoholic extract caused a smaller increase in this parameter compared to the sham group (p<0.05). Also, pretreatment of the kainate group with Dill seed hydroalcoholic extract caused a significant decrease in this inflammatory index compared to the kainate group (p<0.05) (Figure 5).

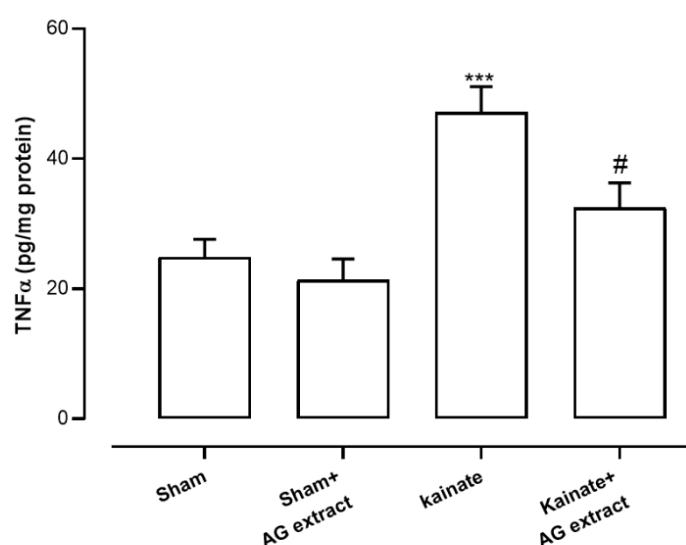


Fig. 5. This figure shows hippocampal level of TNF as an indicator of inflammation in different groups. *A. graveolens* (AG) extract was given at a dose of 400 mg/kg. * p<0.05, *** p<0.001 (compared with the sham group); # p<0.05 (versus the kainate group)

3.3. Behavioral findings on seizure behavior

Figure 6 shows the results of the seizure behavior of the animals based on the Racine classification (ranked from 0 to 5) on the first day after surgery in different groups. In this regard, no seizure behavior was observed in the sham group and the sham pretreated with plant extract. In the

epileptic group with kainic acid, a pronounced seizure behavior was observed with an average score of 4.11, and pretreatment with Dill seed hydroalcoholic extract caused a significant reduction in seizure behavior of the animals with an average score of 2.89 ($p<0.05$).

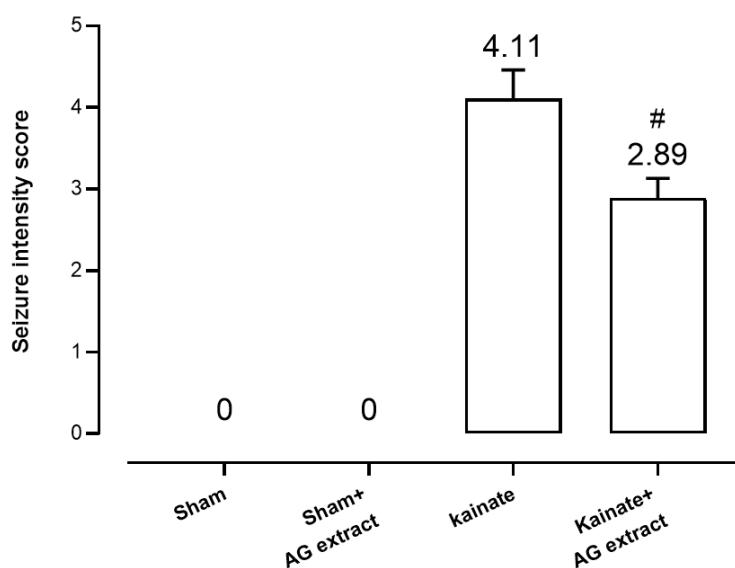


Fig. 6. This figure shows averaged seizure intensity in different groups. *A. graveolens* (AG) extract was given at a dose of 400 mg/kg. # $p<0.05$ (versus the kainate group)

4. Discussion

In this research study, it was shown that administration of the hydroalcoholic extract of *A. graveolens* could reduce kainate-induced seizures. Our finding is in agreement with previous studies which have shown *A. graveolens* extract can attenuate epileptic seizures induced by pentylenetetrazole in mice (21). Thus, the findings of this research may be indicative of its traditional benefits in controlling convulsive seizures, as has been suggested before (19, 20). Components of medicinal plant with potential to combat tonic-clonic seizures in experimental models of epilepsy may be considered effective to control myo-clonic and absence seizures in the human society (22). In this respect, inhibiting

convulsions or increasing the latency to have seizures are appropriate treatment strategies for attaining anticonvulsant activity (23). Our findings demonstrated that *A. graveolens* hydroalcoholic extract has anticonvulsant impact in our kainate model of epilepsy. In this study, we preferred to administer hydroalcoholic extract of the plant to have enough quantity of its active components. In addition, we designed our study in such a way that kainate epileptic rats received the extract daily from 1 week before the study till 1 h before kainate injection. This design allows enough time for the extract to exert its protective effect. It has been shown that *A. graveolens* extract has multiple effective constituents including coumarins, flavonoids, and phenolic acids (24) and these

may have produced its anti-epileptic activity in this study. The anticonvulsant and antiepileptic properties of herbal drugs such as Dill have been documented in previous studies (19-21). There has been evidence on the anti-spasmodic potential of Dill in the mouse. In addition, it has been demonstrated that Dill products could inhibit the entry of calcium into the muscle cells and accordingly reduce contractions (25). Because calcium entry is essential for neuronal excitability, it can be proposed that Dill can reduce kainate-induced seizures in this study through its blocking of calcium channels, however, further studies are still required to investigate this important issue. In our study, by measuring the hippocampal level of cyclooxygenase-2 enzyme, it was shown that in the epileptic kainate group, a significant increase in the level of this enzyme was observed as compared to the sham group, and pretreatment of the kainate group with Dill seed hydroalcoholic extract caused a smaller increase in this parameter compared to the sham group and pretreatment of the kainate group with Dill seed hydroalcoholic extract caused a significant decrease in cyclooxygenase 2 compared to the kainate group. Such reversal effect was also obtained for the inflammatory factor TNFa. Supporting these results, Nam et al in 2021 showed anti-inflammatory and protective

effects of *A. graveolens* seed extract in a rat model of esophageal mucosa damages due to reflux esophagitis which was associated with lower rate of NO production and expression of inflammatory factors (26).

In the current study, part of beneficial effect of *A. graveolens* seed extract in attenuation of kainate epileptic seizures may be attributed to its prevention of lipid peroxidation, as was shown by lower hippocampal levels of MDA. In agreement with this finding, Abbasi et al in 2021 showed that *A. graveolens* can reduce oxidative stress in the liver tissue of rats in a model of non-alcoholic fatty liver disease (27). In addition, it has been shown that oxidative stress is one of the pivotal mechanisms for epilepsy-induced neuronal death. In this regard, it has been clarified that reactive oxygen species (ROS) can have an important role in the seizure-induced neurodegeneration (28). In this respect, part of antioxidant activity of *A. graveolens* can be attributed to its antioxidants such as limonene and sabinene (29).

Conclusion

Pretreatment with Dill hydroalcoholic extract at a dose of 400 mg/kg can reduce seizure intensity and lower hippocampal oxidative stress and inflammation in kainate epileptic rats.

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