http://jbcp.shahed.ac.ir 10.22070/JBCP.2025.20043.1194

Open Access Research Article

Journal of Basic and Clinical Pathophysiology
Print ISSN: 2322-1895, **Online ISSN:** 2345-4334
Vol. 13, No. 1, February 2025

A Semiannual Publication of
Shahed University Press

The effects of *Lavandula angustifolia Mill* extract on status epilepticus and depression-like behavior induced by intrahippocampal kainic acid injection

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Abstract

Background and Objective: Temporal lobe epilepsy (TLE) is a chronic neurological disorder with recurrent seizures, leading to oxidative stress disturbance, hippocampal neuronal damage, and behavior impairment such as depression. Herbal medicines, such as Lavandula angustifolia Mill, have emerged as potential therapeutic agents for various diseases, including epilepsy and depression. This study investigated the protective effects of *L. angustifolia Mill* extract on a rat model of kainic acid (KA)-induced TLE, depressive-like behavior, and oxidative stress.

Materials and Methods: Sixty adult male Wistar rats (250 ± 50 g) were divided into five groups: (1) sham control, (2) sham extract, (3) KA, (4) extract-treated (400 mg/kg), and (5) valproic acid-treated (300mg/kg) epileptic groups (n=12). The extract and valproate were administered via oral gavage daily for 2 weeks before and 4 weeks after intrahippocampal KA injection. Status epilepticus (SE) parameters, depressive-like behavior, and oxidative stress markers were evaluated.

Results: Pretreatment with the extract reduced the onset latency of SE (65 ± 1.5 min), whereas valproic acid increased it (130 ± 2.5 min) compared to the KA group (96.4 ± 1.8 min). The duration of seizures in the extract-treated group (174.3 ± 1.5 min) was longer than in the KA (140.9 ± 1.7 min) and valproic acid-treated groups (102.5 ± 2.6 min). However, the extract reduced the mortality rate (18.75%) more effectively than valproate (31.25%), despite intensifying SE. Additionally, the extract prevented depressive-like behavior induced by epilepsy, reduced hippocampal malondialdehyde (MDA) levels, and enhanced superoxide dismutase (SOD) activity.

Conclusion: Although *L. angustifolia Mill* extract intensified SE, it reduced mortality rates and provided protection against depression, potentially through its antioxidant effects.

Keywords: *Lavandula angustifolia Mill*, Oxidative stress, Depression, Kainic acid, Status epilepticus

1. Introduction

Neurological diseases are the second leading cause of death globally and the primary source of disability, including mood and cognitive impairments or sensorimotor dysfunction, which significantly reduce quality of life. Given the high morbidity rate of neurological disorders such as epilepsy, preventive and therapeutic strategies are crucial (1). Approximately 70 million people worldwide suffer from epilepsy, with the majority residing in low-income countries (2, 3).

The intrahippocampal KA rat model is widely used to study the pathophysiology of TLE and to develop novel therapies for drug-resistant epilepsy. This model replicates critical pathological features of human TLE, such as drug-resistant spontaneous seizures and hippocampal sclerosis (4, 5). Spontaneous recurrent seizures (SRS) alter hippocampal neuronal structures, leading to excitotoxicity, neuronal apoptosis, and necrosis (6). KA, an analog of glutamic acid, induces neurodegenerative conditions (7). Activation of KA receptors triggers intracellular signaling cascades, including reactive oxygen species (ROS) formation, elevated intracellular Ca^{2+}, mitochondrial dysfunction, and other biochemical events that result in neuronal

Received: 21 January 2025**, Revised:** 01 February 2025, **Accepted:** 04 February 2025
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cell death (8). KA-induced SE can lead to SRS and behavioral impairments in rodents (9).

SE is a well-studied model of chronic TLE (10, 11), and is defined as a continuous seizure lasting more than 30 minutes without full recovery of awareness (12). Some minutes after KA administration in anesthetized animals, seizures appear and then develop into SE and lasts for many hours. Prolonged SE can cause neurologic damage and oxidative stress. Additionally, comorbidities such as depression are common in patients with TLE (13, 14).

Conventional treatments for epilepsy are often associated with undesirable side effects or fail to prevent seizure occurrence. Consequently, the therapeutic potential of natural products for neurological diseases has gained attention in recent years (1). Many antiepileptic drugs are ineffective in inhibiting epileptiform activity in TLE (15). Herbal medicines, such as *L. angustifolia Mill*, have been proposed as therapeutic agents for epilepsy and other disorders (13).

L. angustifolia Mill (Lamiaceae), commonly known as "Ustokhodoos" in Iran, has been used in traditional medicine for central nervous system disorders, including epilepsy. Studies suggest that L. angustifolia Mill, or Lavandula officinalis Chaix, is effective in treating nervous disorders such as epilepsy, anxiety, and depression through phytotherapy and aromatherapy (16). Evidence also supports the anticonvulsant properties of lavender family products (17, 18). Protective effects of *Lavandula dentata* in rat models of pilocarpine- or KA-induced TLE have been reported (19, 20).

Lavender essential oil modulates AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor activity, which is overactivated in epilepsy. By acting as an AMPA receptor antagonist, lavender prevents glutamate binding, Ca^{2+} dysregulation, and synaptic dysfunction, thereby exerting neuroprotective effects (21). Compounds in *L. angustifolia Mill* may also coordinate serotonergic neuronal firing by inhibiting glutamate neurotransmission, leading to antidepressant-like actions (22). Furthermore, numerous studies demonstrate lavender's antidepressive effects in the forced swimming test (FST) (13, 23).

Despite these findings, no studies have investigated the effects of L. angustifolia Mill on TLE. This study aims to evaluate the protective effects of L. angustifolia Mill extract against KA-induced refractory TLE and subsequent depressive-like behavior. Additionally, oxidative stress and antioxidant biochemical parameters were examined to elucidate the underlying mechanisms.

2. Materials and Methods

2.1. Animals

Sixty adult male Wistar rats (Pasteur's Institute, Tehran, Iran) weighing 250 ± 50 g were housed under a 12 h light/dark cycle at 22 ± 2 °C with free access to food and water. Animals were acclimatized for one week before experimentation.

2.2. Code of ethics

This study adhered to the National Institutes of Health's Guide for the Care and Use of Laboratory Animals (NIH) and was approved by the Research Ethics Committee of Shahed University (IR.SHAHED.REC.1400.062).

2.3. *Animal groups*

The rats were divided into five groups (n = 12): (1) Sham control (saline); (2) Sham extract (L. angustifolia Mill, 400 mg/kg); (3) KA epileptic group; (4) KA treated extract (KA + extract, 400 mg/kg); (5) KA treated valproic acid (KA + valproic acid, 300mg/kg, and positive control).

2.4. Drugs administration

Hydroalcoholic extract of *L. angustifolia Mill* (Gorgan, Iran), kainic acid (Sigma-Aldrich USA), valproic acid (Damavand Darou, Iran), Enzyme kit for oxidative stress measurement (Zell Bio GmbH, Germany), and ketamine and xylazine (Barmer Germany) for rat anesthesia.

Lavender extract (400 mg/kg) and valproic acid (300 mg/kg) (24) were administered via oral gavage for two weeks before and four weeks after KA injection. KA (1 µg/rat) was dissolved in sterile saline and injected into the right hippocampus using a stereotaxic instrument. Volume of KA injection was 2 µl.

2.5. Plant extraction

L. angustifolia Mill was obtained from Gorgan, Iran, and authenticated by Dr. Amin (Herbarium of Faculty of Pharmacy, Tehran Medical Sciences University; Voucher specimen no. 1338). For extraction, 1 kg aerial parts of the plant was dried and soaked for 3 days in 70% ethanol (1:4) at room temperature (24°C). The solution was filtered three times and dried in a heated bath at 40°C, resulting concentrated to yield a honey-like extract (10% yield), and stored at 4°C until use. The extract was diluted in normal saline and administered via oral gavage at 400 mg/kg (25) for 6 weeks (2 weeks before and 4 weeks after surgery (20, 26).

2.6. Experimental procedure

2.6.1. Animal surgery

After two weeks pretreatments, rats were anesthetized (ketamine 65 mg/kg and xylazine 14 mg/kg, i.p.) and placed in a stereotaxic apparatus (Azma Sanat, Iran) with incisor bar set at 3.3 mm below the interaural line. After exposing the dorsal surface of the skull and drilling a burr hole, KA (1 µg/2 µl) was injected into the right hippocampus with the coordinates of Bregma and Lambda points (AP = -4.8, L = 4.8, and V = 6) from Paxinos atlas. (27). Sham control rats only received the same volume of normal saline. For induction of rat model of TLE, KA injections were performed using Hamilton syringe with a total volume of 5 all. KA (1 µg/2µl) was injected at a rate of 1 min.

2.6.2. SE and mortality rate study

Seizures appeared after decaying of anesthetic effects. SE were recorded for 4 hours post-kainic acid injection with camera and then video recordings were scored using Racine's classification: (28).Summary, Racine's criteria is as follows: 0-No activity mounting, 1-blinking or mild clonus, 2- Head shaking or multiple clonus in head, 3-Myclonic jerks in anterior limbs, 4-Myoclonic convulsion in anterior limbs and standing on the foots, 5-Generalized tonic-clonic seizures and loss of balance. Seizure intensity was considered scales of 3-5 Racine's classification for the SE study. The onset latency as time lasting to SE appearance and SE duration as time spent in SE states during 4 hours was studied. Also, mortality rates were evaluated during protocol.

2.6.3. Depression-like behavior study (FST)

The depression like behavior caused by epilepsy was studied by FST. On the first day of the test (pretest session), rats were individually placed into cylindrical recipients (diameter 30 cm, height 59 cm) containing 25 cm of water at 23-25°C. The rats were left to swim for 15 min before being removed, dried and returned to their cages. 24 h later, test session was performed for 6 minutes, the first 2 minutes were considered for animal adaptation, and in the last 4 minutes, the duration of immobility (time spent floating with the minimal movements to keep the head above the water), and swimming (time spent with active swimming movements) were recorded using a stopwatch (32). Then, animals were dried in warm room and were returned to their cages.

2.6.4. Oxidative stress and antioxidant evaluation 1 and 4 weeks after KA injection

1 and 4 weeks post-KA injection, 4 rats in each groups were sacrificed under anesthesia (ketamine (150 mg/kg) (29). right hippocampal tissues were removed, rinsed with cold 0.9% saline and weighed. The brain samples were homogenized in cold phosphate buffer solution (0.1 mole, pH = 7.4) using an electric homogenizer. The samples were centrifuged at 4000 rpm for 20 minutes, and the supernatant was stored at -80°C. Supernatant was used for biochemical analysis such as MDA and SOD. Also, Protein concentration was measured using the Lowry method (30).

2.6.4.1. Measurement of hippocampal MDA concentration

Lipid peroxidation was assessed by determining MDA content by using a commercial colorimetric assay kit (Zell Bio GmbH, Germany, ZB-MDA). The pink color produced by the interaction of barbituric acid with MDA at high temperature which absorbed maximally at 535 nm using a spectrophotometer (21).

2.6.4.2. SOD activity assay

The activity of SOD was determined by using a colorimetric assay kit from Zell Bio GmbH (Germany, ZB-SOD) and measured at 420 nm. SOD activity is indicator of the decomposition of 1 µ mole of superoxide radical to H2O2 and O2 per minute, and was estimated using a spectrophotometer (31).

2.7. Statistical analysis

The one-way analysis of variance (one-way ANOVA) was used for comparing between groups, followed by pairwise comparisons using the Tukey test, if the data were the parametric. When the data were nonparametric, the Mann-Whitney test was used. ($P \leq 0.05$). was considered as significant. Graphs were generated using Excel 2020, SPSS 16, and GraphPad Prism 8.

3. Results

3.1. SE and mortality rate study

3.1.1. The effects of *L. angustifolia Mill* extract and valproic acid on rat SE behavior induced by intrahippocampal KA injection

SE intensity indices such as onset latency and duration have been shown in Fig. 1A and B respectively. The onset latency of SE (1A) was 96.4±1.8 min in the KA epileptic group, and the extract reduced it (65±1.5 min.), so that SE appeared sooner. However, valproic acid treatment delayed SE occurrence (130±2.5 min.) compared to KA group ($P \leq 0.001$). In this regard, there was significant difference between the extract (65±1.5 min.) and valproic acid-treated rats (130.3±2.5 min.) ($P \leq 0.001$). The duration of SE (1B) in the extract-treated epileptic rats (174.3±1.5 min.) was longer than the KA epileptic group (140.9±1.7 min.) ($P \leq 0.001$). However, valproic acid reduced duration of SE (102.5±2.6 min.) in compared to KA ($P \leq 0.001$). The results showed that the extract not only failed to reduce SE intensity but also enhanced it. On the other hand, valproic acid, as an anti-epileptic drug, could reduce SE intensity.

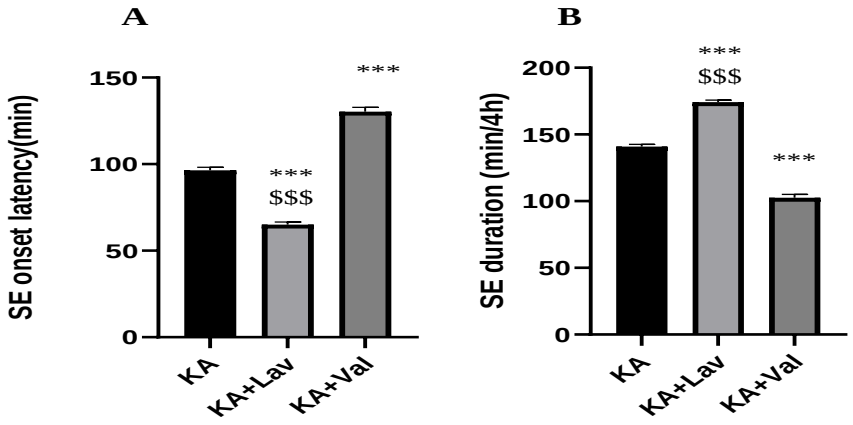

Fig. 1. The effects of L. angustifolia Mill extract (400 mg/kg) and valproate on SE intensity. (A) SE onset latency (min) and (B) SE duration (min) /4 hours). Data are presented as mean ± SEM. Number of rats in each group was n=12. Significant difference is exhibited by *** for the KA epileptic group ($p \leq 0.001$), and by $$$ for the valproate-treated group ($p \leq 0.001$).

3.1.2. Efficacy of *L. angustifolia Mill* extract and valproate on mortality rates caused by KA

Fig. 2 shows the mortality rate (%) in the epileptic groups. The mortality rate In the KA epileptic group was 56.25%, while the extract reduced it to 18.75%, despite of the SE intensification. On the other hand, valproic acid as an antiepileptic drug, also declined the mortality rate to 31.25%. The results explain that the extract protected the animals of mortality, more effectively than valproic acid. These results also indicate that, the extract decreased the death rate of animals, in spite of the SE intensity potentiation.

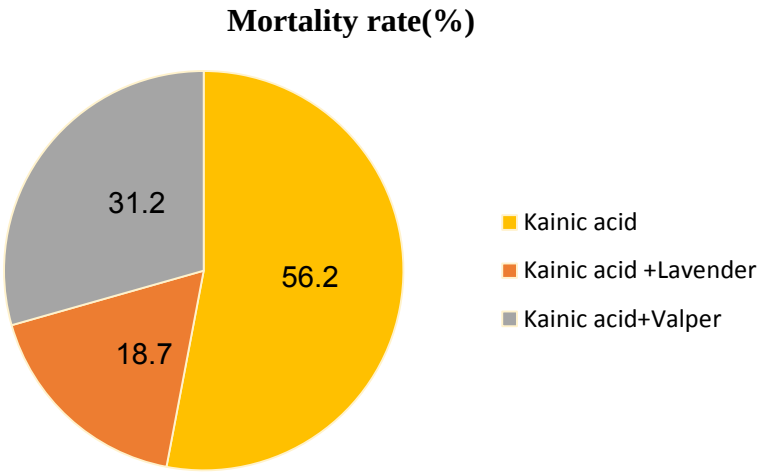

Fig. 2. The effects of *L. angustifolia Mill* extract (400 mg/kg) and valproate on mortality rates (%)

3.2. Depression like behavior induced by KA

3.2.1. The effects of *L. angustifolia Mill* on rat swimming and immobility time in FST

The effects of the Lavender extract (400 mg/kg) on depression like behavior induced by KA were evaluated using the FST (Fig.3.). The results showed that KA induced epilepsy, caused rat depression like behavior as evidenced by decreased swimming time (56±3.6 min). Fig. 3A illustrates that, the extract and valproic acid treatment for 4 weeks post-KA injection, prevented the depression state as evidenced by increased swimming times (215±3.8 and 167.8±3.5 min respectively) ($p \leq 0.001$). On the other hand, Fig.3B shows the time spent floating in the FST (immobility time), in different epileptic and non-epileptic groups. The results explain that, immobility time increased (183.25±3.6 min) significantly, in the KA epileptic rats. While, extract and valproate treatment led to reduction of it (25±3.8 and 72.1±3.5min respectively) ($p \leq 0.001$). It is necessary to emphasize that, the Lavender extract prevented depression like behavior more effectively than valproic acid.

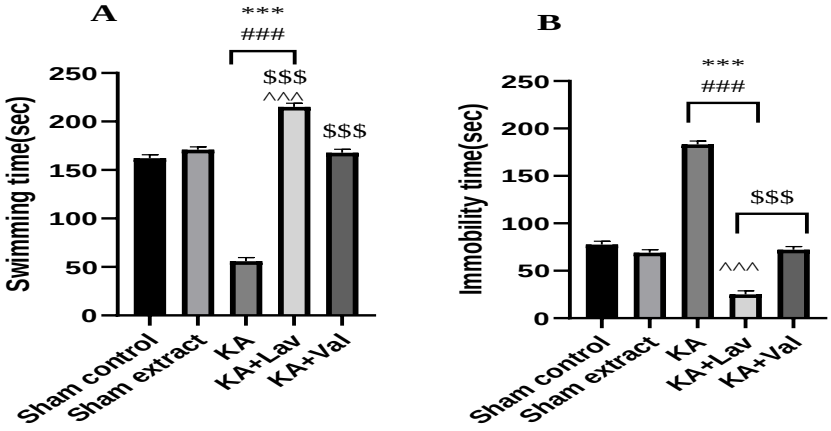

Fig 3. The effects of L. angustifolia Mill extract on swimming (A) and immobility time (B) in FST. Data are presented as mean ± SEM. Number of rats in each group was n=8 ($p \leq 0.001$). Significant difference is indicated by *** for the sham control group, by ### for the sham extract group, by $$$ for the KA epileptic group, and by ^^^ for the valproate-treated group ($p \leq 0.001$).

3.3. Hippocampal oxidative stress and antioxidant activity

3.3.1. Hippocampal MDA levels

1 and 4 weeks post-KA injection, the values of MDA was assessed in epileptic and non-epileptic groups. Fig. 3A shows that one week after hippocampal KA injection, the MDA level in the KA epileptic group (22.5±0.91) was significantly higher ($p \leq 0.05$) than the sham control (11.47±3.1) and the sham extract groups (10.18±3.5). In the other words, KA promoted oxidative stress agents such as MDA. One-week extract treatment (400 mg/kg) post-KA injection, couldn't decrease (21.9±1.3) KA induced MDA elevation. Also, valproic acid treatment (300 mg/kg) did not affect MDA levels (22±0.9). On the other hand, 4 weeks after hippocampal KA injection (Fig. 3B), MDA concentration in KA group was still significantly higher than the sham control (8.9±3) and the sham extract groups (7.1±2.5) ($p \leq 0.05$). The extract treatment (400 mg/kg) for the duration of 4 weeks, unlike valproic acid, declined (18.2±0.3) significantly, MDA enhancement caused by KA ($p \leq 0.05$).

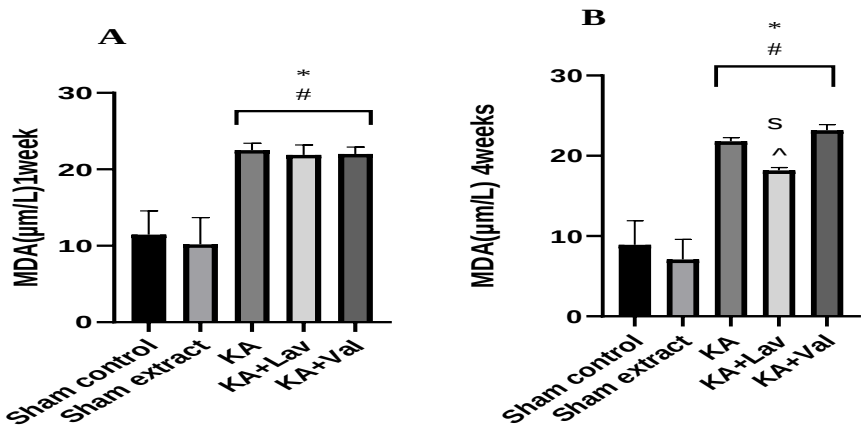

Fig.4. Hippocampal MDA levels in epileptic and non-epileptic groups 1 week (A) and 4 weeks (B) post-KA injection. Data are presented as mean ± SEM. Number of rats in each group was n=4. Significant difference is indicated by ***** for the sham control group (p≤0.05), by **#** for the sham extract group (p≤0.05), by **$** for the KA epileptic group (p≤0.05), and by ^ for the valproate-treated epileptic group (p≤0.05).

3.3.2. Hippocampal SOD levels

SOD activity, as an antioxidant factor, was assessed in epileptic and non-epileptic groups, 1 and 4 weeks after KA injection. Fig. 4. shows that KA administration significantly reduced SOD activity (14.4±3.5) in compared to the sham control (36±3.8) and the sham extract groups (37±4.8) (p≤0.01). 1-week extract and valproic acid treatment (Fig. 4A) unable to recover SOD activity. SOD reduction caused by KA (18±3.1), was still persisted after 4 weeks (p≤0.05) (Fig. 4B). L. angustifolia Mill extract treatment for 4 weeks, partially recovered SOD activity (27.6±2.8), but valproate could not (12.9±4.5). These results demonstrate that repeated administration of Lavender extract improves antioxidant capacity deficit caused by epilepsy.

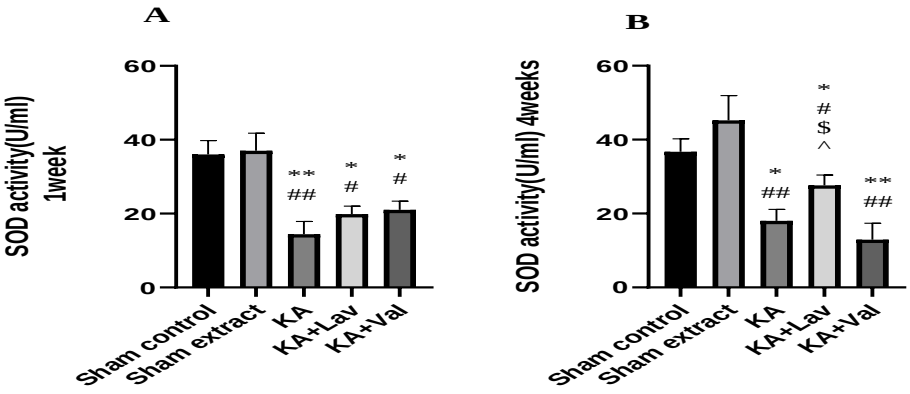

Fig.5. Hippocampal SOD values in epileptic and non-epileptic groups 1 (A) and 4 weeks (B) post-KA injection. Data are presented as mean ± SEM. Number of rats in each group was n=4. ***, **** shows Significant difference with the sham control group (p≤0.05, P≤0.01), **#, ##** with the sham extract group (p≤0.05, P≤0.01), **$** in compared to KA epileptic group (p≤0.05), and ^ relative to valproate-treated group (p≤0.05).

5. Discussion

The intrahippocampal KA rat model is an animal model that extensively used to investigate the pathophysiology of TLE in order to find novel therapies for drug-resistant epilepsy. Following KA injection, three different stages can be identified. 1: continuous seizure activity (SE) that lasts for several hours, then a latent phase of 14–21 days that is followed by the chronic epilepsy phase, with SRS originating from the hippocampus. Hippocampal damage after KA injection involves morphological changes similar to human TLE. It is characterized by loss of neurons in the CA1, CA3, and hilar hippocampal regions, associated with pronounced gliosis, reactive astrocytes and microglia (4, 5, 33). Behavioral and biochemical results of this study showed that intrahippocampal injection of KA induced SE, oxidant-antioxidant balance impairment and finally was caused mood disturbance such as depression-like behavior.

SE induced by KA resulted from imbalance in excitatory and inhibitory neural circuits. For example, GABAergic system impairment is occurred during SE and in the epileptic period. During SE, receptor internalization is increased and the surface expression of GABA receptor subunits is reduced (34). The composition of the GABA A receptor subunit is altered in epilepsy models, associated with drug resistance to GABA A receptor agonists (35).

On the other hand, several evidences explain that epilepsy and depression are comorbid diseases. Indeed, depression is the most common neurological disorder associated with epilepsy, especially temporal lobe epilepsy (36).

Also, it is reported that KA-induced SE leads to oxidative stress promotion in many regions of the brain such as CA1 and CA3 area of the hippocampus. Oxidative stress is one of the main causes of cell death induced by seizures in epilepsy (37-39).

2 weeks pretreatment with L. angustifolia Mill extract (400 mg/kg) led to SE intensification. The extract reduced the onset latency and enhanced total duration of SE. But, in spite of SE augmentation by the extract pretreatment, it declined mortality rate considerably. The results also showed that, L. angustifolia Mill extract (400 mg/kg) treatment for 4 weeks post-KA injection was protected brain from MDA enhancement, SOD reduction and depression like behavior more effectively than valproic acid “as an antiepileptic drug”.

It is reported that *L. angustifolia Mill* is effective in some of nervous disorders such as epilepsy, anxiety and depression through phytotherapy and aromatherapy (16). Also, there are other evidences about anticonvulsive activities of the Lavender family products (17, 18). The molecular mechanisms involved in lavender effects on anxiety and depression have been suggested in previous studies. Some suggestions include: inhibition of GABA-induced currents, inhibition of voltage dependent calcium channels, as an antagonism on the NMDA-receptor and inhibition of serotonin transporter (SERT) (40). Antioxidant and anti-inflammatory mechanism also demonstrated. On the other hand, it has been hypothesized that Lavender antiepileptic mechanism is due to an increase in the inhibitory effect of GABA and potassium current and a decrease in sodium current (41).

Despite numerous reports about lavender's antiseizure effects, this study showed that, pretreatment with L. angustifolia Mill extract (400 mg/kg) intensified SE intensity. Consistent with this data, was another work in our laboratory in which, pretreatment with Lavandula dentata (200 mg/kg) extract augmented SE intensity in KA induced rat model of TLE (20). It seems that elevation of brain serotonin by the extract pretreatment may be a possible reason for enhancement of SE intensity. Recent evidences have explained that, treatment with selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine, adversely has accelerated and escalated epileptogenesis, an effect that may be related to severe pathological neuroplasticity (42, 43). SSRI antidepressants increase the synaptic serotonin concentration, by inhibition of the serotonin reuptake on presynaptic nerve terminals. One study in our laboratory showed that combination of Lavandula officinalis and fluoxetine inhibited depression like behavior more effective than each one alone. This result demonstrates that lavender as well as fluoxetine improve depression behavior probability at least, through enhancement of brain serotonin (44).

In spite of SE amplification, Lavender extracts protected epileptic animals from mortality more effectively than valproic acid, “as an antiepileptic drug”. This result is also agreement with our previous study (20). KA-induced TLE lead to oxidative stress enhancement in many parts of the brain such as CA1 and CA3 regions of the hippocampus. Oxidative stress is the main cause of neural death induced by epilepsy (37, 38, 45). Our previous study showed that, 24 hours after KA injection, brain MDA content had been increased and Lavandula dentate pretreatment prevented it (30). On the other hand, the results of the current study showed that L. angustifolia Mill extract (400 mg/kg) decreased MDA levels more effective than valproic acid. Therefore, it may be suggested that, protective effect of Lavender extract against mortality, was related to oxidative stress reduction. Neurodegenerative diseases are becoming a major public health threat and a leading cause of death in parallel with an increase in life expectancy (46). Despite antioxidant properties, Lavender amplified SE intensity. Excitotoxicity effects of certain compounds such as polyphenols in the Lavender extract can induce apoptosis and decrease cell survival, or conversely, promote cell growth and preservation under specific conditions (47). Additionally, it is

known that not all antioxidants exhibit anticonvulsant activity across all seizure models, indicating that antioxidant properties, necessarily do not lead to inhibition of convulsive behaviors (48). The schedule of lavender extract administration may also play a role, as the timing and schedule of drug administration strongly influence SE outcomes in mice (49). *Nepeta Menthoides Boiss* and Buhse with antioxidant properties also promoted seizure intensity (15).

Mood disorders, including anxiety and depression, occur at higher rates in people with epilepsy than those without epilepsy (50). Epidemiological evidences demonstrate that epilepsy and depression are comorbid disorders. Indeed, depression is the most common mood disorder associated with epilepsy, especially temporal lobe epilepsy (36). The results of this study showed that KA induced SE led to behavioral impairments such as depression like effect. Administration of Lavender extract (400mg/kg) for 4 weeks post-KA injection, prevented and improved depression like behavior as evidenced by increased swimming time and decreased immobility time in FST. These results were consistent with previous studies (23, 51-54). Additive effect of the combination of Lavandula officinalis and fluoxetine on depression like behavior indicates that, Lavender improves it, through enhancement of brain serotonin (51). Also, López, et al. demonstrated that, lavender effects on anxiety and depression may be through NMDA receptor antagonism and inhibition of serotonin transporter (SERT) (40).

Increasing evidences have shown that oxidative stress is a common feature of several neurodegenerative disorders and epilepsy, which causes neural dysfunction, neurotoxicity and death. Therefore, oxidative stress is considered as a possible mechanism in epileptogenesis (26). High levels of polyunsaturated fatty acids and the most oxygen consumption in the brain are the potent substrates for oxidation (26, 39). Elevated oxidative stress is the most important stimulator of neuronal apoptosis by mitochondrial and DNA damaging (26). Kainic acid-induced SE leads to significant increase in the brain oxidative stress, especially in the CA1 and CA3 regions of the hippocampus. Also, oxidative stress is one of the main mechanisms for cell death induced by TLE (37, 38, 45). In the current study, rat model of TLE, induced by intrahippocampal KA injection. This model simulates many pathophysiological features of epilepsy such as elevated the reactive oxygen species (ROS) production, impaired mitochondrial function, impairment of intracellular calcium homeostasis, and neuronal apoptosis in different areas of the brain, especially in the hippocampus (26). It is reported that, MDA, a marker of oxidative damage byproducts of polyunsaturated fatty acid peroxidation, was increased in epilepsy (55). This study showed that MDA values had been increased in epileptic animals, one week after KA injection in hippocampal tissue. This finding is in accord with previous studies (56-58). Also, our results showed that, while, treatment with L. angustifolia Mill extract (400mg/kg) for 1 week post-KA injection did not change MDA elevation induced by SE, but, extract treatment for 4 weeks after surgery mitigated MDA levels, and this is in consistent with previous studies (26, 59-61).

There are several antioxidant agents such as SOD, catalase, and GSH in the brain, against oxidative damage. SOD is an important antioxidant defense in nearly all living cells exposed to oxygen (62). The results of this research indicated that brain SOD activity was reduced as a consequence of SE induced by KA. While, extract administration for 1 week after KA injection could not recover SOD activity, but, extract treatment for 4 weeks after surgery, improved it partially, oppositely valproic acid. This finding is in accord with previous studies (62-65).

Conclusion

The results of this study demonstrate that L. angustifolia Mill extract (400 mg/kg) pretreatment, despite intensifying SE, reduces mortality and protects against depression-like behavior, likely through its antioxidant effects. These findings align with previous studies on lavender's neuroprotective and anti-depressive properties.

Acknowledgement

We thank Baqiyatallah University's Department of Physiology and Medical Physics for providing laboratory facilities.

Conflict of interest

The authors declare no competing interests.

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