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Article

# Effect of amitriptyline on learning and memory consolidation in the male Wistar rats with an experimental model of pentylenetetrazole-induced seizure

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Amitriptyline (AMT) was developed for the treatment of chronic and neuropathic pain. There is also evidence it may be useful in the treatment of neurodegenerative disorders. In this regard, the effect of on the experimental model of seizures and memory impairment caused by seizures in rats is investigated in the present study. Seizures in Wistar rats (200-250 g) were induced by pentylenetetrazole (PTZ, 60 mg/kg, intraperitoneally (i.p.)). The anticonvulsant effect of AMT (10 and 20 mg/kg, i.p.) was evaluated in the seizure model. The effect on memory was assessed using passive avoidance (PA) learning and memory test. After behavioral tests, the animals underwent deep anesthesia and were put down painlessly. Animal serum was isolated for oxidant/antioxidant assays (malondialdehyde (MDA), and glutathione peroxidase (GPx)). Intraperitoneal injection of AMT decreased the mean number of myoclonic jerks and generalized tonic-clonic seizure (GTCS) duration and increased the mean latency of myoclonic jerk and GTCS compared to the PTZ group. Moreover, in the PA test, AMT caused a significant increase in retention latency (RL) and total time spent in the light compartment (TLC) compared to the PTZ group. Biochemical tests showed that AMT was able to significantly increase GPx serum levels and significantly reduce MDA serum levels compared to the PTZ group. Overall, this study suggests the potential neuroprotective effects of the AMT drug in a model of memory impairment caused by seizures via the mechanism of inhibition of the oxidative stress pathway.

**Keywords:** Amitriptyline. Seizure. Pentylenetetrazole. Passive avoidance learning. Oxidative stress.

## INTRODUCTION

Seizure is a condition in which neurons make sudden and simultaneous neural discharges and is often accompanied by changes in the network and neural function. The term epilepsy is also defined as the presence of two or more seizures, which is one of the most common diseases in the world. Epilepsy syndromes refer to a specific set of seizures and electroencephalography and imaging characteristics that typically have age-related characteristics, stimuli, and prognoses. Epilepsy syndromes are the third and final level of diagnosis after seizures and epilepsy. (Katyayan, Diaz-Medina, 2021). Along with seizures, epilepsy is also associated with several other comorbidities, including cognitive deficits, which are very common in patients with epilepsy (Suleymanova, 2021). At present, most cases of epilepsy are treated or controlled with anti-epileptic drugs (AEDs), which, as have been shown, have limitations in performance, safety, and efficacy (Fattorusso *et al*., 2021).

Although there are many studies on how comorbidities with epilepsy develop, there is little information on how a generalized or acute seizure causes memory impairment associated with learning (Carter *et al*., 2017). In addition

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to memory impairment, studies have indicated that acute generalized seizures are associated with increased oxidative stress (OS) and the production of reactive oxygen species (ROS). There is ample evidence that OS plays a pivotal role in promoting seizures and epilepsy, causing membrane lipid peroxidation and depletion of antioxidant enzyme levels (Olowe *et al.*, 2020).

Antidepressants were first used to treat chronic pain more than three decades ago (Hajhashemi *et al.*, 2010). Amitriptyline (AMT) is an antidepressant that has many pharmacological effects. AMT primarily, but not exclusively, binds to serotonin and noradrenaline transporters. Other pharmacological properties at the central and peripheral levels include alpha-adrenergic receptor, endogenous opioid system activation, N-Methyl-D-aspartate (NMDA) receptor antagonists, gamma-Aminobutyric acid (GABA) receptor activation, reduced tumor necrosis factor (TNF) production, and prostaglandin E2 (Rico-Villademoros, Slim, Calandre, 2015). There are reports of the effect of AMT on learning and memory in experimental models of neuropathic pain in rats (Hu *et al.*, 2010; Abdulmajeed *et al.*, 2016).

To the best of our knowledge, so far, there has been no report on the effect of AMT on the seizure process, as well as memory impairment associated with seizures in humans or animal models; likewise, how it affects OS is still unknown. Thus, this study was designed and tested to identify the neuroprotective properties of AMT in seizure-induced rats following memory deficit and to investigate the possible OS mechanisms that AMT may suggest.

## MATERIAL AND METHODS

### Animals

Locally bred male Wistar rats (200-250 g) were used in the present study. These rodents were kept in standard cages in the animal room under controlled conditions (ambient temperature 22 ± 2 °C and 12 h light/dark cycle). Standard food for rats (Pars Animal Feed Co., Iran) as well as water were made available to the animals in an unlimited manner. All the experiments were performed between 9 and 12 A.M. to reduce the effect of the light cycle on the susceptibility to seizures. Working with animals and the implementation of the experiments were completely done in accordance with international ethical principles. The research protocol was also approved by the University's Animal Ethics Committee (IR.BASU.REC.1400.002).

### Drugs and chemicals

Amitriptyline (AMT) (10 mg) was obtained from Darou Pakhsh Pharmaceutical Co., Iran. Pentylenetetrazole (PTZ) was prepared by Sigma Company as a crystalline, white powder.

### Experimental design and treatment protocol

Twenty rats were randomly divided into four groups. It should be noted that the initial sample size was considered thirty-two male Wistar rats, due to drop-out and exclusion criteria in the passive avoidance test, the final sample size was twenty rats (n = 5 per group) which are adequate to reproducibly calculate the variability and statistical differences between the groups as shown by previous works (Ye-wei *et al.*, 2015; Santos *et al.*, 2017; Panahi, Kiani, Feyzi, 2020). Seizures were inducted by intraperitoneal (i.p.) injection of PTZ (60 mg/kg) dissolved in normal saline (Kumar *et al.*, 2018). AMT was injected i.p. at doses of 10 and 20 mg/kg (Ji *et al.*, 2012). The volume of injections in all animals was considered constant at 0.5 mL. The test protocol used to evaluate the effect of AMT on behavioral activities was as follows:

- Group I (control group): Rats that received only physiological saline solution.
- Group II (PTZ group): Rats that received physiological saline solution half an hour before the PTZ injection.
- Group III (AMT 10 group): Rats that received amitriptyline (10 mg/kg, i.p.) half an hour before the PTZ injection.
- Group IV (AMT 20 group): Rats that received amitriptyline (20 mg/kg, i.p.) half an hour before the PTZ injection.

### Behavioral evaluation of seizure manifestation

The motor behavior of the animals in each group was recorded and stored by a computer-connected camera for half an hour after the PTZ injection and was examined by a researcher in a double-blind manner. The latency and number of myoclonic jerks and latency and duration of the generalized tonic-clonic seizure (GTCS) in animals were evaluated based on the stereotypical behavioral manifestations that were displayed after PTZ injections in six stages (TABLE I) (Hosseini, Allahyari, Azizi, 2021).

**TABLE I -** Modified Racine's scale for pentylenetetrazole (PTZ)-induced seizure in rats

| Score | Behavioral manifestation |
|---|---|
| 0 | No behavioral sign |
| 1 | Ear and facial twitching |
| 2 | Head nodding and myoclonic jerks |
| 3 | Unilateral forelimb clonus with lorditic posture |
| 4 | Bilateral forelimb clonus with rearing and falling |
| 5 | Generalized tonic-clonic seizure (GTCS) with loss of postural tone |

### Evaluation of passive avoidance memory

Passive avoidance memory in animals was assessed by a shuttle box device (Borj Sanaat Co., Iran) (Hosseini, Allahyari, Azizi, 2021). The device consists of two dark and light compartments separated by a guillotine door. The floor of this chamber has steel rods that can transmit electric shock to the limbs of living entities. Briefly, on the first day of the acquisition phase, each rat was placed separately in a clear compartment. After the 30 s of habituation, the guillotine door was opened and initial latency (IL) was measured to enter the dark chamber. The rats that showed IL for more than 60 s were excluded from further analysis. When the rats entered the dark area, the guillotine door would quickly closed and an electric foot shock (75 V, 0.2 mA, 50 Hz) was applied to them for 3 s. The animal would be transferred to its cage 30 s after the electric shock and this operation was repeated 5 minutes later. The rats were shocked every time they put all four limbs in the darkness. The training would end when the animal stayed in a bright room for 120 consecutive seconds. The number of shocks (SN) was measured until acquisition (the rats that showed SN for more than 5 were excluded from further analysis). Twenty-four hours later, like before, retention latency (RL) as well as the total light compartment (TLC) was measured after seizure induction, but no electric shock was applied. The retention time was measured in 300 s.

### Animal euthanasia and serum collection

After behavioral tests, the animals underwent deep anesthesia with ketamine and xylazine (3:1), and their blood was collected after cardiac puncture by a sterile syringe. The blood was allowed to clot for half an hour at room temperature and then the serums were separated by a centrifuge at 3000 rpm for 15 min and stored at -20 °C.

### Measurement of oxidative stress markers

In order to measure glutathione peroxidase (GPx) and malondialdehyde (MDA) oxidative stress indices, animal serum samples and conventional kits (Novin Navand Salamat Co., Iran) available in the market were used. The activity of the GPx enzyme was measured according to the kit instructions at a wavelength of 340 nm by microplate reader (BioteTek ELx808, USA) and was reported in mU/ml. In addition, the amount of MDA was measured according to the instructions of the kit and at a wavelength of 532 nm by a microplate reader (BioteTek ELx808, USA) and was reported in terms of nmol/ml.

### Statistical analysis of data

The results of the present study were shown as median (min, max). The normality of the data was tested by the Shapiro-Wilk test. If the data were normal, then one-way ANOVA and Tukey's post hoc test were used to examine the differences between the groups. If the hypothesis of normality of the data was rejected, then the non-parametric Kruskal-Wallis test and Dunn's test post hoc test were used to examine the differences between the groups. All statistical analyzes were performed by

GraphPad Prism software. Moreover, in all analyses, the value of *P* was set at less than 0.05.

## RESULTS

### The effect of AMT on the activity of PTZ-induced seizure

The effect of different treatments on the manifestations of PTZ-induced convulsive behavior is displayed in Figure 1(A-D). Regarding the latency of myoclonic jerk, statistical analysis revealed a significant increase in the AMT 10, and AMT 20 groups vis-à-vis the PTZ group (P = 0.009 and P < 0.001, respectively). Further, Tukey's post hoc analysis also showed a significant difference in the latency of myoclonic jerk between the AMT 10 group and the AMT 20 group (p = 0.023) (Figure 1A). As exhibited in Figure 1B, the number of myoclonic jerks in different groups was affected; the effect had a significant decrease in the AMT 10, and AMT 20 groups compared to the PTZ group (P = 0.006 and P = 0.002, respectively). Regarding the GTCS latency factor, a significant increase was witnessed in the AMT 10, and AMT 20 groups compared to the PTZ group (P = 0.031 and P < 0.001, respectively) (Figure 1C). In the scrutiny of factors, GTCS duration revealed a significant decrease in the AMT 10, and AMT 20 groups in comparison to the PTZ group (P < 0.001) (Figure 1D).

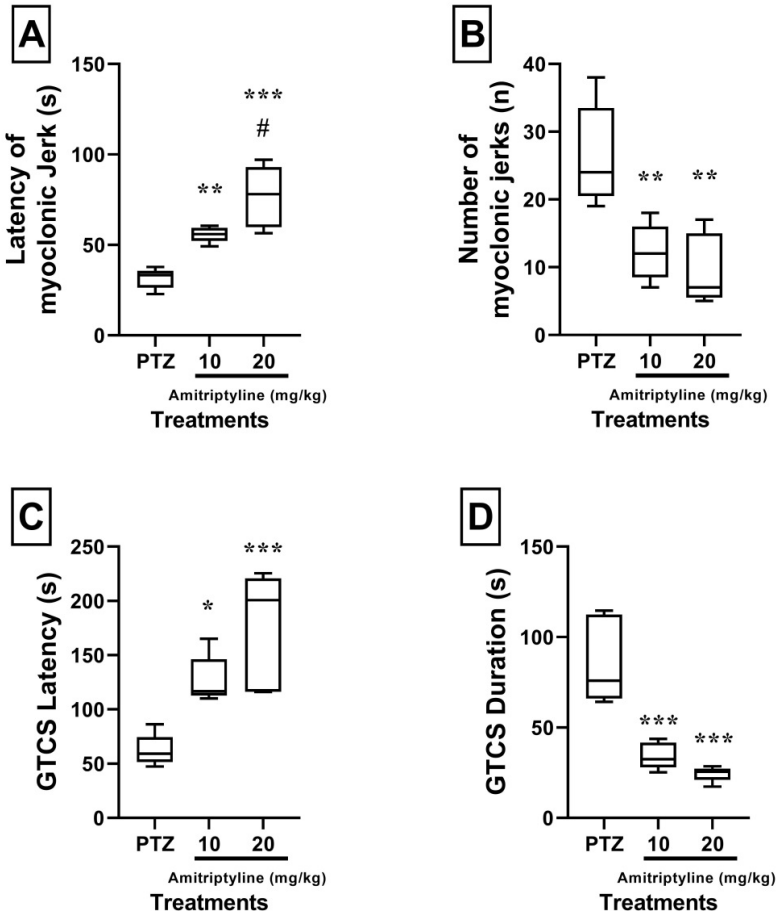


**FIGURE 1 -** The effect of AMT (10, and 20 mg/kg, i.p., 30 min prior to testing) after PTZ treatment (60 mg/kg, i.p.) on the latency of myoclonic jerk (**A**), number of myoclonic jerks (**B**), GTCS latency (**C**), and GTCS duration (**D**) in male Wistar rats. In a box plot, the central line represents the median value (n = 5 rats per group). *p < 0.05; **p < 0.01; ***p < 0.001 significant difference between AMT (10 or 20 mg/kg) treatment with PTZ group. #p < 0.05 significant difference between AMT (10 mg/kg) treatment and with AMT (20 mg/kg) group. Abbreviations: *AMT*: amitriptyline, *PTZ*: pentylenetetrazole, *GTCS*: generalized tonic-clonic seizure.

### The effect of AMT on passive avoidance memory

There was no statistically significant difference between IL (Figure 2A) and SN (Figure 2B) in different treatment groups. However, RL in the PTZ group showed a significant decrease compared to the control group, indicating memory impairment ($P < 0.001$). The AMT 10 group did not reveal a significant difference in RL in comparison with the PTZ group. Conversely, the AMT 20 group increased the RL level significantly compared to the PTZ group ($P = 0.005$) (Figure 2C). Regarding the TLC factor, the PTZ group exhibited a significant decrease compared to the control group ($P < 0.001$). Both AMT 10 and AMT 20 groups statistically significantly increased TLC compared to the PTZ group ($P = 0.003$ and $P < 0.001$, respectively) (Figure 2D).

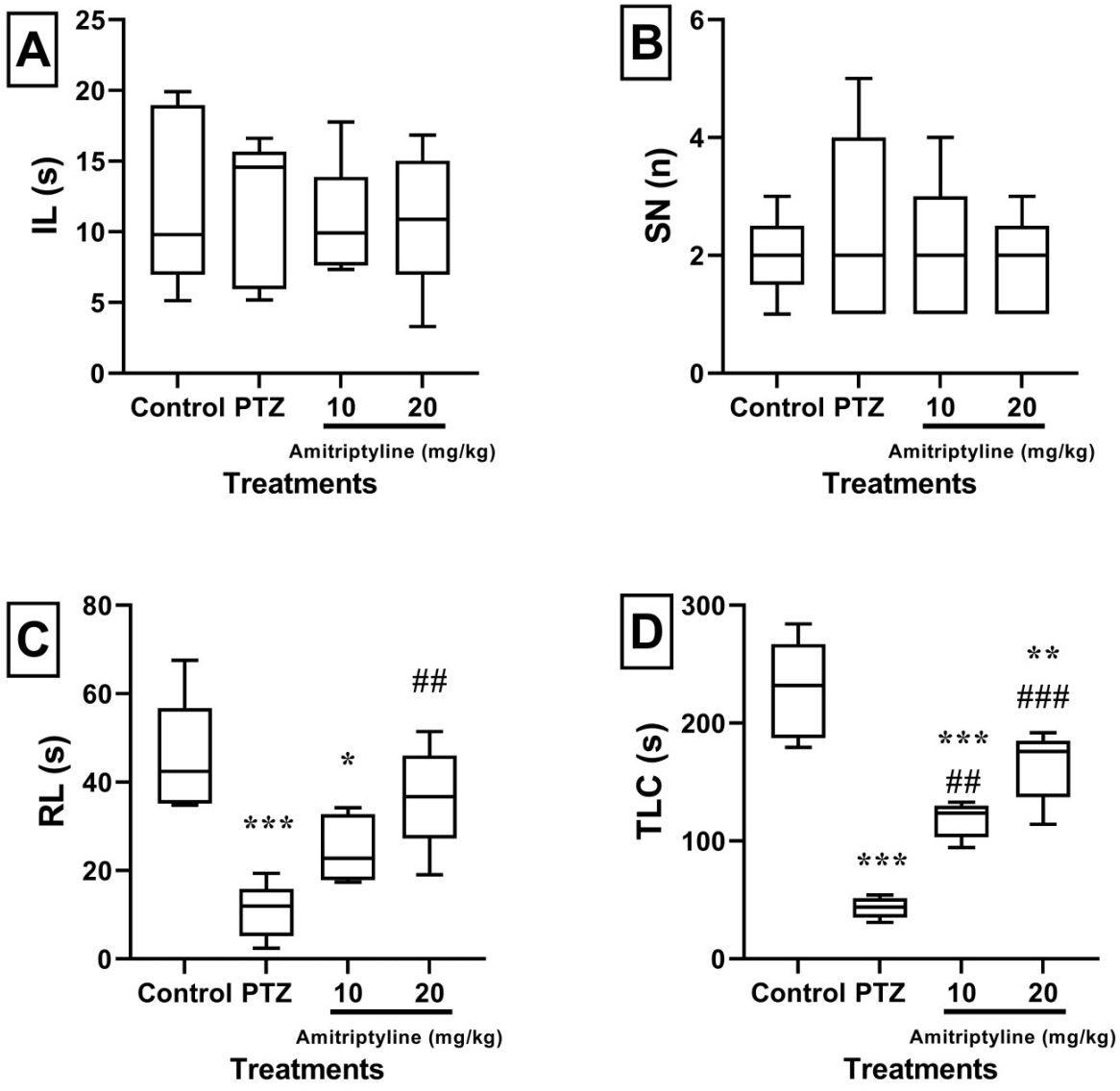


**FIGURE 2 -** The effect of AMT (10, and 20 mg/kg, i.p., 30 min prior to testing) after PTZ treatment (60 mg/kg, i.p.) on IL (**A**), SN (**B**), RL (**C**), and TLC (**D**) in male Wistar rats. In a box plot, the central line represents the median value (n = 5 rats per group). *p < 0.05; **p < 0.01; ***p < 0.001 significant difference between PTZ or AMT (10 or 20 mg/kg) treatment with the control group. ##p < 0.01; ###p < 0.001 significant difference between AMT (10 or 20 mg/kg) treatment with PTZ group. Abbreviations: *AMT*: amitriptyline, *PTZ*: pentylenetetrazole, *IL*: initial latency, *SN*: shock number, *RL*: retention latency, *TLC*: total light compartment.

### The effect of AMT on oxidative stress markers

As shown in Figure 3A, there was a significant increase in serum MDA levels in the PTZ group compared to the control group ($P < 0.001$). Moreover, AMT 20 group caused a significant decrease in the serum level of MDA compared to the PTZ group ($P < 0.001$). However, statistical analysis revealed that there was no significant difference in the serum MDA levels between AMT 10 and PTZ groups. Statistical analysis of GPx serum level in the PTZ group displayed a significant decrease compared to the control group ($P < 0.001$). Conversely, in the AMT 10 and AMT 20 groups, there was no significant difference observed *vis-à-vis* the control group. Further statistical analysis signaled that there was a significant difference in terms of increasing serum GPx levels in the AMT 20 group in comparison with the PTZ group ($P = 0.004$) (Figure 3B).

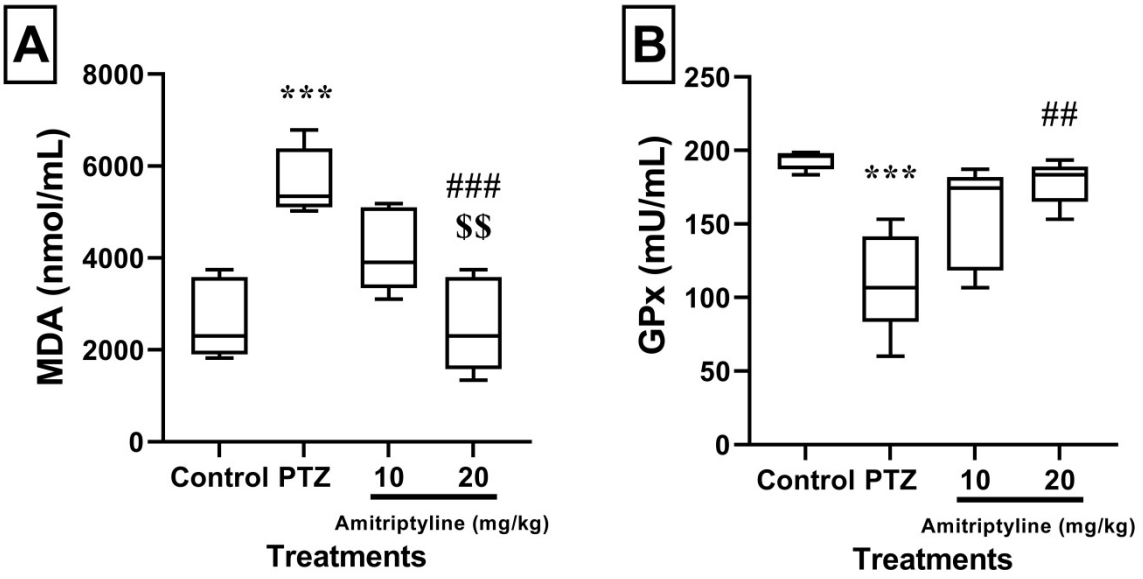


**FIGURE 3 -** The effect of AMT (10, and 20 mg/kg, i.p., 30 min prior to testing) after PTZ treatment (60 mg/kg, i.p.) on serum level of MDA (**A**), and GPx (**B**), in male Wistar rats. In a box plot, the central line represents the median value (n = 5 rats per group). ***p < 0.001 significant difference between PTZ treatment and with the control group. ##p < 0.01; ###p < 0.001 significant difference between AMT (20 mg/kg) treatment with PTZ group. $$p < 0.01 significant difference between AMT (10 mg/kg) treatment and with AMT (20 mg/kg) group. Abbreviations: *AMT*: amitriptyline, *GPx*: glutathione peroxidase, *MDA*: malondialdehyde, *PTZ*: pentylenetetrazole.

## DISCUSSION

In the present study, the effect of AMT on seizures and PTZ-induced avoidance memory deficits in rats were investigated. The results revealed that AMT has a statistically significant effect on seizure behavioral manifestation compared to the PTZ group. The PA test also showed that PTZ reduced RL and TLC, resulting in memory impairment in animals receiving PTZ. The results of this study are in line with reports that have been documented on memory impairment due to PTZ-induced seizures (Nagib *et al.*, 2018; Aghaie *et al.*, 2021; Hosseini, Allahyari, Azizi, 2021). With its effect on RL and TLC and its significant increase compared to the PTZ group, AMT reverses the effect of PTZ-induced memory impairment in rats, indicating its protective role against seizures and seizure-induced memory impairment. While no studies have been reported on the anticonvulsant effect or the effect on AMT memory so far, there are some reports on the inhibitory effects of AMT on neuropathic pain as well as the progression of underlying diseases associated with it (Hu *et al.*, 2010; Abdulmajeed *et al.*, 2016).

Various mechanisms have been proposed for how PTZ injection causes seizures as well as the associated memory impairment. One of the most important factors in the development of seizures as well as the resulting behavioral changes is the OS and the deviation of ROS from its normal level (Olowe *et al.*, 2020). In the present study, the results showed a decrease in the GPx serum levels and an increase in MDA following the PTZ injection. The present study, similar to various prior studies, showed that the injection of PTZ in animal models increases OS and lipid peroxidation and decreases antioxidant levels (Pahuja *et al.*, 2013; Kumar *et al.*, 2018; Hosseini, Allahyari, Azizi, 2021). MDA, as its name implies, is an aldehyde compound, which is active and highly reactive and is produced during the peroxidation reaction of unsaturated fatty acids. Therefore, by measuring the amount of MDA in different biological samples, the extent of lipid peroxidation can be determined. Lipid peroxidation occurs due to cell damage in plants and animals and is used as an indicator to measure the OS levels in cells and tissues (Pahuja *et al.*, 2013; Kumar *et al.*, 2018; Hosseini, Allahyari, Azizi, 2021). The results of this study showed that AMT, influencing MDA serum levels, reduced its effect on serum compared to the PTZ group. GPx is an enzyme found in the cytoplasmic and mitochondrial parts of cells. Glutathione peroxidases are a group of enzymes that play an important role in protecting organisms from oxidative damage. This enzyme converts reduced glutathione (GSH) to oxidized glutathione (GSSG) during the reduction of fatty hydroperoxides to alcohol or a change of free hydrogen peroxide to water. Normal levels of this enzyme can be linked to the prevention of many diseases, including cancer and neurological diseases (Munguía-Martínez *et al.*, 2019; Wang *et al.*, 2021). In the present study, AMT affected the serum level of GPx and counteracted the effects of PTZ by increasing it. The effects of AMT on MDA and GPx have not been reported on the status epilepticus condition, but in a previously reported study, AMT, decreased MDA in the mouse model of sepsis-induced brain damage (Zhang *et al.*, 2020) and in another study AMT with rosuvastatin increased GSH in the blood of rats (Herbet *et al.*, 2013). Therefore, the inhibitory effects of AMT on seizures as well as the improvement of memory impairment caused by seizures which were observed in the present study can be partially ascribed to the antioxidant properties of AMT.

The present study for the first time examined the antioxidant effects of AMT, as well as its possible pathway. The elicited results could pave the way for future studies. Despite this strength, the present study had a limitation: this study did not investigate the molecular pathway or inflammatory cytokines due to the small number of samples and time constraints. This issue can be addressed in future research designs.

## CONCLUSION

Overall, the present study provided evidence for the potential neuroprotective effects of the AMT drug. In addition, it was shown that AMT can be protective against oxidative stress induced during seizures. Therefore, a treatment strategy that could address the potential therapeutic effect of AMT with AEDs in the treatment of seizures as well as memory impairment associated with seizures calls for further research. Additional study designs are also needed to fully elucidate the mechanisms of anticonvulsant function as well as safety in their chronic use.

## DECLARATION

### Ethics approval

The research protocol was approved by the University's Animal Ethics Committee (IR.BASU.REC.1400.002).

## FUNDING

None received.

## CONSENT TO PARTICIPATE

Not applicable.

## CONSENT FOR PUBLICATION

The authors agree with this publication.

## CONFLICT OF INTEREST

The authors state that there was no conflict of interest in this study.

## OPEN PRACTICES STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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