Protective effect of pantothenic acid in kainic acid-induced status epilepticus and associated neurodegeneration in mice

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Abstract

Pantothenic acid (PA) is a water-soluble vitamin (Vitamin B) that has recently been investigated in various chemical-induced neurotoxicity studies. The present study was designed to explore the biological importance of PA as a neuromodulator by releasing monoamine oxidase (MAO)-A and MAO-B in kainic acid (KA)-induced status epilepticus and the associated neurodegeneration in mice. The mice were intraperitoneally administered with KA at a dose of 10 mg/kg, and the injection solution was maintained at pH 7.2 ± 0.1 before the injection. Subsequently, the mice were observed for various behavioral changes, such as grooming, rearing, hind limb scratching, urination, defecation, jaw movements, salivation, head nodding, incidence of convulsions, and their latency or any mortality, which were recorded during a 4-h period. Further, the animals were euthanized for biochemical and histopathological analysis. The oxidative stress status was determined by measuring levels of glutathione, superoxide dismutase, nitrites, and catalase enzymes. The MAO-A and MAO-B activities, which represent an indicator of brain memory function, and the level of tumor necrosis factor alpha, which is an inflammatory marker in brain tissues, were also measured. The PA pre-treated mice showed a significant increase in retention with latency, as demonstrated in the passive avoidance test, which indicate its protective effect against the KA-induced cognitive deficit. The results showed that the anti-oxidative and anti-inflammatory potential of PA is due to the change in lipid peroxidation, which may prevent mitochondrial damage in neuronal cell, thereby conferring neuroprotection.

Keywords: Epilepsy; Kainic acid; Pantothenic acid; Pharmacological activity; Biochemical analysis; Histopathology

1. Introduction

Epilepsy is one of the most prominent neurocognitive conditions[1]. Complex partial epilepsy has the poorest prognosis among all patients with temporal lobe epilepsy (TLE), with 60 – 70% of patients experiencing incurable seizures[1,2]. Furthermore, cognitive disorders in human TLE are more frequent[3] but the primary etiology is not clearly known. Administration of kainic acid (KA) as a single infusion has been reported to cause an epileptic state in mice, which results in recurrent seizures and memory impairments[4,5]. KA is a molecular analog of glutamate, an excitatory amino acid neurotransmitter. The
KA-induced epilepsy model has been commonly reported in clinical TLE research\[6\].

The stimulation of an excitatory amino acid receptor has been reported to cause the production of reactive oxygen species (ROS)\[9\]. Not only does this pathological loop contribute to the induction of long-lasting seizures, but it may also lead to neuronal damage if not treated\[7,8\]. Status epilepticus (SE) is an epidemic state where seizures are prolonged and neurological injuries occur in uncontrolled manner\[9,10\]. Systemic or intracerebroventricular injection of KA induces SE, which causes nerve cell injury and damages to various regions of the limbic system\[11\]. ROS appears to be involved in the pathway associated with the pathogenesis of SE\[12\]. Several scientific investigations have demonstrated that antioxidants can facilitate the inhibition of neurotoxicity caused by glutamic agents. The most feasible strategy to determine antioxidant capability would be to scavenge free radicals using non-enzymatic exogenous antioxidants\[13\].

Treatment offered to SE patients includes drugs that interfere with inflammatory processes, which alter the expression of interleukin (IL)-1β, tumor necrosis factor alpha (TNF-α), and IL-6 in in certain brain regions\[14\]. The results of recent preclinical studies of seizure and primary care indicate the potential role of the inflammatory process in epilepsy etiopathogenesis\[14,15\]. Pantothenic acid (PA) is a derivative of β-alanine and is available in the dextrorotatory form of calcium salts\[16,17\]. In humans, deficiency in PA causes different behavioral symptoms, such as depression, personality changes, frequent infection, fatigue, and sleep disturbance, as well as different histological changes in tissues leading to cardiac instability, abdominal pain, and muscle weakness\[13,14,19\]. Studies have also suggested that PA deficiency causes neurological disturbances\[20\]. Therefore, the present study was designed to evaluate the effect of PA on KA-induced SE and the associated neurodegeneration in mice.

The anticonvulsant activity of many antioxidant compounds, such as curcumin and vineatrol, has been investigated earlier, and we aimed to examine the anticonvulsant activity of PA using the KA epileptic model. Therefore, the purpose of the present study was to evaluate the effect of PA on epileptic status, oxidative stress, and cognitive impairment in KA-induced mice. In addition, we also examined its modulation effects on the release of TNF-α, a proinflammatory cytokine\[6,16\].

2. Materials and methods
2.1. Drugs and chemicals
PA (CAS 79-83-4), KA (CAS 487-79-6), diazepam (CAS 439-14-5), radioimmuno precipitation assay lysis buffer, and dimethyl sulfoxide (Cat. No. 102952) were purchased from Sigma Chemical Co. (Sigma, St. Louis, MO, USA). Protease inhibitor cocktail (Cat. No. 78430) was purchased from Roche Applied Science (Mannheim, Germany). Enzyme-linked immunosorbent assay kits were obtained from Pierce Biotechnology Inc. (Rockford, IL, USA). All other materials were of the analytical grade.

2.2. Animals
Young Wistar albino mice (3 – 4-weeks-old) of both sexes, weighing 20 – 25 g were used in this study. The animals were housed in cages with padded husk bedding that was changed daily. The mice were kept in a group of six (two males and four females) under room temperature (25 ± 1°C) with polypropylene cages maintained on a 12-h light-dark cycle. Unrestricted access to water and food was permitted for the mice (standard pallet). All protocols for the experiments were approved and implemented according to committee guidelines (approval no. CPCSEA/474/2021-08).

2.3. Experimental design
KA was administered intraperitoneally (i.p.) to mice at a dose of 10 mg/kg in a solution maintained at pH 7.2 ± 0.1. Following KA treatment, behavioral changes (grooming, rearing, and rubbing of the hind paws, urination, defecation, moist dog shakes, jaw motions, salivation, and head nodding), frequency and delay of seizures, and survival were monitored in mice and recorded for a maximum of 4 h\[16\]. On the last day of the experiment, all mice were euthanized, the blood (serum) was collected, and the tissues were harvested for histological analysis. The levels of a series of biochemical parameters, such as glutathione (GSH), superoxide dismutase (SOD), nitrite, catalase, acetylcholine esterase (ACHE), MAO-A, and MAO-B, were determined. The brain TNF-α level was also determined to assess the extent of inflammation.

2.4. Animal grouping
The mice were divided into several groups and treated as indicated.

Group 1 serves as the control group and was given 0.9% normal saline.

Group 2 serves as the vehicle-treated KA group and was given 10 mg/kg KA i.p. The vehicle (saline 10 mL/kg, i.p.) was administered for 7 consecutive days. KA (10 mg/kg, i.p.) was administered on the 7th day 30 min after the administration of vehicle and animals were observed over a period of 4 h for any change in behavioral parameters, incidence, and latency of convulsions.

Group 3 serves as the positive control group. Diazepam (5 mg/kg, i.p.) was administered on the 7th day, followed by
KA (10 mg/kg, i.p.) administration, which was performed 30 min after the administration of diazepam. The mice, thereafter, were observed over a period of 4 h for any change in behavioral parameters, incidence, and latency of convulsions. In Groups 4, 5, and 6, KA (10 mg/kg, i.p.) and PA at doses of 30, 60, and 90 mg/kg were given to the groups, respectively, for 7 days. The mice, thereafter, were observed over a period of 4 h for any change in behavioral parameters, incidence, and latency of convulsions.

2.5. Behavioural tests

2.5.1. Single-trial passive avoidance test

Memory retention deficit was evaluated by step through passive avoidance apparatus. The apparatus consists of equal sized light and dark compartments (30 × 20 × 30 cm). A 40-W lamp was fixed 30 cm above its floor in the center of the light compartment. The floor consists of metal grid connected to a shock scrambler. The two compartments were separated by a trap door that could be raised to 10 cm. Twenty-four h after the administration of KA, mice were placed in the light compartment and the time lapse before each animal entered the dark compartment and had all four paws inside it was measured in seconds and termed as "initial latency" (IL). Immediately, after the mice entered the dark chamber with all the four paws inside the dark chamber, the trap door was closed and an electric foot shock (50 V a.c.) was delivered for 3 s. Five s later, the mice was removed from the dark chamber and returned to its home cage. Twenty-four h after the IL, the latency time was measured again in the same way as in the acquisition trial and was termed as the retention latency (RL). However, during the retention trial, no foot shock was delivered, and the latency time was recorded to a maximum of 600 s. To improve the reliability and validity of the foot shock avoidance test, the grid as well as the mice paw was moistened with water before delivering the foot shock as this is known to reduce the wide inter animal variability in paw skin resistance of the mice.

2.5.2. Evaluation

The animals were sacrificed by cervical dislocation. The whole brain was removed from the skull immediately after dislocation. For preparation of the homogenate, the fresh whole brain was weighed and transferred to a glass homogenizer and 10% (w/v) tissue homogenates were prepared in 0.1 M phosphate buffer (pH 7.4, stored at 2 – 8°C). The homogenate was centrifuged at 3000 rpm for 10 min and the resultant cloudy supernatant liquid was used for various neurochemical estimations.

2.5.3. Choline esterase enzyme determination

The enzyme level was measured by the method described by Ellman with slight modifications. The sample absorbance was taken at 412 nm for a continued 7-min interval of 1 min. The results were expressed as nM/L/min/gm of tissue.

2.5.4. GSH estimation

The GSH level was measured using the Butler method with minor modifications. The absorption was spectrophotometrically measured at 412 nm (X-Rite 640B spectrophotometer). Different GSH standard concentrations were also treated simultaneously to create a standard curve (1 – 50 μg). Results were reported as GSH nmol/mg protein.

2.5.5. Catalase estimation

Catalase activity was measured using a previously described method, wherein the breakdown of H₂O₂ was measured. The processed sample homogenate absorbance was taken at 240 nm. The results were expressed as micromoles of H₂O₂ decomposed/min/mg of protein.

2.5.6. SOD enzyme activity

The SOD activity was measured with the enzyme kit from RANDOX Ransod. This procedure uses xanthine and xanthine oxidase-produced radicals of superoxides that react with the red formazan dye using 2-(4-iodophenyl)-3-(4-nitrophene)-5-phenyltetrazolium-chloride. The degree of inhibition of the SOD activity was measured.

2.5.7. Nitrites content estimation

It was measured by previously described method. 0.2 mL of supernatant from the brain homogenate was mixed with freshly prepared Griess reagent solution and spectrophotometrically measured at 546 nm. The results were calculated as nM/mg of protein.

2.5.8. Determination of MAO activity

MAO activity was assessed by spectrophotometry. The assay mixture contains 4 mm of serotonin as a specific substrate for MAO-A, 250 μL solution of brain homogenate, and 100 nm of sodium phosphate buffer (pH 7.4) up to a final volume of 1 mL. The action was allowed to proceed at 37°C for 20 min and stopped by adding 1 M HCl (200 μL). The reaction product was extracted with 5 mL of butyl acetate. Blank samples were prepared by adding 1 M HCl (200 μL) before the reaction and worked subsequently in the same manner.

2.5.9. Histopathology study of the rat brain

The cortex and hippocampus of control and experimental rats were fixed in 4% formalin and embedded in paraffin. Next, they were sliced into 5 μm sections using a section cutter (Leica, Germany). The sections were stained with hematoxylin and eosin and examined under a light microscope.
2.5.10. Statistics and data analysis

The data were analyzed using Graph Pad Prism 7.0 software and the results expressed as mean ± standard error of the mean, followed by a two-way analysis of variance (ANOVA) or one-way ANOVA when applicable; individual comparison was done using with Tukey's multiple comparison test for statistical significance set to \( P < 0.001 \).

3. Results

3.1. Effect of PA on KA-induced SE in mice

The behavioral signs, seizures, and the latency was found to be increased in each animal with each dose of PA. At doses of 30, 60, and 90 mg/kg, PA improved the latency of behavioral symptoms to 14.25 ± 0.97 (\( P < 0.01 \)), 26.54 ± 0.88, and 29.81 ± 2.09 min (\( P < 0.001 \)), respectively, as compared with KA alone. In addition, the epilepsy latency was also significantly increased to 45.7 ± 1.83 (\( P < 0.05 \)), 78.5 ± 1.77 (\( P < 0.01 \)), and 91.0 ± 1.08 (\( P < 0.01 \)), respectively, with PA treatment at 30, 60, and 90 mg/kg doses as compared to 37.02 ± 1.31 vehicle-treated KA group (Figure 1).

3.2. Effect of PA on cognitive impairment in KA-induced SE in mice

The retention latency appeared lower in the initial phase (48 h) in KA-treated mice (\( P < 0.001 \)) as compared to control group mice, suggesting KA induced major cognitive dysfunction. Dose-dependent changes in retention latencies (\( P < 0.05 \) at 30 mg/kg, \( P < 0.01 \) at 60 mg/kg, and \( P < 0.001 \) at 90 mg/kg, i.p.) were observed, suggesting a reversal in the retention latencies in the PA (30, 60, and 90 mg/kg, i.p.) + KA-treated groups. The control, vehicle-treated KA, diazepam, and 30, 60, and 90 mg/kg PA-treated groups showed change in retention latencies of 287.14 ± 6.28 s, 86.11 ± 1.56 s, 218.7 ± 1.89 s, 107.4 ± 2.65 s, 167.1 ± 2.6, and 272.7 ± 2.19 s, respectively (Figure 2). The mice pretreated with diazepam did not show any behavioral signs and convulsions.

3.3. Effect of PA on other biochemical parameters

The KA-treated mice showed higher levels of the AChE enzyme and nitrite content as compared to the control group mice. The PA-treated mice showed dose-dependent reduction in levels of AChE and nitrite as compared with KA-treated Group 2. The levels of the other enzymes, catalase, and SOD were significantly decreased in the KA-treated Group 2, which was ameliorated by PA treatment. The greatest protection against enzyme reduction is shown at a dose of 90 mg/kg by PA (Table 1).

3.4. Effect of PA on thiobarbituric acid reactive substances (TBARS) in KA-induced SE in mice

The brain TBARS levels were significantly higher in KA-induced group (3.72 ± 0.32 nM/mg of protein) as compared with control group (1.31 ± 0.05 nM/mg of protein; \( P < 0.001 \)). TBARS levels were 3.09 ± 0.98, 2.68 ± 0.4, and 1.94 ± 0.8 nM/mg of protein in mice treated with PA at 30, 60, and 90 mg/kg (i.p.), respectively. The PA at the tested doses showed significant antioxidant activity compared with the vehicle treatment using KA (Table 1).
3.5. Effect of PA on GSH levels in KA-induced SE in mice

Brain GSH levels were measured in the control, vehicle-treated KA-induced, and PA-treated mice. GSH levels were found to be lower (2.9 ± 0.92 nM/mg of protein) in the vehicle-treated KA group (P < 0.001) than in the control group (7.37 ± 0.13 nM/mg of protein). GSH levels were 4.67 ± 1.32, 5.98 ± 0.7, and 7.1 ± 0.54 nM/mg of protein in the mice treated with PA at 30, 60 and 90 mg/kg (i.p.), respectively. Furthermore, the levels were found to be maximum in animals treated with the dose of 90 mg/kg as compared to KA-treated Group 2 (P < 0.001, Table 1).

3.6. Effect of PA on TNF-α level in KA-induced SE in mice

The brain levels of TNF-α were significantly increased after KA administration as compared to level found in the control group (804.09 ± 19.02 pg/mL and 481.31 ± 7.67 pg/mL, respectively, P < 0.001). PA treatment caused a dose-dependent reduction in brain levels of TNF-α (Figure 3), with the highest inhibition occurred at the dose of 90 mg/kg (P < 0.001).

3.7. Effects on body and brain weight

The mice body weight and brain weight decreased in KA-induced mice, whereas other groups also showed changes in size and body weight. Mice treated with PA improved the hypotrophy of their brains caused by KA induction in the absence of interventional treatment (Table 2).

3.8. Effect of PA on MAO-A and MAO-B levels

The effects of PA on the MAO concentration are shown in Table 3. The MAO-A and MAO-B activity levels of the control group were 26.1 ± 0.32 and 23.2 ± 0.24 nmol/mg of protein, respectively. Oral (p.o.) administration of 60 mg/kg PA inhibited MAO-A and MAO-B by 21% and 35%, respectively, and PA (90 mg/kg, p.o.) resulted in significant inhibition of both MAO isoforms by 35% and 65%, respectively (Table 3).

3.9. Histopathological changes in brain tissue

From the histopathological study, it was observed that the normal control group or Group 1 (Figure 4A) showed a normal brain parenchyma with normal neuronal morphology. KA-treated mice in Group 2 (Figure 4B) showed neuronal degradation in the brain parenchyma, small pyknotic nuclei, and extracellular eosinophilic deposition. In the standard group or Group 3 (Figure 4C), animals showed mild changes in neuronal degeneration, and many nuclei were pyknotic and closely packed. The mice in Group 4 (Figure 4D) and Group 5 (Figure 4E),
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which were treated with PA 30 mg/kg and 60 mg/kg, respectively, showed focal areas of cellular degeneration, although certain areas were morphologically normal. The mice in Group 6 (Figure 4F), which were treated with PA (90 mg/kg), showed improvement in the near normal brain parenchyma with minimal degenerative changes.

4. Discussion

The present study found that KA significantly induced the SE state of epilepsy and PA ameliorates the damage and the associated neurodegeneration caused by KA administration in mice. In clinical practice, epilepsy is the most common neurological condition. In the U.S., 2.2 million individuals have epilepsy, while 3% of the population will develop epilepsy later in life. At present, significant progress has been made in the diagnosis and treatment of neurological conditions and research is ongoing, especially on neuronal signaling to neighboring cells. The basic cause of seizure progression has not yet been established, but excessive activation of excitatory amino acid receptors or GABAergic system inhibition has been observed in mice. Excessive stimulation of excitatory amino acid receptors has been clearly demonstrated to induce prolonged seizures.

Table 2. Effect of pantothenic acid on kainic acid-induced changes in body and brain weight of mice with epilepsy

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in body weight (BW, g)</th>
<th>Brain weight (g)</th>
<th>Brain/BW ratio/100 g of mice weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>1</td>
<td>0.44±0.11</td>
<td>−0.41±0.24</td>
<td>1.06±0.32</td>
</tr>
<tr>
<td>2</td>
<td>1.07±0.19</td>
<td>0.19±0.08</td>
<td>0.73±0.19</td>
</tr>
<tr>
<td>3</td>
<td>−2.53±0.89*</td>
<td>−2.92±0.82*</td>
<td>0.86±0.22*</td>
</tr>
<tr>
<td>4</td>
<td>−1.76±0.76</td>
<td>−3.95±0.65</td>
<td>0.96±0.43*</td>
</tr>
<tr>
<td>5</td>
<td>−2.32±0.43*</td>
<td>−3.69±0.76</td>
<td>1.08±0.13**</td>
</tr>
<tr>
<td>6</td>
<td>−4.51±1.07**</td>
<td>−3.06±0.74*</td>
<td>1.12±0.22**</td>
</tr>
</tbody>
</table>

Table 3. Effect of pantothenic acid on monoamine oxidase level in brain tissues

<table>
<thead>
<tr>
<th>Group</th>
<th>MAO-A</th>
<th>MAO-B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level (nM/mg protein·h)</td>
<td>Inhibition (%)</td>
</tr>
<tr>
<td>1</td>
<td>22.1±0.32</td>
<td>23.2±0.24</td>
</tr>
<tr>
<td>2</td>
<td>27.4±0.82</td>
<td>32.1±0.76</td>
</tr>
<tr>
<td>3</td>
<td>27.1±0.43*</td>
<td>3.89</td>
</tr>
<tr>
<td>4</td>
<td>25.76±0.36</td>
<td>10.0</td>
</tr>
<tr>
<td>5</td>
<td>22.8±0.54*</td>
<td>21.0</td>
</tr>
<tr>
<td>6</td>
<td>21.3±0.33**</td>
<td>35.0</td>
</tr>
</tbody>
</table>

Figure 4. Histopathology of brain tissue (cerebral cortex) showing neuronal degeneration and inflammation. (A) Mice from normal control group. (B) Untreated kainic acid (KA)-induced mice. (C) Diazepam-treated KA-induced mice. (D) Pantothenic acid (30 mg/kg, p.o.)-treated KA-induced mice. (E) Pantothenic acid (60 mg/kg, p.o.)-treated KA-induced mice. (F) Pantothenic acid (90 mg/kg, p.o.)-treated KA-induced mice. Arrow indicates neuronal vacuolation.
Stress and free radicals have been reported to excite excitatory receptors, leading to a transition between seizure phases. In this study, KA induced behavioral changes and seizures in all mice. Compared with KA treatment, pre-treatment with different doses of PA delayed the initiation of seizures and improved memory retention. Furthermore, i.p. pre-treatment with PA (30, 60, and 90 mg/kg) protected mice against KA-induced neurodegeneration. In the KA-treated group, GSH content declined dramatically, indicating the development of oxidative stress.

PA (90 mg/kg) treatment contributed to more significant effects on MDA and GSH levels than KA treatment alone. Elevated MDA content is an indicator of free radical production. The PA-treated groups (Groups 3, 4, and 5) showed a greater increase in the GSH content than the KA-treated group did. GSH interacts with free radicals and can shield cells from the effects of singlet oxygen, hydroxyl radicals, and superoxide. GSH is the most common intracellular thiol and low-molecular-weight tripeptide present in cells. The inhibition of KA-induced reduction of GSH levels by PA suggests that it improves the endogenous protective potential of the brain against KA-induced oxidative stress.

PA has been hypothesized as an agent for preventing mitochondrial damage by modulating lipid peroxidation, thereby conferring neuroprotection. This indicates that PA helps minimize mitochondrial oxidative stress. When the threshold value of excitation is crossed after administration of KA, animals will experience seizures. The administration of KA activates glutamate receptors to boost ROS, thus increasing glutaminergic activity. PA has been reported to modulate glutamatergic activity. The extent to which minimizing the work is difficult to predict, but the disruptive chain is noticeable, which reduces excitotoxicity and, hence, demonstrates a defensive effect.

Therefore, it is difficult to rule out the dual effects of PA as an antioxidant and an anti-excitotoxic agent. The change in neurological conditions is also correlated with the occurrence of inflammation in neuronal cells, especially in the prognosis of epilepsy and SA. Higher levels of cells (such as microglia), effects (such as astrocyte activation), and production of cytokines (such as TNF-α, IL-1β, IL-6, and related molecules) have been reported in the process of inflammation in clinical and preclinical models of epilepsy. These cytokines are actively involved in immune protection in the central nervous system. Compounds such as PA and other vitamins have rich antioxidant activities that affect the function of microglia. Cytokines such as TNF-α, IL-1, and IL-1β are directly involved in stress, over-firing of signals in seizures, and prolongation of disease stage.

KA-induced animals are an accepted preclinical model for studying neurological disorders, such as epilepsy, Huntington’s chorea, and Alzheimer’s disease, which involve excitotoxicity and inflammation. PA treatment at 30 mg/kg (i.p.) showed no effect on TNF-α levels, whereas 60 and 90 mg/kg (i.p.) significantly attenuated the increase of brain TNF-α levels (P < 0.001) in the PA + KA groups compared with that in the KA-induced group. In the previous studies, PA has also been reported to attenuate TNF-α levels, inhibit inducible nitric oxide synthase (iNOS) expression, and suppress apoptosis through its anti-inflammatory activity. The latter effect could, at least in part, explain the beneficial effects of PA on diseases involving inflammation. These effects are mediated by the inhibition of nuclear factor kappa B (NF-κB) activation. Cyclooxygenase 2 (COX-2), the inducible isoform expressed at the injury or inflammatory sites and the central nervous system, plays a significant role in neurodegeneration linked to increased excitatory activity.

Glutamate, an active N-methyl-D-aspartate (NMDA) receptor excitatory neurotransmitter, increases the expression of COX-2 and results in higher prostaglandin synthesis (unpublished observations). This result was confirmed in studies by Vanamala et al. who reported that PA decreased the levels of iNOS and COX-2 by inhibiting NF-κB activation. In view of the above findings, it may be fair to conclude that the antiepileptic activities of PA are mediated by its significant antioxidant and anti-inflammatory effects.

In this study, KA administration resulted in seizures related to cognitive dysfunction, as shown by the decrease in the passive avoidance behavior of retentive latency. The results were similar to those of the previous studies that demonstrated cognitive damage and epilepsy following KA administration. The disease progression of seizures, indicated by increased retention latency in the passive avoidance test following 7 consecutive days of treatment, leads to cognitive deficits. There is uncertainty about the degree of cognitive dysfunction, which is a limitation associated with all major antiepileptic drugs.

The present study has shown the beneficial effect of PA on reducing seizures and cognitive impairment induced by KA. Thus, PA has the potential to be utilized in clinical SE management. Furthermore, this study shows that PA could prevent cognitive impairment and serve as a useful conventional antiepileptic treatment.

5. Conclusions

This pharmacological study demonstrated that PA has major anti-inflammatory, antioxidant, and neuromodulator activities against epilepsy induced by KA in mice.
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Conflict of interest
The authors have no conflict of interest to declare.

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Writing – review & editing: Souravh Bais, Shanti Lal Singune

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