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Corilagin Reduces the Frequency of Seizures and Improves Cognitive Function in a Rat Model of Chronic Epilepsy

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Worldwide, epilepsy is an important chronic neurological condition. The aim of this study was to evaluate the effects of corilagin, an ellagitannin extracted from medicinal plants, on the frequency of seizures and cognitive function in a rat model of chronic epilepsy.

Material/Methods: Chronic epilepsy was induced in male Wistar rats by intraperitoneal (IP) injection of pentylenetetrazol (PTZ) for 36 days. Corilagin, 10 mg/kg and 20 mg/kg, was injected IP into treated rats, 24 days before the start of PTZ treatment, until the end of the protocol. The effects of corilagin were assessed by the pattern of epileptic seizures; cognitive function was assessed using the Morris water maze (MWM) navigation test. The mechanism of action of corilagin was investigated by measuring cytokine levels and oxidative stress parameters, including reactive oxygen species (ROS) production, and carbonic anhydrase inhibitory (CAI) activity. Histological analysis of fixed brain tissue sections included cresyl violet acetate staining (Nissl staining) for Nissl substance in the neuronal cytoplasm.

Results: The corilagin-treated rats, compared with the control group, showed a significantly lower rate of epileptic events, improved cognitive function, reduced level of cytokines, reduced ROS production reduced CAI activity in the brain tissues ($P<0.01$). Histology of the rat brain tissues study showed that corilagin treatment maintained the neuronal cellular structure and number of surviving cells compared with the control group of rats.

Conclusions: The findings of this study showed that corilagin reduced the frequency of seizures and improved the cognitive function in a rat model of chronic epilepsy.

MeSH Keywords: **Cytokines • Epilepsia Partialis Continua • Neurologic Manifestations**

Abbreviations: **CAT** – catalase; **ELISA** – enzyme-linked immunosorbent assay; **IL10** – interlukin 10; **LPO** – lipid peroxidation; **MDA** – malondialdehyde; **MWM** – Morris water maze; **PTZ** – pentylenetetrazol; **ROS** – reactive oxygen species; **SOD** – superoxide dismutase; **TNF**α – tumor necrosis factor alpha

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Background

Worldwide, epilepsy is an important chronic neurological condition [1]. Epileptic seizures have been reported to develop from oxidative stress, with toxicity resulting in damage to neurons and neuronal mitochondria [2]. Although there are now several drugs that are used to treat epilepsy, most anti-epileptic drugs only control the symptoms. Also, anti-epileptic drugs can have adverse effects on the patient, including impaired cognitive function.

The pathogenesis of seizures in epilepsy remains unclear, but studies have shown that increased intracellular pH and potassium ions may be associated with the onset of seizures [3]. Carbonic anhydrase maintains the pH within the intracellular and extracellular space; carbonic anhydrase inhibitors (CAI) are used to prevent seizures in the clinical management of patients with epilepsy [4].

Epileptic seizures generate free radicals that alter the activity of mitochondria, which contributes to cognitive impairment in chronic epilepsy [5]. Neuronal cells are prone to damage due to an increase in reactive oxygen species (ROS) that damages protein, DNA, mitochondria, and cell membranes, which also activates the apoptosis pathway by increasing the expression of caspase-3 [6,7]. Therefore, antioxidants may have potential in the management of chronic epilepsy or may protect against cognitive impairment associated with epilepsy.

Corilagin ($C_{27}H_{22}O_{18}$), or beta-1-O-galloyl-3, 6-(R)-hexahydroxydiphenoyl-D-glucose, is an ellagitannin that can be extracted from several medicinal plants, including *Caesalpinia coriaria, Alchornea glandulosa, Phyllanthus amarus* and the leaves of *Punica granatum* (pomegranate) [8]. Previously reported studies have shown that corilagin has anti-oxidant, anti-inflammatory, analgesic, antihypertensive, and antitumor effects, and also acts as a CAI [9–12].

The aim of this study was to evaluate the effects of corilagin on the frequency of seizures and on cognitive function in a rat model of chronic epilepsy.

Material and Methods

Animals

Six-week-old male Wistar rats (n=40) weighing between 200–250 g were included in this study. All the animals were maintained under optimal conditions, according to the animal welfare guidelines of the Association for the Assessment and Accreditation of Laboratory Animal Care International, and were provided with pellet feed and water, ad libitum. The study protocols were approved by the Ethical Committee of our institution (Ref: XYCH/IAEC/2016/18).

Materials

Corilagin and pentylenetetrazol (PTZ) were obtained from Sigma Aldrich (USA). An enzyme-linked immunosorbent assay (ELISA) kit was used to measure the cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-10 (Nanjing, China). Flow cytometry was performed using the BD FACSAria™ (BD Biosciences, Ill, USA) for the measurement of reactive oxygen species (ROS).

Pentylenetetrazol (PTZ) rat model of epilepsy

Forty rats were included in this study, and were divided into four groups: a) The control group (n=10) received an intraperitoneal (IP) injection of vehicle (normal saline) for 60 days; b) The negative control group (n=10) received an IP injection of vehicle (normal saline) for the period of 24 days, followed by treatment with an IP injection of PTZ (35 mg/kg) for 36 days; c) The PTZ + corilagin group (n=10) treated with IP corilagin (10 mg/kg) for the first 24 days, followed by corilagin given 30 min prior to IP PTZ (35 mg/kg) for the next 36 days; d) PTZ + corilagin group (n=10) treated with IP corilagin alone (15 mg/kg) for first 24 days, followed by treatment with corilagin given 30 min prior to IP PTZ (35 mg/kg) for the following 36 days [13]. During the treatment period, the rats were observed for seizure occurrence, length, and frequency.

All rats underwent cognitive function testing using the Morris water maze (MWM) navigation test and sacrificed after this test. The rat brains were removed and examined for the evaluation of oxidative stress, ROS generation, cytokines, and carbonic anhydrase activity. Histology was also performed on brain tissues using cresyl violet acetate staining (Nissl staining) for Nissl substance in the neuronal cytoplasm.

Assessment of epileptic seizures

Epileptic seizures were observed for one hour for each animal following the administration of PTZ, and the intensity of the seizure was assessed using Racine's scale (stage) of intensity: Stage 0: the absence of any response; Stage 1: hyperactivity and twitching; Stage 2: myoclonic jerking or head-nodding; Stage 4: rearing (standing on its hind legs); Stage 5: clonic-tonic seizures and the absence of reflexes; the frequency and duration of seizures were also observed [14].

Evaluation of cognitive function using the Morris water maze (MWM) navigation test

Cognitive function was evaluated by the Morris water maze (MWM) navigation test in which rats were evaluated on their

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ability to locate a hidden platform to escape from water using a maze tank measuring 180 cm in diameter and 70 cm in height. The maze tank was separated into four labeled quadrants, and the stage was maintained at 2 cm below the water level. All the rats were trained for five days, twice daily in two-hour sessions. Four trials in each session were performed at an interval of 30 sec. Each rat was placed in a quadrant and permitted to search for the stage in each trial. If the rat was not able to complete the stage within 2 minutes, the rats were placed at a particular stage for a specific duration to determine the escape latency for 2 minutes. The spatial memory of the trained rats was investigated by removing the stage from the quadrant, and measuring the duration of time spent by each rat in a specified quadrant on the sixth day of the study, and performed at the same time of day [15].

Preparation of brain tissue homogenates

Rats were sacrificed, and the brain from each rat was removed, washed thoroughly with normal saline solution and divided into two halves. One-half of the brain of each rat was homogenized immediately in a solution containing Tris-HCl (50 mM, pH 7.4) and sucrose (300 mM). The brain tissue homogenate was centrifuged at 10,000 rpm for 10 minutes, and the supernatant was separated for biochemical analysis. The other half of the brain of each rat was fixed for histology.

Measurement of oxidative stress markers: superoxide dismutase (SOD), lipid peroxidation (LPO), malondialdehyde (MDA), and catalase (CAT) activity

Superoxide dismutase (SOD) levels were measured in the brain tissue of the rats using the-the riboflavin-sensitized photo-oxidation of horseradish apoperoxidase method, and the alteration in absorbance was measured for 4 min at 460 nm [16]. The levels of lipid peroxidation (LPO) in the tissue homogenates were measured using the method described by Ohkawa et al., and the amount of malondialdehyde (MDA) was measured at 532 nm [17]. The activity of catalase (CAT) in the brain tissue was assessed on the ability of catalase to oxidize H_2O_2; the alteration in the level of absorbance was measured in triplicate at 1 min intervals at 240 nm [18].

Measurement of cytokines

The level of cytokines in the brain homogenates was measured using an enzyme-linked immunosorbent assay (ELISA) kit [19,20].

Measurement of ROS production and degree of swelling of neuronal mitochondria

Measurement of ROS was performed according to the method of He et al. [21]. Tissue homogenates were analyzed by flow cytometry with measurement of the intensity of fluorescence at a wavelength of 488 nm excitation and 530 nm emission. Swelling of the mitochondria was evaluated by measuring the optical density at a wavelength of 520 nm as previously described, with the degree of swelling of the mitochondria reflected by the turbidity of the reactant product [21].

Measurement of carbonic anhydrase activity

Carbonic anhydrase activity was measured using an electrometric and colorimetric method [22]. A carbonic anhydrase kit (Worthington Biochemical Corp., NJ) was used to measure the activity as the time required to lower the pH of tris buffer (0.012 M) using a CO2 solution [22].

Nissl staining for Nissl substance in the neuronal cytoplasm

Isolated rat brain sections were fixed 3% formalin 24 hours and processed, dehydrated with alcohol, paraffin-embedded and 5 µm thick sections were cut onto glass slides. Tissue sections were stained with cresyl violet acetate staining (Nissl staining) for Nissl substance in the neuronal cytoplasm. The number of surviving intact pyramidal cells per mm length of the hippocampal CA1 subfield in both hemispheres was counted by two independent observers, blinded to the treatment history and using high magnification (×400 objective) light microscopy [13].

Statistical analysis

Experimental data were expressed as the mean ±SD. Statistical analysis included one-way ANOVA and Dunnett's *post hoc* test, using GraphPad Prism 6.1. $P<0.05$ was considered to be statistically significant.

Results

Assessment of epileptic seizures

The effect of corilagin on epileptic seizure activity in the rat model of chronic epilepsy is shown in Figure 1. The frequency of seizures was found to be significantly decreased in the corilagin pretreated rat groups compared with the negative controls ($P<0.01$) (Figure 1A). Also, the high seizure duration, which was found to be up to 46 seconds in the controls, was decreased in the corilagin-treated group of rats. Higher doses of corilagin were found to significantly reduce the frequency of seizures when compared with the negative controls ($P<0.05$) (Figure 1B). The effects of corilagin on the stages of seizures in the rat model are shown in Figure 1C. Therefore, in the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy, there

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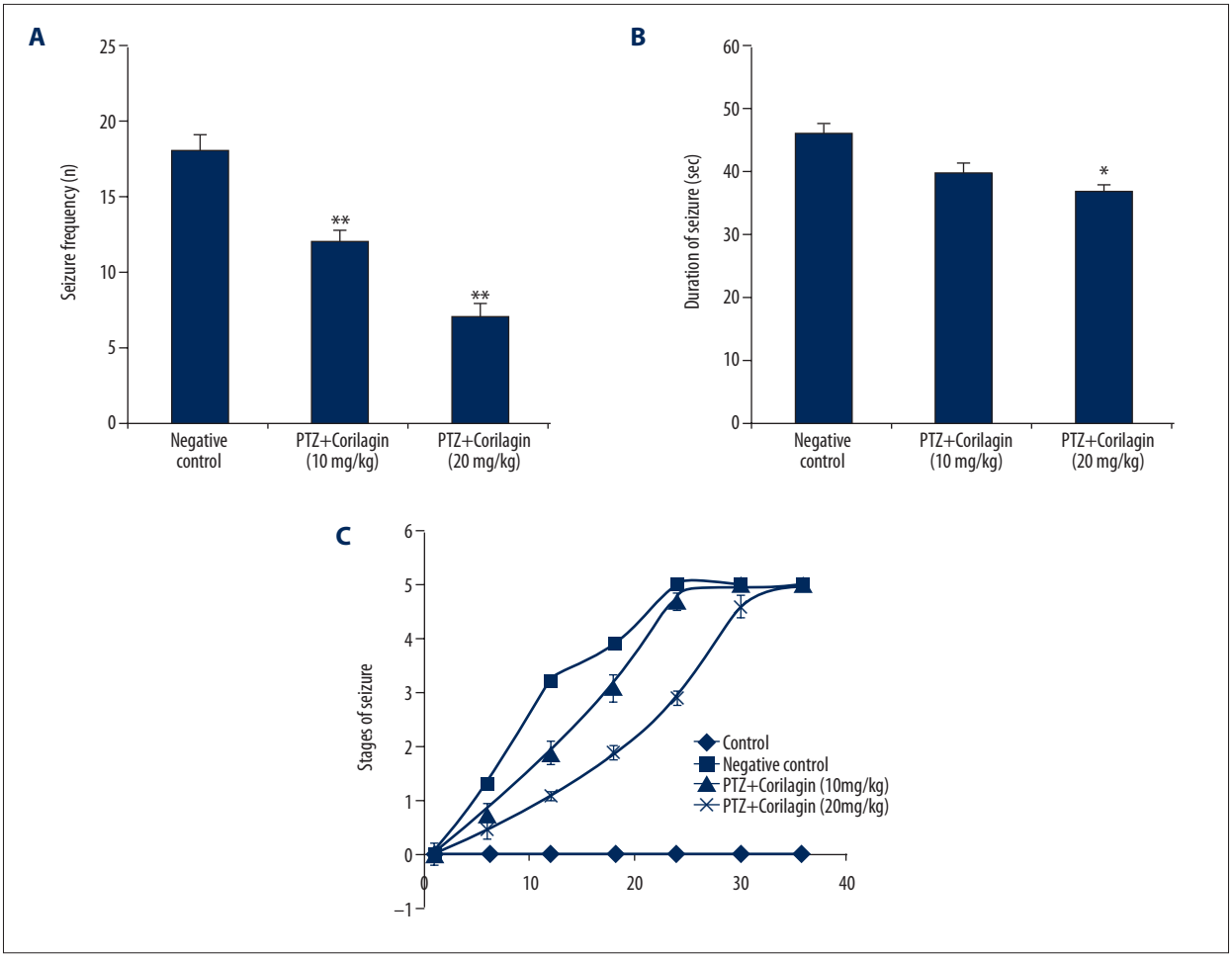

Figure 1. Effect of corilagin on the seizure behavior in the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy. (**A**) The frequency of seizures. (**B**) The duration of seizures. (**C**) The stages of seizures. Values are expressed as mean ±SD (n=10). @ P<0.01 (*vs.* control group); ** P<0.01 (*vs.* negative control group).

was a significant effect on duration, stage, and frequency of seizures following pretreatment with corilagin.

Evaluation of cognitive function using the Morris water maze (MWM) navigation test

Corilagin treatment reduced memory impairment in the PTZ-induced chronic epilepsy rat model, as shown in Figure 2. During the training period in the Morris water maze (MWM) navigation test, the escape latency of the treated group was found to decrease over time. There was an increase in the duration of the escape latency in the PTZ-induced group of rats compared with the control group of rats. This increased duration of escape latency was found to be significantly reduced in the corilagin-treated group compared with the negative control group of rats (Figure 2A) (P<0.001).

The effect of corilagin on time spent in the target quadrant in MWM is shown in Figure 2B. It was observed that the time spent in the target quadrant was significantly increased in the negative control group of rats compared with the control group of rats (P<0.01). However, time spent in the target quadrant was significantly decreased in the corilagin treated group compared with the negative control group (P<0.01).

In the MWM study, cognitive function was assessed by measuring the number of crossings in the MWM test, and treatment with corilagin significantly increased the number of crossings compared with the negative control group of rats (Figure 2C). The effects of corilagin on the improvement of cognitive function was found to occur in a dose-dependent manner.

Measurement of oxidative stress markers: superoxide dismutase (SOD), lipid peroxidation (LPO), malondialdehyde (MDA), and catalase (CAT) activity

Table 1 summarizes the results of the effects of corilagin on SOD, LPO, MDA, and CAT activity in the brain tissue of PTZ-induced

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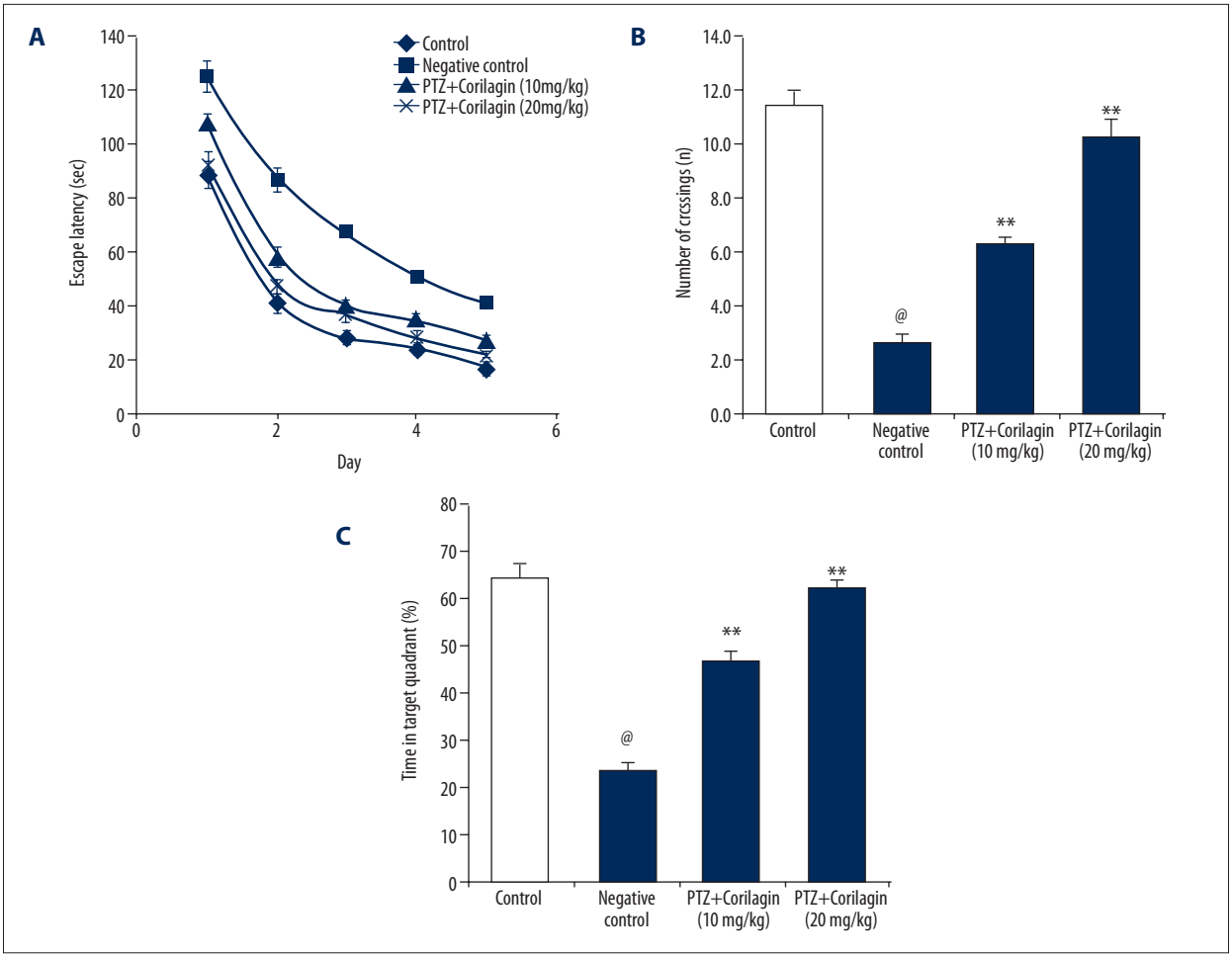

Figure 2. Assessment of cognitive function by the Morris water maze (MWM) navigation test in the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy (**A**) Escape latency in the training period. (**B**) Target quadrants in the spent time. (**C**) The quantity of target crossings. Values are means ±SD (n=10). @ P<0.01 (*vs.* control group); ** P<0.01 (*vs.* negative control group).

chronic epilepsy in the rat model. PTZ-induced chronic epilepsy resulted in a significant decrease in the levels of SOD (P<0.01) and an increase in the LPO and CAT levels compared with the control group of rats (P<0.01). However, treatment with corilagin significantly improved the SOD level in the brain tissues compared with the negative control group of rats. LPO and CAT levels were found to be significantly decreased (P<0.01) in the brain tissues of the corilagin treated the group of rats compared with the negative control group of rats. Also, the findings of this study showed that this improvement in the level of oxidative stress parameters was dose-dependent.

Measurement of cytokines

Figure 3 shows the effect of corilagin on the cytokine levels in brain tissues of rats with PTZ-induced chronic epilepsy. There was a significant increase in the level of TNF-α in the brain tissues in the rats with PTZ-induced chronic epilepsy (negative control) compared with the control group (P<0.01). Corilagin significantly reduced cerebral injury induced by epilepsy (P<0.01) compared with the negative control group (Figure 3A). Also, the level of IL-10 was significantly increased in the (P<0.01) in the corilagin-treated group compared with the negative control group (P<0.01) (Figure 3B). The effect of corilagin on TNF-α and IL-10 levels were dose-dependent.

Measurement of reactive oxygen species (ROS) production and degree of swelling of neuronal mitochondria

Figure 4 shows the effects of corilagin effect on ROS production and mitochondrial swelling in the brain tissues of rats with PTZ-induced chronic epilepsy. There was a significant increase in ROS production in brain tissues of rats with PTZ-induced chronic epilepsy compared with the control group, which significantly decreased in the corilagin-treated group of rats (P<0.01) (Figure 4A). Treatment with corilagin significantly decreased (P<0.01) in the prevalence of mitochondrial swelling compared with the negative control group of rats (P<0.01) (Figure 4B).

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Table 1. Effect of corilagin on superoxide dismutase (SOD), lipid peroxidation (LPO), and catalase (CAT) in the brain tissue of rats in the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy.

Sr. No.	Group	SOD (Unit/mg protein)	LPO (nmol MDA/mg protein)	CAT (µmol H_2O_2 consumed/min/mg protein)
1	Control	14.2±1.2	7.9±0.5	49.1±2.1
2	Negative control	3.8±0.4@	15.1±1.3@	72.5±5.5@
3	PTZ+Corilagin (10 mg/kg)	10.2±1.1**	10.3±0.6**	60.3±3.2**
4	PTZ+Corilagin (20 mg/kg)	13.1±1.3**	8.3±0.3**	53.9±2.4**

Values are means ±SD (n=10). @ P<0.01 (*vs.* control group); ** P<0.01 (*vs.* negative control group).

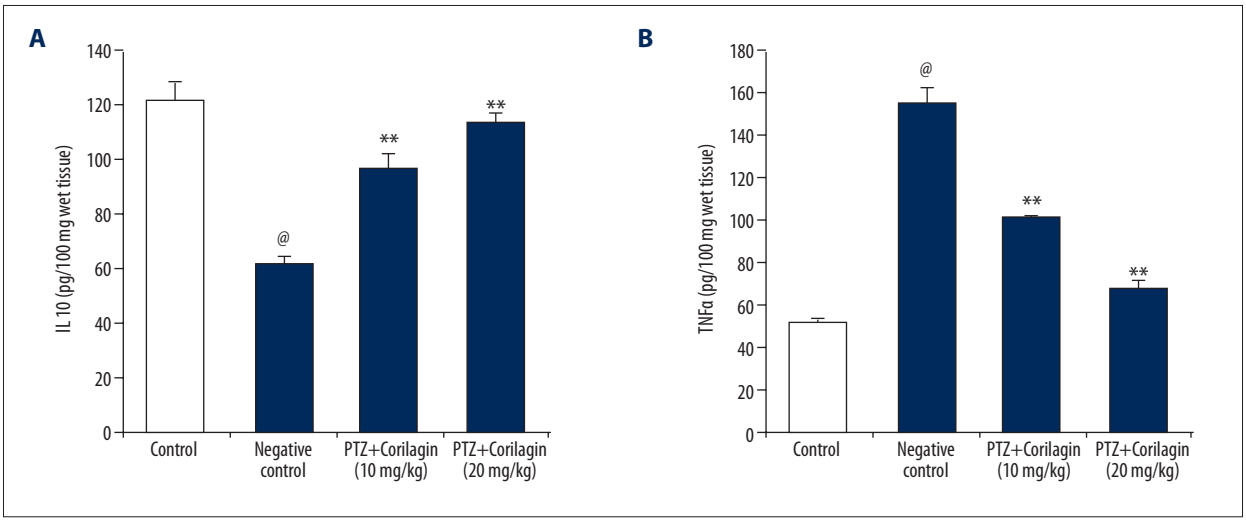

Figure 3. Effect of corilagin on cytokine in the brain tissues of rats in the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy. (**A**) Interleukin (IL)-10. (**B**) Tumor necrosis factor (TNF)-α. Values are means ±SD (n=10); @ P<0.01 (*vs.* control group); ** P<0.01 (*vs.* negative control group).

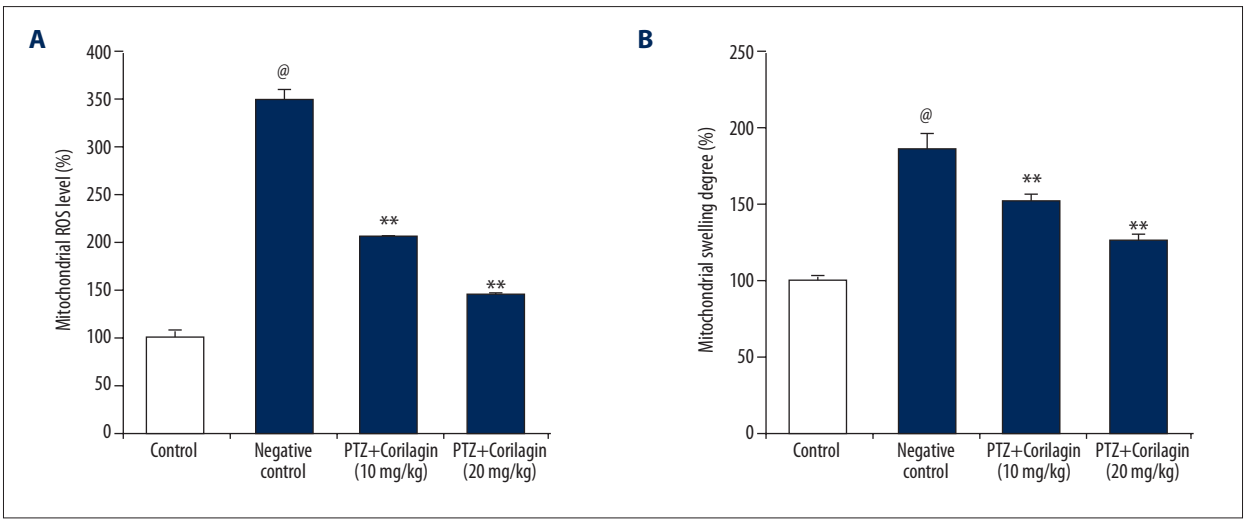

Figure 4. Effect of corilagin on mitochondrial status in the brain tissues of the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy. (**A**) Mitochondrial reactive oxygen species (ROS) production. (**B**) Mitochondrial swelling. Values are means ±SD (n=10). @ P<0.01 (*vs.* control group); ** P<0.01 (*vs.* negative control group).

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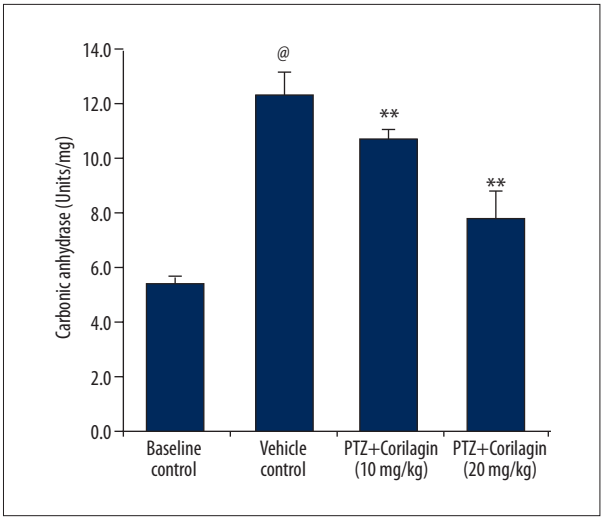

Figure 5. Effect of corilagin on carbonic anhydrase activity in the brain tissues of the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy. Values are means ±SD (n=10). @ P<0.01 (*vs.* control group); ** P<0.01 (*vs.* negative control group)

Measurement of carbonic anhydrase activity

Figure 5 shows the effect of corilagin on carbonic anhydrase activity in the brain tissues of rats with PTZ-induced chronic epilepsy, which was shown to increase. However, treatment with corilagin inhibited the activity of carbonic anhydrase enzyme compared with the negative control group of rats.

Nissl staining for Nissl substance in the neuronal cytoplasm

Nissl staining (cresyl violet) of neuronal Nissl bodies of rough endoplasmic reticulum (RER) and ribosomes, representing sites of protein synthesis were abnormal in morphology in the control groups but appeared to be more normal in the corilagin-treated rats. This reversal of the histological changes in the neuronal cells due to corilagin treatment was found to be dose-dependent (Figures 6, 7).

Discussion

The rat model of chronic epilepsy induced by pentylenetetrazol (PTZ) is an established experimental animal model [23]. The pathogenesis of epilepsy is now believed to involve increased oxidative stress, altered cellular ion levels, and inflammation [24]. Previously published literature has shown that chronic epilepsy is associated with cognitive impairment due to damage to the neuronal cells [25].

The aims of this study were to evaluate the effects of corilagin, an ellagitannin extracted from medicinal plants, on the frequency of seizures and cognitive function in rats with PTZ-induced chronic epilepsy. The findings of this study supported previously published studies that have shown that frequent or persistent epileptic seizures result in the development of cognitive impairment [26].

In this study, treatment with corilagin was shown to decrease the frequency of epileptic seizures, and in higher doses, corilagin decreased the duration of seizures. Corilagin also delayed the development of the epilepsy stage in rats with PTZ-induced chronic epilepsy. Also, corilagin treatment reduced memory impairment and significantly improved the cognitive function in rats with PTZ-induced chronic epilepsy (P<0.01).

Oxidative stress and inflammation are the possible factors responsible for the development of epileptic seizures [24]. The findings of this study, in a rat model, also suggested that chronic epilepsy results in increased level of the cytokine TNF-α and a decrease in IL-10 in the brain tissues. Treatment with corilagin significantly decreased TNF-α and increased IL-10 in the brain tissues of rats with PTZ-induced chronic epilepsy (P<0.01). Previously published literature has shown that IL-10 reduces tissue inflammation, either by inhibiting the activity of mononuclear cells or by inhibiting secretion of many inflammatory cytokines and chemokines or by opposing the effects of TNF-α [27].

Reactive oxygen species (ROS) is primarily produced in the mitochondria. ROS are highly reactive molecules that may damage DNA and mitochondrial function [28]. Impaired mitochondrial function increases the susceptibility to seizures and neuronal damage [29]. Therefore, the use of antioxidants may protect mitochondria and protect against epileptic seizures. In this study, treatment with corilagin significantly reduced mitochondrial ROS production and mitochondrial swelling compared with the negative control group of rats (P<0.01). Previously published literature has shown that persistent epileptic seizures are associated with enhanced production of ROS in mitochondria [4].

Carbonic anhydrase is an endogenous enzyme that maintains acid-base balance, with 13 different types of carbonic anhydrase being present in humans and rodents, and some of them being present in mitochondria [30]. Therefore, altered activity of carbonic anhydrase may also affect mitochondrial function, resulting in the production of ROS, damaging the mitochondria and inducing apoptosis [31]. The findings of this study showed that treatment with corilagin significantly decreased carbonic anhydrase activity when compared with the negative controls (P<0.01), possibly by reducing oxidative stress.

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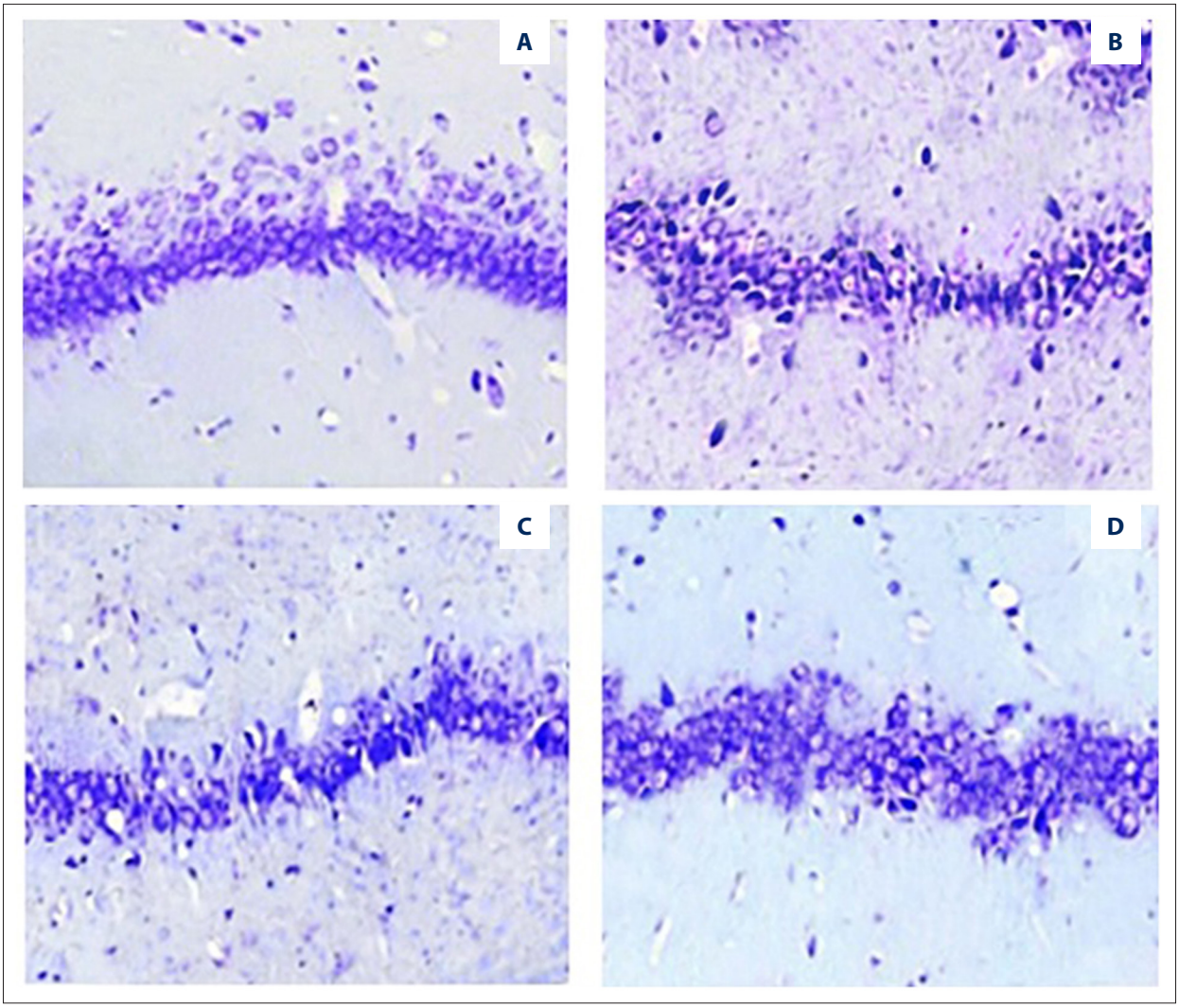

Figure 6. Effect of corilagin on CA1 neurons in the pentylenetetrazol (PTZ)-induced rat model of chronic epilepsy using Nissl staining. (**A**) Control group: regular cellular bodies. (**B**) Negative control group: altered cell morphology and nuclei. (**C**) PTZ + corilagin (10 mg/kg). (**D**) PTZ + corilagin (20 mg/kg): improvement in the cell morphology.

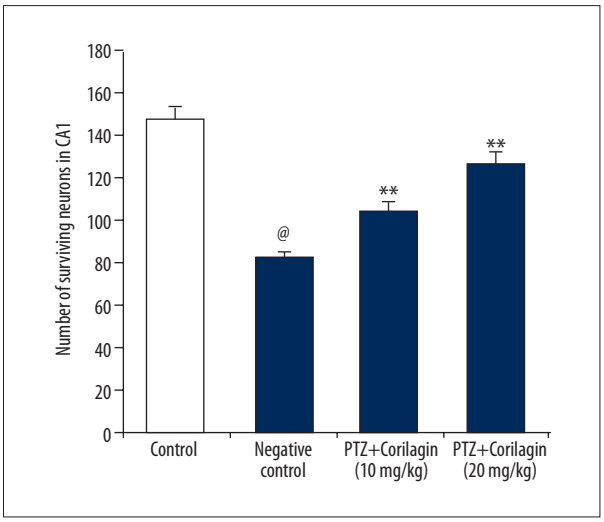

Figure 7. Effect of corilagin on number of surviving neurons by using Nissl staining of carbonic anhydrase inhibitory (CAI) activity in the hippocampus. Values are means ±SD (n=10). @ P<0.01 (*vs.* control group); ** P<0.01 (*vs.* negative control group).

Conclusions

The findings of the present study showed that corilagin significantly reduced the frequency of seizures and improved cognitive function in rats with PTZ-induced chronic epilepsy by reducing oxidative stress, cytokines, mitochondrial damage, and carbonic anhydrase activity in the brain tissues.

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Conflict of Interest

None.

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