Original Article

Impact of *Gastrodia elata* on Neuroinflammation and Epilepsy in a Rat Model

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Abstract

Background: *Gastrodia elata* (GE) is a traditional Chinese herb, a type of Orchidaceae, which has antiepileptic and anti-inflammatory effects. **Objectives:** To investigate the impact of GE on behavioral changes and inflammation after induction of seizures in rats using pentylenetetrazole. **Materials and Methods:** Adult male albino rats aged between 10 and 12 weeks, weighing 250–300 g were enrolled in this study. A total of 25 rats were divided into five groups: group 1: control group; group 2: pentylenetetrazole (40 mg/kg); group 3: pentylenetetrazole (40 mg/kg) and GE (883.56 mg/kg); group 4: pentylenetetrazole (40 mg/kg) and lacosamide (LCM, 50 mg/kg); and group 5: LCM (50 mg/kg). The rats were sacrificed by decapitation after 15 days of treatment, and brain tissue homogenate for the estimation of biochemical parameters, such as tumor necrosis factor-alpha (TNF-α), histology, and behavioral tests (latency, duration, and severity of fits). **Results:** TNF-α in group 2 was increased compared with group 1, but it was significantly decreased in groups 3, 4, and 5 compared with group 2. Histopathological results demonstrated moderate inflammation in group 2 compared with group 1, groups 3, 4, and 5 presented with mild inflammation compared with group 2. Latency of fits was significantly increased in groups 3, 4, and 5, whereas in group 2, it was significantly decreased; duration and severity of fits were significantly decreased in groups 3, 4, and 5. **Conclusion:** GE had anti-inflammatory effects and alleviated the severity, decreased the duration, and increased the latency of fits.

Keywords: Epilepsy, *Gastrodia elata*, inflammation, lacosamide, pentylenetetrazole

Introduction

Epilepsy is a brain disorder characterized by recurrent seizures that might be associated with cognitive, psychological, neurobiological, and social consequences.[1] Epilepsy occurs at all ages and affects around 50 million people worldwide annually, according to the World Health Organization (WHO). In systematic studies of the incidence, it has been found that the rate of epilepsy was 61.4 per 100,000 patients/years.[2]

The first classification of a seizure was officially made by the International League Against Epilepsy (ILAE) in 1989.[3] The classification can help to use a specific drug that is, effective for a certain type of seizure and also to identify the comorbidities and prognosis related to a specific type of seizure[4] Seizure classification by ILAE based on these features: seizure origin in the brain, awareness degree during seizure, and movement level of the body. Nearly, 50% of epilepsy patients present with acquired epilepsy, and different studies have reported various risk factors, including iron deficiency,[5] hemosiderin deposition, and selective neuronal damage leading to abnormal electrical discharge.[6] In recent years, researchers have shown that inflammation plays a significant role as an insult in the development of epilepsy caused by stroke and other brain traumas. New research studies suggested that inflammatory processes may have had a role in both epilepsies of the temporal lobe epilepsies and epilepsy associated with

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cortical abnormalities.[7] The neuronal dysfunction, microgliosis, and gliosis, together with the heightened intensity and neuroinflammatory activity, all lead to epileptogenesis.[8] It has a crucial role as a cytokine in the inflammatory process. The process of systemic inflammation contributes to the activation, proliferation, differentiation, and extravasation of immune-competent cells inside the central nervous system.[9] Tumor necrosis factor-alpha (TNF-α) was generated from astrocytes, and the activation of microglia resulted in its production.

Clinical investigation has shown that increased levels of cytokines interleukin (IL)-6, IL-1β, and TNF-α in cerebrospinal fluids are associated with epilepsy.[10] There are now 25 medications that have been approved for use in the treatment of epilepsy; however, studies have shown that these treatments were only ever successful in treating 60%–70% of patients. Hence, there is a pressing need for novel antiepileptic drugs that are efficacious against refractory epilepsy but also have a better safety profile.[11] Lacosamide (LCM) is an anti-seizure medication that is, considered to be of the third generation and is licensed for the treatment of focal epilepsy as well as primary generalized seizure. It was found that the delayed inactivation of voltage-gated sodium channels.[12]

Gastrodia elata (GE), an orchid from the family Orchidaceae, is a well-known traditional Chinese herb that has been utilized for hundreds of years. In China, GE was widely employed in the treatment of a wide variety of conditions, including spasms, headache, epilepsy, dizziness, convulsion, stroke, forgetfulness, and many others, in ancient times. Antidepressant, neuroprotective, anticonvulsive, antioxidant, and anti-inflammatory impacts are some of the therapeutic uses that were discovered as a consequence of a multitude of investigations. These findings have led to its use in a wide range of therapeutic applications.[13]

This study aimed to investigate the impact of GE on behavioral changes and inflammation after induction of seizures in a rat model of epilepsy.

Materials and Methods

Animals

A total of 25 adult male Wistar albino rats aged between 10 and 12 weeks, weighing 250–300 g were enrolled. Five rats were housed in a cage and habituated under conditions at 25°C, given standard commercial water and food. The environment was maintained in 12-h light/12-h dark cycles.

Chemicals and reagents

Pentylenetetrazol was purchased from Santa Cruz (CA, USA). TNF-α, using sandwich enzyme-linked immunosorbent assay principle, was procured from Elabscience Biotechnology (USA). LCM was purchased from Union Chimique Belge UCB (Belgium).

Preparation of plant

The GE powder was dissolved in distilled water for oral administration.

Study design and experimental protocols

Rats were divided into five groups randomly with five rats in each group as follows: group 1: control group in this group rats received intraperitoneal, per os (p.o.) normal saline only, and were exposed to the same condition; group 2: rats received pentylenetetrazole (PTZ) 40 mg/kg every other day for 15 days; group 3: rats received genome editing (GE) 883.56 and 40 mg/kg PTZ; group 4: rats received LCM 50 mg/kg; and PTZ 40 mg/kg, and group 5: rats received p.o. LCM 50 mg/kg.

Behavioral evaluation by Racine's scale

Racine's scale has been used to determine the behavioral changes of rats; seizure activity has been observed 30 min after kindling with PTZ. Behavioral characteristics like convulsion, duration, latency, and severity have been investigated for 30 min post-every dose of PTZ, and the following measures from Racine's scale.[14] magnitude has been documented as follows:

Stage intensity of fits

0 No response
1 Hyperactivity, restlessness, and vibrissae twitching
2 Head nodding, head clonus, and myoclonic jerks
3 Unilateral or bilateral limb clonus
4 Forelimb clonic seizures
5 Generalized clonic seizures with falling
6 Hind limb extensor
7 Death

Isolation of the brain

Post-PTZ-kindling, the animals were sacrificed by decapitation 24 h after the last medication. The forebrain and midbrain were removed, weighed, and washed with phosphate-buffered saline solution in Eppendorf tubes. One half was immersed in formaldehyde and embedded in paraffin for histological study, then frozen on dry ice and then kept in deep freeze at −20°C.

Statistical analysis

Five biological replicates and three technical replicates were used in this study. Results were reported as mean ± standard deviation (SD). Statistical comparisons were made using either one-way analysis of variance (with a Dennett's correction for multiple comparisons) using Statistical Package for Social Sciences version 1.0.0.1406 (IBM Corp., Armonk, NY, USA).

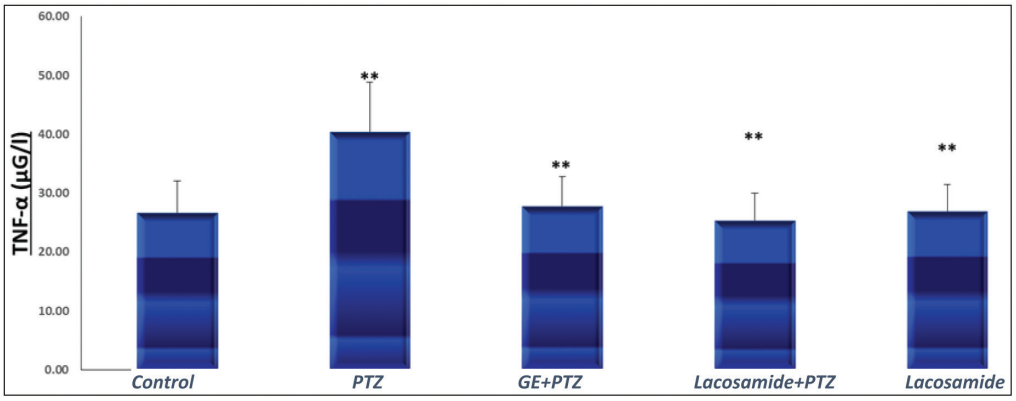


Figure 1: Impact of pentylenetetrazole (PTZ; 40 mg/kg), intraperitoneal, genome editing (GE; 883.56 mg/kg) + PTZ, per os, lacosamide (LCM) 50 mg/kg + PTZ, LCM on tumor necrosis factor-alpha level (µg/L) in rats' brains. Significantly increased in the PTZ group compared with the control and other groups. Results ($n = 5$) have been stated as the average (±standard deviation). (*$P < 0.05$; **$P < 0.001$)

Differences were considered significant at a P value of ≤0.05.

Ethical approval

The study protocol was reviewed and approved by a local ethics committee according to document number 409, on July 28, 2022.

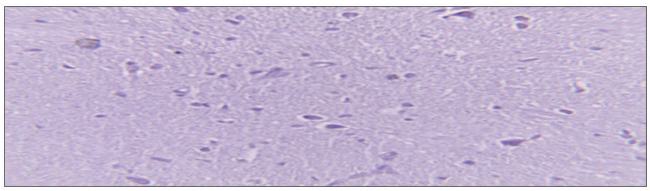
Results

Inflammation biomarkers

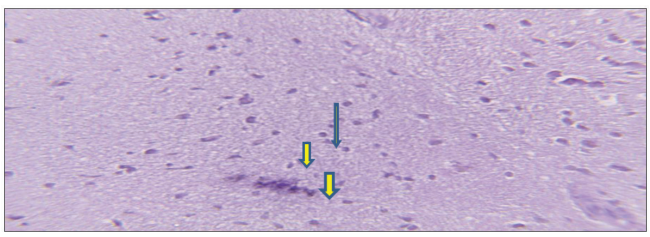
TNF-α biomarker

Impact of PTZ, GE + PTZ, LCM + PTZ, and LCM on TNF-α level (µg/L) in rats' brains after PTZ—kindling every 48 h for 15 days and exposure to other GE and LCM every day. The results are shown in Figure 1.

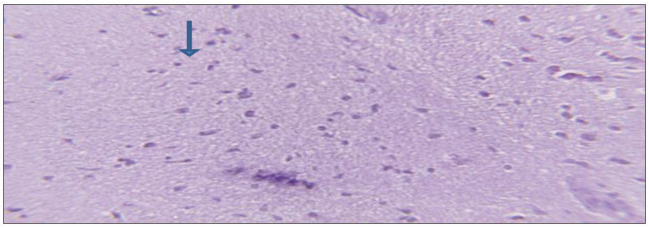
Histological results



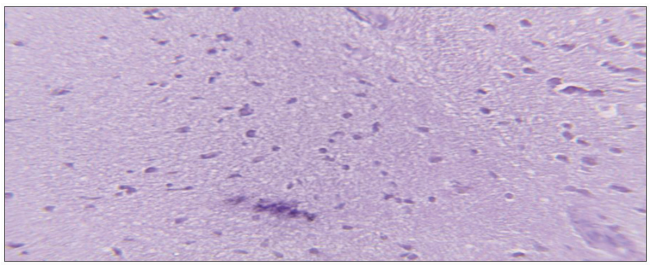
Picture 1: Rat brain, normal histology shows astrocytes with capillary blood vessels (hematoxylin and eosin ×400; control group 1)



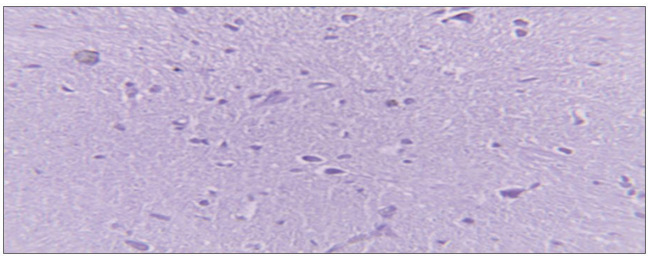
Picture 2: Rat brain, showing moderate inflammation with frequent acute inflammatory cells infiltrate, arrow (hematoxylin and eosin ×400; pentylenetetrazole group 2)



Picture 3: Rat brain, mild inflammation showing astrocytes with acute inflammatory cells infiltrate, arrow (hematoxylin and eosin ×400; genome editing + pentylenetetrazole group 3)



Picture 4: Rat brain, mild inflammation shows astrocytes with acute inflammatory cells infiltrate (hematoxylin and eosin ×400; lacosamide + pentylenetetrazole group 4)



Picture 5: Rat brain, normal histology shows astrocytes with capillary blood vessels (hematoxylin and eosin ×400; lacosamide group 5)

Behavioral test results

Latency

Impact of PTZ, GE + PTZ, LCM + PTZ, and LCM on latency (min) in rat's brain after each 48 h. Of the PTZ

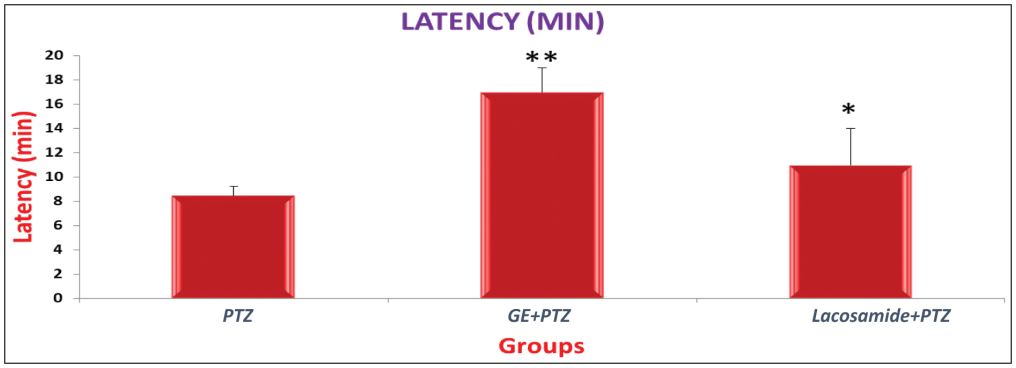


Figure 2: Impacts of pentylenetetrazole (PTZ; 40 mg/kg), intraperitoneal, genome editing (GE; 883.56 mg/kg), per os, oral administration of lacosamide + PTZ, on latency (min) in rat's brain. The effect of GE significantly increased the onset of fits compared with the PTZ group. Results ($n = 5$) have been stated as the average (±standard deviation). (*$P < 0.05$; **$P < 0.001$)

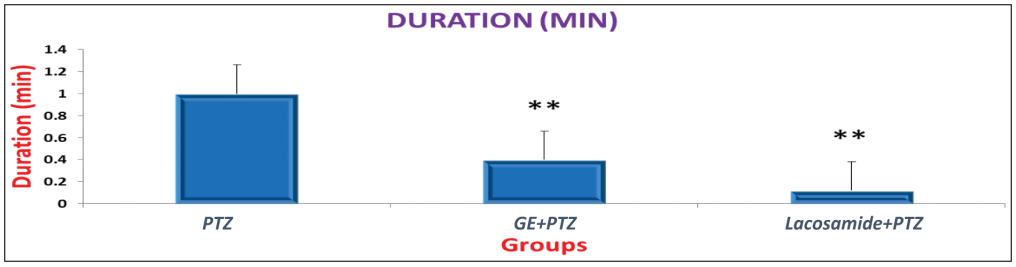


Figure 3: Impacts of pentylenetetrazole (PTZ; 40 mg/kg), intraperitoneal, genome editing (GE; 883.56 mg/kg), per os, oral administration of lacosamide on the duration of fits. In the PTZ group, the duration of fits increased compared with other groups. Results ($n = 5$) have been stated as the average (±standard deviation). (*$P < 0.05$; **$P < 0.001$)

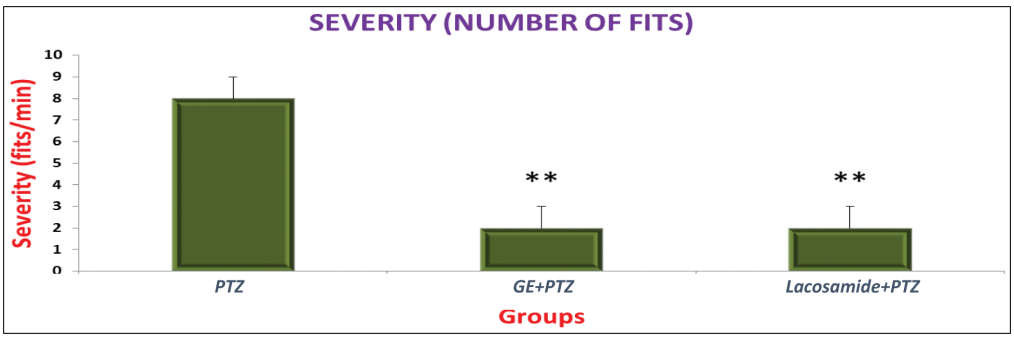


Figure 4: Impacts of pentylenetetrazole (PTZ; 40 mg/kg), intraperitoneal, genome editing (GE; 883.56 mg/kg), per os, oral administration of lacosamide on severity (fits/min) in rats' brains. GE alleviated the severity of fits compared with the PTZ-kindling group. Results ($n = 5$) have been stated as the average (±standard deviation). (*$P < 0.05$; **$P < 0.001$)

group, and 15 days of exposure for other groups as shown in Figure 2.

Duration

Impact of PTZ, GE + PTZ, LCM + PTZ, and LCM on duration (min) in rat's brain after every other day for the PTZ group, and 15-day exposure for other groups as shown in Figure 3.

Severity

Impact of PTZ, GE + PTZ, LCM + PTZ, and LCM on severity (fits/min) in rat's brain after every other day for the PTZ group, and 15-day exposure for other groups as shown in Figure 4.

Discussion

Seizures artificially induced have been investigated to have an inflammatory response in many areas of the brain that have been able to cause propagation of the initiation of epilepsy.[15] According to previous studies, seizures induced either electrically or chemically resulted in increased cytokines in the brains of rat models.[7] In the present study, PTZ (group 2) demonstrated a significant elevation in pro-inflammatory cytokines, TNF-α compared with the control (group 1). This result was in line with previous studies that showed TNF-α was present at very low levels in the normal brain of rats, but pro-inflammatory cytokines rapidly increased after the induction of seizures (≤30 min) and lowered to basal

levels during (48–72 h) from the latency of seizures.[16] Additionally, rat kindling might exacerbate the effects of the amino-3-hydroxy-5-methylisoxazole-4-propionic acid -receptor, which facilitated excitotoxicity based on the amount of time the tissue was exposed to the kindling and the extracellular amount of these cytokines throughout the injury.[17] GE + PTZ (group 3) was investigated with a significantly decreased TNF-α level compared with PTZ (group 2). These results agreed with previous studies that highlighted the administration of GE could alleviate inflammation by decreasing the cytokine levels in the brains of rats that were induction seizures using PTZ.[18] LCM decreased microglial cell activation in the brain and TNF-α expression.[19]

In the present study, it has been found a significant decrease in the levels of cytokines such as TNF-α and IL-1β, IL-6 in (group 5) LCM + PTZ, compared with (group 2) PTZ-kindling, which was in agreement with other recent studies that demonstrated decreased levels of these pro-inflammatory cytokines and produced a mild amelioration in inflammatory effects in the hippocampus.[20]

The duration and severity of seizures were significantly increased in the PTZ (group 2) when compared with the control (group 1) because PTZ-kindling acts by antagonizing the gamma-aminobutyric (GABA)-A receptor.[21] PTZ suppressed the inhibitory synaptic functions and subsequently caused an increase in neuronal activity. GE prevented a large proportion of rats from developing seizures, decreased the duration and severity, and increased the latency because it reversed the decrease of GABA level in the synaptic cleft via inhibiting its degradation,[22] furthermore, decreased the glutamate (Glu) activity found that GE could reduce the number Glu immune-histochemically positive cells.

The present study found that the latent onset of PTZ-induced seizures increased, and a significant decrease in the duration of seizures compared with the PTZ (group 2). LCM is an antiepileptic drug approved for use as an anticonvulsant agent that prevents seizures. This outcome is consistent with several other past findings that confirmed the impact of LCM on suppressing epileptiform activity, thereby minimizing the long-term consequences of epileptic seizures and decreasing the number of seizures a patient experiences once the medication is managed early.[23] Kindling with PTZ has been found to display significant morphological alterations and severe inflammation. PTZ-kindling (group 2) in the present study demonstrated histological alterations in the brain of the rat model and caused moderate inflammation compared with the control group 1. These results were consistent with the previous studies, which concluded that PTZ administration induced histological aberration in the brain hippocampus with significantly elevated inflammatory infiltration, pyknosis, and necrosis as compared to normal rats, which did not show any pyknosis.[24] PTZ-kindling induced abnormal migration of newborn granule neurons.[25]

Treatment with GE has been found to ameliorate the histopathological damage by a greater number of surviving neurons and a milder inflammatory area of the brain compared with the PTZ group 2.

In the current study, GE in group 3 decreased the effect of PTZ-kindling that produced inflammation by decreasing the inflammatory cell infiltration, congestion, and necrosis pyknosis as compared with the PTZ-kindling group 2. These results were in agreement with other studies' data that further suggested that GE prevented the activation of microglia in the rat's neuroinflamed hippocampus.[26] LCM + PTZ in group 5, was found to decrease the inflammation as mentioned before, so it reduced the effect of PTZ from moderate to mild as compared with group 2, PTZ-kindling.

Previous results by other studies further demonstrated the effect of LCM on inflammation by decreasing the activated microglia with increasing ramified microglia under inflammatory conditions caused by pathological or induction with chemical agents, this role of LCS supported its beneficial effect in epilepsy associated with neuroinflammation.[27]

Conclusion

This study has concluded that GE might improve epileptic control and neuroinflammation profiles.

Acknowledgement

Not applicable.

Data availability

Not applicable.

Ethical policy and Institutional Review Board statement

Not applicable.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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