IJBPAS, April, 2022, 11(4): 1829-1846

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)
'A Bridge Between Laboratory and Reader'

www.ijbpas.com

THE NEUROPROTECTIVE EFFECT OF ELLAGIC ACID ON COGNITIVE IMPAIRMENT AND OXIDATIVE STRESS INDUCED BY PTZ-KINDLING IN RATS

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Received 26th May 2021; Revised 18th June 2021; Accepted 22nd July 2021; Available online 1st April 2022

https://doi.org/10.31032/IJBPAS/2022/11.4.6017

ABSTRACT

PTZ-induced kindling causes memory disruption in rats is a consequence of changes within the central nervous system that are secondary to impaired oxidative stress. Treatment with antioxidants are reported to produce beneficial effects in animal models. Ellagic acid reported to exhibit antioxidant effect. However, no report is available on the influence of ellagic acid on PTZ-induced kindling causes memory impairment. Therefore, we tested its influence against cognitive dysfunction in PTZ-induced epileptic rats using passive avoidance test. Lipid peroxidation and glutathione levels as parameter of oxidative stress were assessed in the hippocampus. After induction of epilepsy PTZ treated rats showed a severe deficit in learning and memory associated with increased lipid peroxidation, decreased glutathione activity. In contrast, treatment with ellagic acid (7.5-30 mg/kg, p.o.) improved cognitive performance, and lowered oxidative stress in PTZ treated rats. In conclusion, the present study demonstrates that treatment with ellagic acid prevents the changes in oxidative stress and consequently memory impairment in PTZ treated rats.

Keywords: Ellagic acid; PTZ-induced kindling; Memory impairment; Oxidative stress, Passive avoidance test

INTRODUCTION

Epilepsy is one of the most common neurological disorders characterized by recurrent epileptic seizures and cognitive and behavior impairment **[1, 2]**. In worldwide, approximately 70 million peoples of all age are suffering from this disorder **[3]**. Patients with epilepsy frequently manifest cognitive and affective disorders such as spatial memory deficit and impaired emotional learning **[4]**. Some studies have demonstrated that prolonged or recurrent seizures cause spatial and emotional deficits **[5]** but other studies observed that after recurrent seizures, spatial memory remains intact **[6]**.

Kindling results due to repeated seizures, which induces a permanent and progressive enhancement of epilepsy. It is an activity-dependent neural circuit plasticity phenomenon which involves a permanent structural and functional modifications due to induction of various, molecular, cellular, and functional alterations in neural circuits **[7]**. Pentylenetetrazol (PTZ) is widely used to induce seizures and to assess the effectiveness of antiepileptic drugs. Kindling induced by repeated PTZ administration has helped researchers to identify the pathophysiological pathways of epilepsy. This model has also helped researcher to discover new as well as effective therapeutic options to manage this condition **[8, 9]**.

PTZ is a chloride channel blocker of choice that binds to the GABA-A receptor complex, and is a chemical inducer of seizure used to study antiepileptic drugs (AEDs) in animal models. It has been argued that PTZ exerts adverse effects on neuronal membrane, affects potassium and calcium channels, releases intracellular calcium ion reserves, and reduces the neurotransmitter-induced chloride conductance **[10]**. Oxidative stress is likely to play a role in the onset and progression of epileptic seizures. It has been reported that epileptic seizures are associated with the hemostatic imbalance of antioxidants and oxidants **[11]**. Animal studies have indicated that PTZ-induced epileptic seizures are associated with significant increase in lipid peroxidation and significant decrease in the antioxidant activity of superoxide dismutase (SOD) and catalase (CAT) as well as glutathione levels in the red blood cells, liver, and brain **[11, 12]**. Neuroprotective effects of natural products with anti-oxidant properties have been fully documented in epilepsy and seizure **[13]**.

Ellagic acid (EA) (3, 7, 8-tetrahydroxy [1]-benzopyrano [5, 4, 3-

benzopyran-5,10-dione) is a member of flavonoids. It is a naturally occurring polyphenolic compound which has been reported to possess multiple pharmacological effects such as antioxidant, antifibrotic **[14, 15]**, anti-inflammatory **[16]**. Many research demonstrated the neuroprotective role of EA in several central nervous system diseases **[17]**. Farbood *et al* **[18]** reported that EA alleviates brain injury-induced cognitive dysfunction via inhibition of neuroinflammation. Notably, Sarkaki *et al* **[19]** demonstrated that EA mitigates the symptoms of Parkinson's disease induced by 6-hydroxydopamine, and this effect may be attributed to its antioxidant properties **[20]**.

There were several studies have also focused on the effects of ellagic acid on cognition and memory in different models of memory impairment in different animals. However, no report is available on the influence of ellagic acid on PTZ-induced epilepsy causes memory impairment. Therefore, the present study was designed to investigate the protective role of ellagic acid on cognitive dysfunction in pentylenetetrazol-induced epilepsy in rats.

MATERIALS AND METHODS

Subjects

Adult male Wistar rats born and reared in the Animal House of the Agnihotri College of Pharmacy, Wardha, from a stock originally purchased from Shree Farms, Bhandara, India were used in the present study. Young, healthy male rats (150-200 g) were group housed (three per cage) and maintained at 23 ± 2 °C under 12:12 h light (08:00-20:00 h) /dark cycle with free access to rodent chow and tap water. Animals were naive to drug treatments and experimentation at the beginning of all studies. All tests were conducted between 08:00 and 13:00 h. All experimental protocol were approved by the Institutional Animal Ethics Committee and carried out under strict compliance with ethical principles and guidelines of Committee for Purpose of Control and Supervision of Experimental Animals, Ministry of Environment and Forests, Government of India, New Delhi, India.

Drugs and solutions

Ellagic acid and pentylenetetrazole was purchased from Sigma (Sigma-Aldrich, St. Louis, MO, USA) were used in present study. All the drugs were dissolved in double distilled water (DDW). Drug solutions were prepared fresh and their doses are expressed in terms of their free bases.

Treatment schedule

The animals were randomly divided into five groups with six animals in each group. Group I (control group) received double distilled water i.p. every other day (3.5 ml/kg, 13 injections total). Group II (PTZ group) received double distilled water pretreatment along with PTZ (30 mg/kg, i.p.) every other day. Groups III, IV and V (PTZ + ellagic acid groups) received ellagic acid pretreatment in doses of 30 mg/kg, i.p. PTZ and 7.5, 15 and 30 mg/kg, p.o. ellagic acid respectively, in alternate day treatment. In these groups, ellagic acid was given 30 min before PTZ. Cognition was assessed after 24 h of the last PTZ injection. At the end of cognition assessment animals were rapidly sacrificed by decapitation and brains were collected for biochemical measurements.

PTZ- induced kindling in rats

For PTZ kindling, a subconvulsant dose of PTZ 30 mg/kg body weight was injected intraperitoneally on every second day. The animals were observed for 30 min after each PTZ administration. The latency to myoclonic jerks and the generalized tonic clonic seizures (GTCS), as well as the duration of GTCS were recorded. Seizure stage was evaluated using the following scale: Stage 0: no response; Stage 1: hyperactivity and vibrissae twitching; Stage 2: head nodding, head clonus and myoclonic jerk; Stage 3: unilateral forelimb clonus; Stage 4: rearing with bilateral forelimb clonus; Stage 5: generalized tonicclonic seizure (GTCS) with loss of postural control. The PTZ injections were stopped when the animals showed adequate kindling, i.e. seizure score of 5 on three consecutive injections. The first incidence of seizure with score five was observed between Day 27 and Day 31. Thus, in no case did the PTZ schedule exceed Day 35 **[21]**.

Assessment of cognitive function

Passive avoidance test

Memory retention deficit was evaluated using a step-through passive avoidance apparatus as described earlier **[22]**. The learning box consisted of two compartments, one light (white compartment, 20×20×30 cm) and the other dark (black compartment, 20×20×30 cm). A guillotinedoor opening (6×6 cm) was made on the floor in the center of the partition between the two compartments. The floor of the dark compartment consists of stainlesssteel grids to produce the foot shock. All animals were allowed to habituate in the experimental room for at least 30 minutes prior to the experiments. After habituation, each animal was gently placed in the light compartment of the apparatus; after 5 seconds, the guillotine door was opened and the animal was allowed to enter the dark compartment. The latency to the animal's entry into the dark compartment was recorded. Animals that waited more than 100 seconds to cross into the dark compartment were eliminated from the experiments. Once the animal crossed with all four paws into the next compartment, the guillotine door was closed and the rat was returned to its home cage. The acquisition trial was carried out 30 minutes after the habituation trial. The animal was placed in the light compartment, the guillotine door was opened 5 seconds later, and as soon as the animal crossed into the dark compartment, the door was closed and a foot shock (50 Hz, 5 seconds, 0.2-mA intensity) was immediately delivered to the grid floor of the dark room with an insulated stimulator. After 20 seconds, the rat was removed from the apparatus and placed in its home cage. Training was terminated when the rat remained in the light compartment for 120 consecutive seconds. One day following training, the retention tests were performed to evaluate memory. Each animal was placed in the light compartment for 20 seconds, the door was opened, and the step through latency to entry into the dark compartment was measured. The session ended either when the animal entered the dark compartment or when it remained in the light compartment for 300 seconds. During these sessions, no electric shock was applied.

Biochemical estimation

Post-mitochondrial supernatant preparation

After behavioral tests, the animals were submitted to euthanasia being previously anesthetized with ethyl ether and brain structures were removed and separated the whole hippocampus. Hippocampus were rinsed with ice cold saline (0.9% sodium chloride) and homogenized in chilled phosphate buffer (pH 7.4). The homogenates were centrifuged at 800 ×g for 5 min at 4 °C to separate the nuclear debris. The supernatant thus obtained was centrifuged at 10,500 ×g for 20 min at 4 °C to get the post-mitochondrial supernatant, which was used to assay lipid peroxidation and reduced glutathione activity.

Estimation of lipid peroxidation (LPO)

The malondialdehyde (MDA) content, a measure of lipid peroxidation, was assayed in the form of thiobarbituric acid reactive substances (TBARSs) by the method of Wills (1965). Briefly, 0.5 ml of post-mitochondrial supernatant and 0.5 ml of Tris HCl were incubated at 37 °C for 2 h. After incubation 1 ml of 10% trichloroacetic acid was added and centrifuged at 1000 ×g for 10 min. To 1 ml of supernatant, 1 ml of 0.67% thiobarbituric acid was added and the tubes were kept in boiling water for 10 min. After cooling 1 ml double distilled water was added and absorbance was measured at 532 nm. Thiobarbituric acid reactive substances were quantified using an extinction coefficient of 1.56 × 105 M^{-1} cm^{-1} and expressed as nmol of malondialdehyde per mg protein. Tissue protein was estimated using the Biuret method and the brain malondialdehyde content expressed as nmol of malondialdehyde per mg of protein **[23]**.

Estimation of glutathione

Glutathione (GSH) estimation was done according to the method of Ellman (1959). Briefly, 160 μl of supernatant was added to 2 ml of Ellman's reagent (5′5 dithiobis [2-nitrobenzoic acid] 10 mM, $NaHCO_3$ 15 mM) and the mixture was incubated at room temperature for 5 min and absorbance was read at 412 nm **[24]**.

Statistical analysis

Results were expressed as mean ± S.E.M. The data were analyzed by two-way or one-way analysis of variance (ANOVA) followed by Bonferroni and Tukey's multiple comparison tests, respectively. Statistical significance was considered at $P < 0.05$ in all the cases.

RESULTS

Effect of ellagic acid on seizures in PTZ kindled rats

Latency to myoclonic jerks, latency to clonic seizures, latency to GTCS, number of myoclonic jerks, duration of GTCS and seizure score were used to assess the severity of seizures in rats. Ellagic acid caused dose-dependent increase in the latency of myoclonic jerks [$F(3,23) = 40.10$, $P = 0.0001$] as well as the latency to GTCS [$F(3,23) = 65.72$, $P = 0.0001$] and a decrease in number of myoclonic jerks [$F(3,23) = 18.64$, $P = 0.0001$] as compared to the PTZ treated rats. Pretreatment with ellagic acid caused a significant increase in the latency to myoclonic jerks from 31.33 ± 4.201 s in the PTZ treated rats to 55.67 ± 3.313 s, 80.17 ± 7.812 s and 111.5 ± 5.252 s in the groups administered ellagic acid 7.5, 15 and 30 mg/kg, respectively **(Figure 1C)**. The number of myoclonic jerks decreased from 38.33 ± 4.425 in the PTZ treated rats to 16.33 ± 3.007, 12.83 ± 2.104 and 9.83 ± 1.701 in the groups administered ellagic acid 7.5, 15 and 30 mg/kg, respectively **(Figure 1B)**. A significant difference in the onset of clonic seizures was observed [$F(3,23) = 188.8$, $P = 0.0001$]. Post hoc analysis revealed that ellagic acid at doses of 7.5, 15 and 30 mg/kg significantly increased the latency to clonic seizures from 37.50 ± 3.766 s in the PTZ treated rats to 90.33 ± 2.613 s (***P< 0.001), 122.0 ± 5.645 s (***P< 0.001) and 176.7 ±

4.364 s (***P< 0.001) in silyamrin 7.5, 15 and 30 mg/kg treated groups, respectively **(Figure 1A)**. Ellagic acid significantly increased the latency of GTCS from 146.3±7.911 s in the PTZ treated rats to 217.2 ± 10.87 s, 246.3 ± 7.856 s, and 323.2 ± 9.138 s in the groups administered ellagic acid 7.5, 15 and 30 mg/kg, respectively **(Figure 1D)**. There was a significant difference in the duration of GTCS amongst the different groups [F(3,23) = 14.82, P = 0.0001]. ellagic acid decreased the duration of GTCS from 15.50 ± 1.057 s in the PTZ treated rats to 10.50 ± 0.718 s (**P< 0.01), 9.50 ± 0.763 s (*P< 0.01) and 6.667 ± 1.202 s (***P< 0.001) in the groups administered 7.5, 15 and 30 mg/kg of ellagic acid respectively **(Figure 1E)**.

Effects of ellagic acid on PTZ-induced cognitive dysfunction

Effects of ellagic acid on passive avoidance task (step-through paradigm) in PTZ kindled rats

Passive avoidance task assesses the ability of the animals to retain and recall information. The mean the retention latency was significantly different between the groups [F(4, 29) = 10.00, *P*< 0.0001]. Tukey's post hoc test revealed that PTZ treated rats led to a significant decrease in retention latency in the passive avoidance paradigm as compared to the DDW control group. The retention latency decreased from 111 ± 4.940 s in the control rats to 61.50 ± 9.461 s in the PTZ group (*P*< 0.05). When ellagic acid was administered with PTZ, it produced significant dose-dependent increase in retention latency as compared to the PTZ treated group. The retention latency increased from 61.50 ± 9.461 s in PTZ administered rats to 80.83 ± 4.820 s, 94.83 ± 4.347 s and 108.00 ± 7.317s (*P*< 0.0001) in the groups administered ellagic acid 7.5, 15 and 30 mg/kg, respectively **(Figure 2)**.

Effect of ellagic acid on parameters of oxidative stress in brain

Effect of ellagic acid on PTZ-induced kindling changes in lipid peroxidation

Effects of ellagic acid lipid peroxidation (LPO) are depicted in **Figure 3**. There was a significant rise in MDA levels in hippocampal [F(4, 29) = 9.455, *P*< 0.0001] tissue of rat brain in PTZ treated rats as compared to DDW control rats. Ellagic acid (7.5, 15 and 30 mg/kg) treatment significantly reduced MDA levels as compared to PTZ treated rats in hippocampus (*P*< 0.05). **(Figure 3)**.

Effect of ellagic acid on PTZ-induced kindling changes in glutathione levels

Effects of ellagic acid on GSH levels are depicted in **Figure 4**. There was a significant fall in GSH levels in hippocampal [F(4, 29) = 8.745, $P< 0.0001$] tissue of rat brain in PTZ treated rats as compared to DDW control rats. ellagic acid (7.5, 15 and 30 mg/kg) treatment significantly increased GSH levels as compared to PTZ treated rats ($P< 0.05$) **(Figure 4)**.

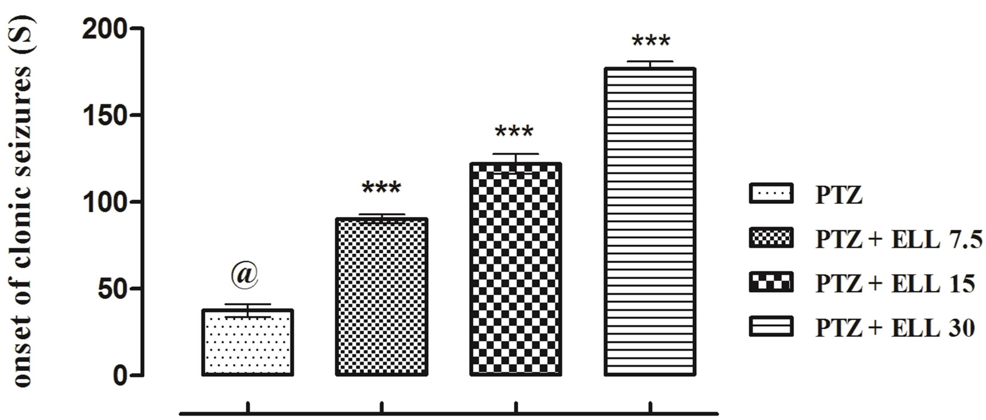

Figure 1A: Onset of clonic seizures

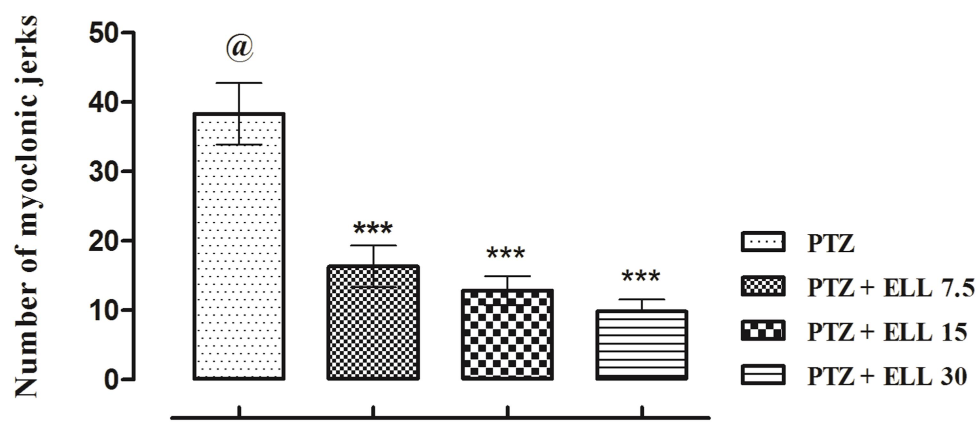

Figure 1B: Number of myoclonic jerks

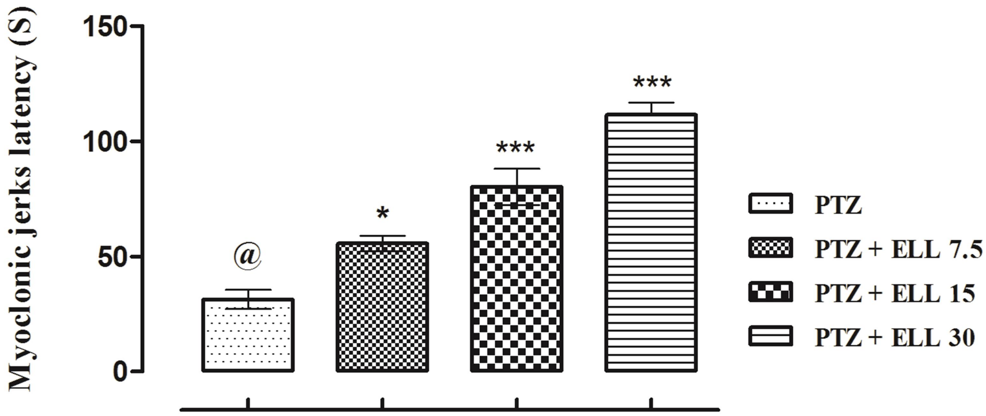

Figure 1C: Myoclonic jerks latency

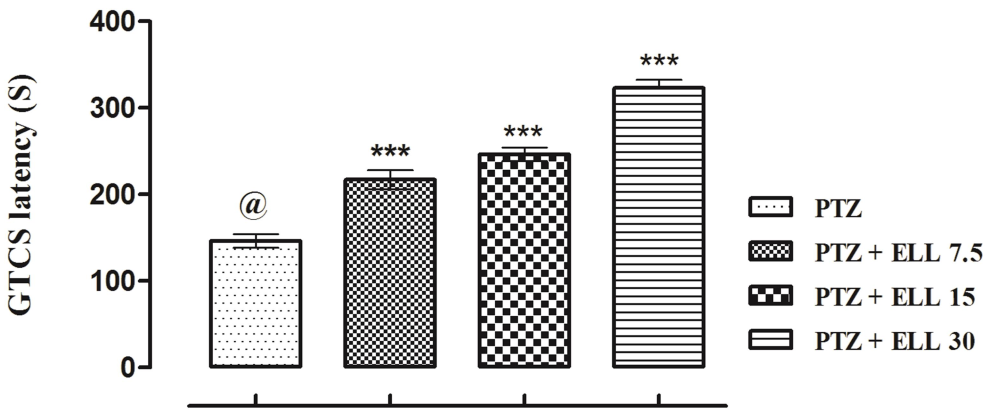

Figure 1D: GTCS latency

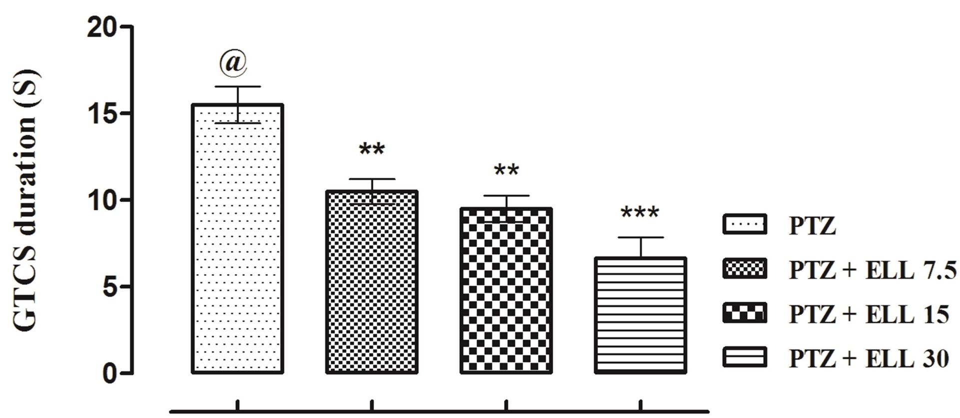

Figure 1E: GTCS duration

Figure 1: Effect of repeated administration of ellagic acid in doses 7.5, 15, 30 mg/kg, p.o. on the development of pentylenetetrazole kindling in rats. (A) Onset of clonic seizures. (B) Number of myoclonic jerks. (C) Myoclonic jerks latency. (D) GTCS latency. (E) GTCS duration

Each value represents mean ± S.E.M. of 5-6 observations. *P<0.05, **P<0.01 and ***P<0.001 vs. PTZ treated group (One-way ANOVA followed by Tukey's post hoc test). PTZ control: pentylenetetrazole control; PTZ + ELL 7.5: pentylenetetrazole ellagic acid (7.5 mg/kg) treated; PTZ + ELL 15: pentylenetetrazole ellagic acid (15 mg/kg) treated; PTZ + ELL 30: pentylenetetrazole ellagic acid (30 mg/kg) treated

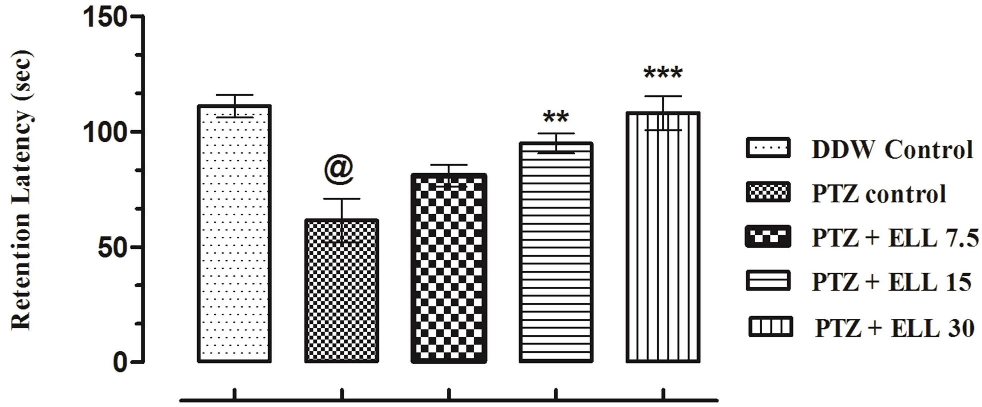

Figure 2: Effects of ellagic acid on passive avoidance test in PTZ kindled rats

Each value represents mean ± S.E.M. of 5-6 observations. @*P*<0.001 vs. DDW control group, ***P*<0.01 and ****P*<0.001 vs. PTZ treated group (One-way ANOVA followed by Tukey's post hoc test). DDW control: Double Distilled Water control; PTZ control: pentylenetetrazole control; PTZ + ELL 7.5: pentylenetetrazole ellagic acid (7.5 mg/kg) treated; PTZ + ELL 15: pentylenetetrazole ellagic acid (15 mg/kg) treated; PTZ + ELL 30: pentylenetetrazole ellagic acid (30 mg/kg) treated

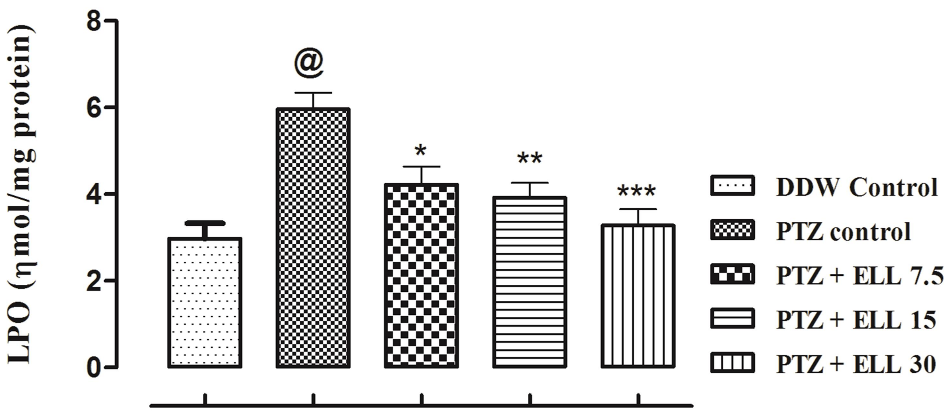

Figure 3: Effect of ellagic acid on PTZ-induced kindling changes in lipid peroxidation levels in hippocampus of rat brain
Each value represents mean ± S.E.M. of 5-6 observations. @*P*<0.001 vs. DDW control group, **P*<0.05, ***P*<0.01 and ****P*<0.001 vs. PTZ treated group (One-way ANOVA followed by Tukey's post hoc test). DDW control: Double Distilled Water control; PTZ control: pentylenetetrazole control; PTZ + ELL 7.5: pentylenetetrazole ellagic acid (7.5 mg/kg) treated; PTZ + ELL 15 : pentylenetetrazole ellagic acid (15 mg/kg) treated; PTZ + ELL 30: pentylenetetrazole ellagic acid (30 mg/kg) treated.

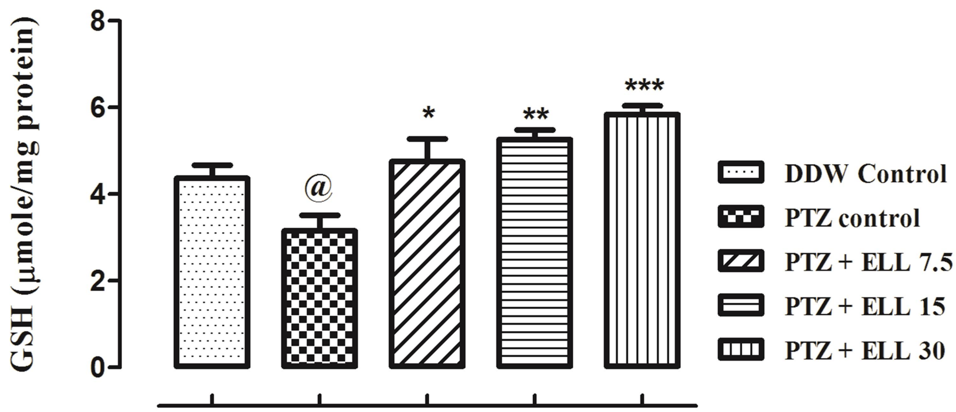

Figure 4: Effect of ellagic acid on PTZ-induced kindling changes in glutathione levels in hippocampus of rat brain
Each value represents mean ± S.E.M. of 5-6 observations. [@]*P*<0.001 vs. DDW control group, ****P*<0.05, *****P*<0.01 and ******P*<0.001 vs. PTZ treated group (One-way ANOVA followed by Tukey's post hoc test). DDW control: Double Distilled Water control; PTZ control: pentylenetetrazole control; PTZ + ELL 7.5: pentylenetetrazole ellagic acid (7.5 mg/kg) treated; PTZ + ELL 15 : pentylenetetrazole ellagic acid (15 mg/kg) treated; PTZ + ELL 30: pentylenetetrazole ellagic acid (30 mg/kg) treated

DISCUSSION

In the present study, we studied the effect of ellagic acid on the development of PTZ-induced kindling rats. Pretreatment with ellagic acid in doses 7.5, 15 and 30mg/kg attenuated seizure severity from the beginning of the kindling procedure by loweringthe mean seizure stage, seizure latency and duration. These effects of ellagic acid at higher doses are more significant.

In addition, pretreatment with ellagic acid before administration of PTZ every other day, and prior to training, is associated with enhanced memory retrieval in rats. Ellagic acid (7.5, 15 and 30 mg/kg) significantly increased retrieval of memory in the retention tests of a passive avoidance task, compared with PTZ-treated group. The cognitive enhancing effect of ellagic acid was also observed at 7.5 mg/kg. Epilepsy characterized by repetitive unprovoked seizures leading to devastating neurological results on the patients **[25]**, which requires long time therapy with antiepileptic drugs (AEDs), but presently available AEDs are not capable to provide sufficient seizures control in almost one-third of the patients and also do not stop the underlying epileptogenic alterations **[26]**. Currently, temporal lobe epilepsy related cognitive disorders have been characterized by experimental models and memory and learning deficits were compared after preconditioning **[27, 28]**. However, standardized neuropsychological tests to analyze memory impairment in epileptic rat models remain indefinable. Animal models for kindling provide an acceptable approach to quantify epileptogenesis **[29]**.

In the present study, sub-convulsive dose of PTZ when given intraperitoneally on alternate days induced kindling in the control rats. The groups which were administered ellagic acid showed dose dependent protection against seizures. Ellagic acid significantly increased the latencies to myoclonic jerks, clonic seizures and GTCS as well as duration of GTCS as compared to the PTZ kindled rats **(Figure 1A and 1C-1E)**. The number of myoclonic jerks was also decreased by ellagic acid in a dose-dependent manner **(Figure 1B)**. Ellagic acid produced maximum seizure protective effect in the dose of 30 mg/kg. Results of the current study showed that ellagic acid administration decreases the intensity of convulsive attacks in rat. Temporal lobe epilepsy is a focal type of seizure that is manifested by repeated convulsive attacks **[30]**. In the present study, the protective effect of ellagic acid was evaluated against cognitive impairment induced by seizures in the PTZ kindled rats. Ellagic acid exhibited dose-dependent protective effect against seizures, oxidative stress and cognitive impairment in rats.

The frequent incidence of epileptic seizures significantly declines learning rate and memory in patients with epilepsy. It has been demonstrated that pentylenetetrazol (PTZ)-induced chemical kindling can lead to learning disorders in laboratory animals **[31]**. The hippocampus is not only effective on memory and learning, but also on the onset, generalization, and termination of seizure. The brain neurodegeneration, especially in the CA1 region of the hippocampus, and change in the function of changeable synapses that store the information, are a possible explanation of the observed learning disorder following kindling **[32]**. This imbalance between oxidant and antioxidant defense mechanism in the body may result into seizures and cognitive deficit.

In present study, PTZ caused a significant decrease in retention latency in the passive avoidance task which indicates impairment of memory of rats. In the groups that were administered ellagic acid, the rats exhibited significantly increased retention latencies in the passive avoidance paradigm as compared to the animals administered PTZ alone **(Figure 2)**. These improvements in cognition of kindled rats with ellagic acid were dose-dependent with the maximum benefit at 30 mg/kg dose. The protective effect of ellagic acid on cognitive impairment observed in the present study may be due to its anticonvulsant effect. In the present study, ellagic acid showed anti-seizure activity which may be at least partially responsible for the improvement in cognitive function in the groups treated with ellagic acid. Many evidences have unveiled the anti-apoptotic and anti-inflammatory effects of EGA through modulation of PI3-kinase-eNOS signaling **[33]**. Neuroprotective action of EGA against Aβ25–35, STZ and traumatic brain injury (TBI) has been demonstrated in animal studies **[34]**. EGA is able to restore endothelial dysfunction in mice and memory deficits in scopolamine- and diazepam-treated rats **[35, 36]**. The role of oxidative stress in epilepsy and cognitive impairment is well established **[37]**, Therefore, the present study focused mainly on the oxidative stress and role of antioxidant properties of ellagic acid. MDA is an end product of free radical-mediated oxidative cell damage and lipid peroxidation **[38]**.

In the present study, PTZ kindling increased the level of lipid peroxidation and decreased the glutathione in rat hippocampus. PTZ thus caused an imbalance between oxidant stress and antioxidant defense system which may be at least partially responsible for seizures and cognitive impairment. This is supported by Liu *et al.* (2012) who observed that increased oxidative stress by PTZ kindling may be one of the factors responsible for the cognitive impairment seen with chronic seizures **[39]**.

Co-administration of ellagic acid prevented the rise in brain MDA levels in a dose-dependent manner. The significant decrease in brain MDA levels with concomitant ellagic acid administration as compared to PTZ alone treated rats indicates an attenuation of lipid peroxidation. A significant decrease in GSH level was observed in PTZ kindled rats as compared to the control group. Additionally, a significant reversal in the brain GSH levels was observed in the groups coadministered ellagic acid. Ellagic acid (30 mg/kg, p.o) per se caused a significant increase in the hippocampal GSH level when compared to the control group. Chronic EGA administration attenuated the brain lipid peroxidation (TBARS) and prevented waning of GSH, SOD and CAT activity in STZICV-treated rats. These results are consistent with findings reported in earlier studies as the antioxidative property of EGA has been explored in a number of disorders such as cancer, colitis and diabetes **[40]**.

Therefore, in the present study, ellagic acid have protected epilepsy-associated memory impaiement by reducing oxidative stress in PTZ-induced rats.

In conclusion, the findings of the present investigation suggest that ellagic acid exerts its beneficial effects on PTZ-induced kindling memory impairment and it may be attributed to its antioxidant activity. Thus ellagic acid may be projected in the treatment of cognitive and neural dysfunction associated with PTZ-induced epilepsy.

Acknowledgement

The authors would like to thank Mr. Shankarprasad Agnihotri, President and Mr. Sachin Agnihotri, Secretary, Jai Mahakali Shikshan Sanstha, Wardha, for funding the research under the head of Excellence in Research and Academics.

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