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Original Research Article

Curcuma longa Extract Attenuates Pentylenetetrazole-Induced Neurotoxicity in the Cerebral Cortex of Wistar Rats: Evidence for Neuroprotective Effect

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ABSTRACT

Curcuma longa, commonly known as turmeric, has been traditionally used for various medicinal purposes, including the treatment of neurological disorders. The present study aimed to investigate the neuroprotective effects of *Curcuma longa* (turmeric) on pentylenetetrazole (PTZ)-induced neurotoxicity in rats. Thirty-five (35) Wistar rats were divided into five groups (n =7), and treated as follows; Group A received distilled water (control), Group B received 35 mg/kg of PTZ and DZP (diazepam), Group C received PTZ intraperitoneally to induce epilepsy, Group D received 250 mg/kg of *C. longa* with 35 mg/kg of PTZ, and Group E received 500 mg/kg of *C. longa* with 35 mg/kg of PTZ. The extract was administered once daily for 28 days, during which period seizure severity and frequency were assessed. At the end of the treatment period, the levels of antioxidant enzyme glutathione (GSH), and oxidative stress biomarker malondialdehyde (MDA) were measured. The results revealed that PTZ administration significantly increased seizure severity, and increased oxidative stress by decreasing GSH concentration and increasing MDA level in the cerebral cortex. Treatment with *C. longa* extract at 250 mg/kg and 500 mg/kg exhibit anticonvulsant effect by reducing seizure severity in PTZ-induced Wistar rats. In addition, *C. longa* extract reduced oxidative stress and improved neuroprotection by significantly ($P < 0.05$) increasing GSH level, and decreasing MDA level in the cerebral tissues of PTZ-induced Wistar rats. These findings indicate that *C. longa* extract has neuroprotective effects and anticonvulsant properties, making it a promising candidate for adjunctive therapy in epilepsy management.
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Keywords: Epilepsy, *Curcuma longa*, Pentylenetetrazol, Seizure, Neuroprotection, Anticonvulsant.

Introduction

Epilepsy is a neurological disease characterized by the recurrence of paroxysmal clinical episodes, resulting from abnormal and hypersynchronous discharge from one or many groups of brain neurons.[1] Epilepsy affects nearly 1% of the world's population and remains a major global public health problem.[2] Faced with this concern, numerous studies have been undertaken for many years to better understand this pathology and to find therapeutic solutions for those suffering from the disease. The use of medicinal plants for the treatment of many diseases is a major component of folk medicine from different parts of the world.[3,4] Natural products from some plants, fungi, bacteria, and other organisms continue to be used in pharmaceutical preparations either as pure compounds or as extracts. *Curcuma longa* commonly called turmeric is a flowering plant belonging to the ginger family (Zingiberaceae). The plant is effective in reducing post-surgical inflammation, it also helps to prevent atherosclerosis by reducing the formation of blood clots.

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Curcumin a major bioactive compound in *Curcuma longa* possess antioxidant, anti-inflammatory, antiviral, and antifungal activities.[6] Curcumin exerts its anti-inflammatory activity by inhibiting several different molecules that play an important role in inflammation.[7] In addition, the anti-inflammatory and anti-arthritic actions of the volatile oil of *C. longa L*. have been demonstrated.[8]

Epilepsy is the second most common neurological disorder, with the global prevalence estimated at about 1-2%.[9] Epileptic patients often do not respond to one-drug treatment, and multi-drug therapy are associated with many side effects. In addition, 30% of patients with recurrent seizures are resistant to anticonvulsant medications.[10] Therefore, there is the need to search for anti-epileptic medications with fewer side effects.

Materials and Methods

Chemicals and reagents

The chemicals used in the study include Pentylenetetrazol (PTZ) (Ultra Pure Lab Chem Industry), distilled water, diazepam (Ernest Chemist Limited), ketamine (Pfizer Inc.), formol-calcium, Hematoxylin and Eosin stain.

Plant collection and identification

Fresh *Curcuma longa* (Turmeric) was bought on 9th September 2024 from an open market in Jere Local Government Area, Borno State, Nigeria. The plant was identified at the herbarium unit, Faculty of Pharmacy, University of Maiduguri, Borno State, Nigeria, where a herbarium specimen with voucher number UMM/FPH/ZIG/003 was deposited.

*Extraction of the plant material*The whole plant was dried in a shady environment at 26°C for 30 days. The dried whole plant was pulverized using a mortar and pestle, then weighed. The powdered turmeric (368.25 g) was macerated in distilled water (3.68 L) at room temperature for 24 hours. The aqueous extract was oven dried at 40°C for 16 hours. The dried extract (32 g) obtained was placed in a sealed container and kept in the refrigerator until further use.

Preparation of Curcuma longa extract solution
A stock solution of the aqueous extract (100 mg/mL) was prepared by dissolving 1 g of the aqueous *C. longa* extract in 10 mL of distilled water and allowed to completely dissolve until a homogenous mixture was obtained.

Animals
Thirty-five (35) healthy Wistar rats weighing 150 – 180 g were obtained from the animal house, Department of Biochemistry, University of Maiduguri. The rats were kept in separate, well-ventilated cages and were fed with rodent pellets (vital feeds) with free access to drinking water. The rats were acclimatized to the laboratory condition for two weeks before the commencement of extract administration.

Ethical approval
Ethical approval for this study was obtained from the research ethics committee of the Faculty of Basic Medical Sciences, University of Maiduguri, Maiduguri, Nigeria, with approval number UNIMAID/AUEC/2024/07.

Experimental design
The rats were randomly allotted into five groups (A – E) of seven rats per group. the rats were treated as follows;
Group A: Normal control group administered feed and distilled water only.
Group B: Positive control received intraperitoneal injection of 5 mg/kg of diazepam, followed by subcutaneous injection of 35 mg/kg PTZ after one hour.
Group C: Negative control received a subcutaneous injection of 35 mg/kg PTZ only.
Group D: The low dose (therapeutic or T250) group was administered 250 mg/kg aqueous extract of *C. longa* orally, followed by subcutaneous injection of 35 mg/kg of PTZ after one hour.
Group E: The high dose (therapeutic or T500) group was administered 500 mg/kg aqueous extract of *C. longa* orally, followed by subcutaneous injection of 35 mg/kg PTZ after one hour.
The extract was administered once daily for 28 days. Chronic epilepsy was induced by the kindling method.[11,12] Kindling was achieved by subcutaneous injections of sub-convulsive doses (35 mg/kg) of PTZ to the animals. However, based on the different groups, the Sub-convulsive PTZ dose injections were made consecutively, at 24-hour intervals. After each injection, animals were placed individually in cages and observed for 30 minutes. The intensity/severity of convulsions was characterized using the 6-point grid of the Racine scale (0 – 5) as described by Pahuja *et al.*[11] Stage 0: no response observed, Stage 1: the animals expressed contraction of the ears, face, and tail, Stage 2: the animals expressed tilt of the head, clonies of the head, and myoclonic shaking of the body, Stage 3: unilateral front paw clonies of the body, Stage 4: bilateral clonies of the front legs, Stage 5: generalized tonic-clonic seizures with loss of normal reflexes.
Kindling was considered successful on the appearance of stage 4 or stage 5 characteristics in PTZ-treated animals during the second consecutive trial.[13] The following day after the kindling, animals were sacrificed via cervical dislocation, the brain tissue was dissected, weighed, after which the right hemisphere of the fresh cerebral cortex of the rats were homogenized using the tissue homogenizer at 40°C using phosphate buffered saline as the solvent for the brain tissue homogenate. The tissue homogenate was centrifuged at 10,000 rpm for 10 min, and the supernatant was used for the assessment of the levels of glutathione (GSH) and malondialdehyde (MDA).
Tissue processing
The left hemisphere of the fresh dissected cerebral cortex was fixed in formol-calcium for one week, processed, and stained using Hematoxylin and Eosin for histological assessment.

Statistical analysis
Data were analysed using GraphPad Prism 5 software for Windows. The results were presented as mean ± standard error of mean (S.E.M), differences between the means of the treatment groups were analyzed using one-way analysis of variance (ANOVA), and statistical significant difference between mean values was established at $p < 0.05$.

Results and Discussion

Anticonvulsant effect of aqueous extract of turmeric (Curcuma longa) in pentylenetetrazol (PTZ)-induced seizure in Wistar rats
Figure 1 shows the anticonvulsant effect of aqueous extract of *C. longa* in rats. The seizure score of control rats (Group A) was at zero throughout the period of the experiment. The subcutaneous injection of PTZ (35 mg/kg) induced seizure in rats characterized by generalized tonic-clonic seizures with loss of normal reflexes. However, the administration of *C. longa* extract at 250 mg/kg and 500 mg/kg doses (Groups D and E) mitigated the PTZ-induced seizure marked by a significant ($P < 0.05$) reduction in seizure score compared to the PTZ group (Group C). As expected, the positive control (Diazepam, Group B) also attenuated PTZ-induced seizure resulting in a much lower seizure score.

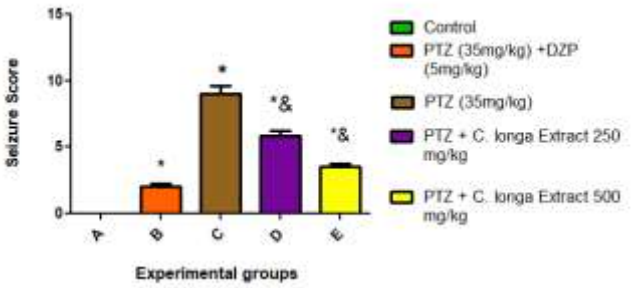

Figure 1: Effects of aqueous extract of turmeric (*Curcuma longa*) on seizure severity in Pentylenetetrazol (PTZ)-kindled Wistar rat Data represent Mean ± Standard Error of Mean (S.E.M), n = 7. '*' Indicates significant difference ($p < 0.05$) compared to the normal control group; '&' Indicates significant difference ($p < 0.05$) compared to the PTZ group. PTZ = Pentylenetetrazole, DZP = Diazepam.

Effects of aqueous extract of turmeric (Curcuma longa) on GSH and MDA levels in Pentylenetetrazol (PTZ)-kindled Wistar rat
The present study investigated the effect of *Curcuma longa* extract on oxidative stress in a rat model of seizures induced by pentylenetetrazole (PTZ). The results showed that PTZ-induced seizures decreased GSH level and increased MDA level in rats' cerebral cortex, indicating enhanced lipid peroxidation and oxidative stress. Co-treatment with diazepam (DZP) and PTZ significantly increased cerebral GSH level and decreased cerebral MDA level compared to the PTZ-only group (Figures 2 and 3), suggesting that DZP has an antioxidant effect, mitigating the oxidative stress caused by PTZ-induced seizures. This finding is consistent with a previous study, which reported the antioxidant properties of DZP in rat model of acute stress.[14] Similarly, treatment with both 250 mg/kg and 500 mg/kg of *C. longa* extract significantly ($P < 0.05$) increased GSH and reduced MDA levels in the cerebral cortex of PTZ-induced rats compared to the PTZ-only group, suggesting the antioxidant and neuroprotective effects of *Curcuma longa* extract.
The effects of *C. longa* (turmeric) on GSH and MDA levels in PTZ-kindled Wistar rat are presented in Figures 2 and 3. The result showed that the administration of turmeric extract prevented PTZ-induced oxidative stress by increasing GSH and decreasing MDA levels in a dose-dependent manner.

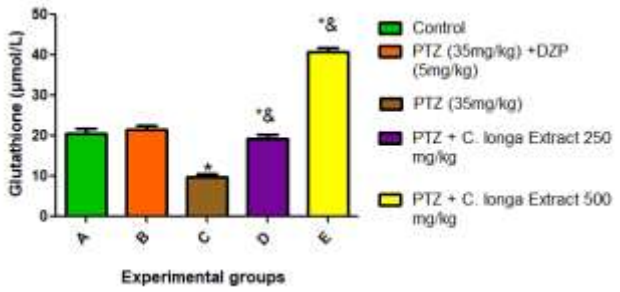

Figure 2: Effects of aqueous extract of turmeric (*Curcuma longa*) on glutathione (GSH) levels in Pentylenetetrazol (PTZ)-kindled Wistar rat. Data represent Mean ± Standard Error of Mean (S.E.M), n = 7. '*' Indicates significant difference ($p < 0.05$) compared to the normal control group; '&' Indicates significant difference ($p < 0.05$) compared to the PTZ group. PTZ = Pentylenetetrazole, DZP = Diazepam.

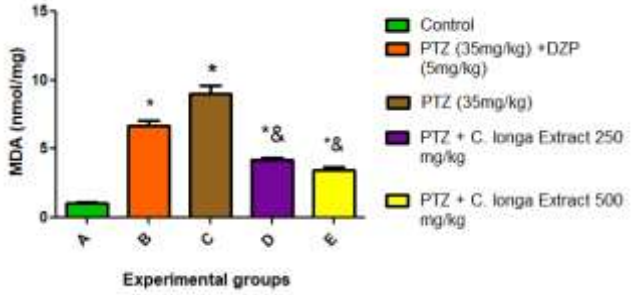

Figure 3: Effects of aqueous extract of turmeric (*Curcuma longa*) on malondialdehyde (MDA) levels in Pentylenetetrazol (PTZ)-kindled Wistar rat Data represent Mean ± Standard Error of Mean (S.E.M), n = 7. '*' Indicates significant difference ($p < 0.05$) compared to the normal control group; '&' Indicates significant difference ($p < 0.05$) compared to the PTZ group. PTZ = Pentylenetetrazole, DZP = Diazepam.

At 250 mg/kg, the extract maintained cerebral GSH concentration at level (19.50 ± 0.30 µmol/L) comparable to that of the normal control (20.43 ± 0.09 µmol/L). At a higher dose of 500 mg/kg, *C. longa* extract resulted in a significant ($p < 0.05$) increase in cerebral glutathione level up to a concentration of 39.48 ± 0.30 µmol/L, which was twice that seen in the normal control. MDA levels on the other hand decreased from 10.15 ± 0.12 nmol/mg in the PTZ-induced rats (Group C) to 4.34 ± 0.15 nmol/mg in the 250 mg/kg *C. longa* extract-treated group (Group D), and to 3.21 ± 0.10 nmol/mg in the 500 mg/kg *C. longa* extract-treated group (Group E).

Histological observation of the cerebrum

The photomicrograph of the cerebrum of normal control, the PTZ + DZP group, and the PTZ + *C. longa* extract (500 mg/kg) group all showed normal histological layer and histoarchitecture of the granular cells (Figure 4A, B and E). Inter granular spaces in the granular layer were seen in the group administered 35 mg/kg PTZ only (Figure 4C) which indicates degeneration of neurons. The group that received 250 mg/kg of *C. longa* followed by 35 mg/kg PTZ showed no inter-granular space in the granular layer, but there was congestion of the granular cells indicating a mild neuroprotective effect of the extract (Figure 4D). In addition, the histoarchitecture of the positive control (PTZ + Diazepam) showed a proliferation of granular cells, which indicates a mild level of recovery and preservation of neuronal cells from PTZ-induced neurodegeneration. Treatment with *C. longa* extract shows a fast-healing process and a good architecture of the histomorphology of the cerebrum, which was dose-dependent. These findings are consistent with previous studies, which reported the antioxidant and anti-inflammatory properties of *C. longa* extract.[15] The neuroprotective effects of *C. longa* extract may be attributed to its ability to scavenge free radicals and reduce oxidative stress.[16]

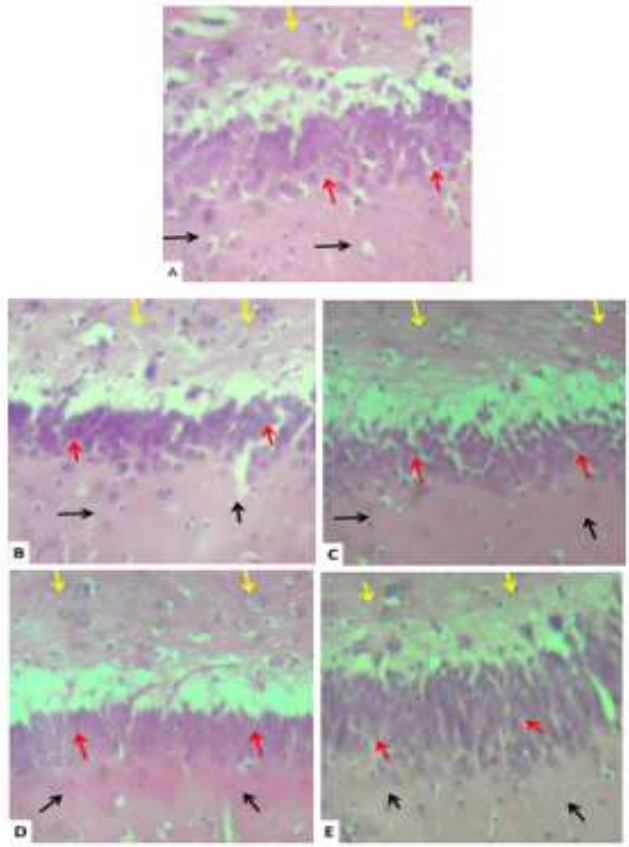

Figure 4: Photomicrograph of H&E-stained section of the cerebral cortex (x200 magnification). **(A)** Control, **(B)** PTZ + DZP, **(C)** 35 mg/kg PTZ, **(D)** PTZ + 250 mg/kg *C. longa*, and **(E)** PTZ + 500 mg/kg *C. longa*. Black arrow: granular layer laden with granular cells. Yellow arrow: polymorphic layer. Red arrow: inter-granular space due to degeneration (B and D), with fairly restored histomorphology of the granule cells (D), enclosed due to the protective effect of *C. longa extract* (E).

Conclusion

The present study investigated the antioxidant and neuroprotective effects of *Curcuma Longa* extract on pentylenetetrazole (PTZ)-induced seizures in rats. The results showed that *C. longa* extract significantly reduced oxidative stress and lipid peroxidation in the brain by increasing GSH, and reducing MDA levels in rats' cerebral cortex. Histological examination of the cerebral cortex indicated that *C. longa* extract promotes the recovery and offered neuroprotective effect against PTZ-induced neurodegeneration. These findings suggest that *C. longa* extract may be a potential therapeutic agent for the management of epilepsy and other neurodegenerative disorders.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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