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Neuroprotective Effects of *Centella asiatica* in the Management of Epilepsy

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Abstract: ***Epilepsy is a chronic neurological disorder characterized by recurrent seizures resulting from abnormal neuronal excitability and synchronization. Despite the availability of several antiepileptic drugs, long-term therapy is often associated with adverse effects and incomplete seizure control, necessitating the exploration of safer and more effective alternatives.*** **Centella asiatica,** ***a well-known medicinal plant used in traditional systems of medicine, has gained considerable attention for its neuroprotective and cognitive-enhancing properties. This study investigates the neuroprotective role of Centella asiatica in managing epilepsy using a pentylenetetrazole (PTZ)-induced seizure model in Wistar rats. The methanol extract of the plant was evaluated for its influence on oxidative stress markers, specifically superoxide dismutase (SOD) and catalase (CAT), across various brain regions. Rats pre-treated with C. asiatica extract demonstrated a significant increase in antioxidant enzyme activities compared to the PTZ-only group, indicating reduced oxidative damage. The results suggest that C. asiatica may offer neuroprotective benefits and serve as a complementary therapy in epilepsy management. However, further clinical studies are necessary to confirm its efficacy and safety in humans. Experimental studies suggest that*** **Centella asiatica** ***modulates neurotransmitter balance, reduces oxidative stress, stabilizes neuronal membranes and enhances γ-aminobutyric acid (GABA) activity, thereby suppressing seizure activity. Additionally, its ability to protect hippocampal neurons and improve synaptic plasticity may help prevent epilepsy-associated cognitive impairment. The plant also exhibits minimal toxicity, supporting its potential as an adjunct or alternative therapy. Although preclinical findings are promising, well-designed clinical trials are required to establish its efficacy, safety, dosage and mechanism of action in human epilepsy. Overall,*** **Centella asiatica** ***represents a promising neuroprotective herbal candidate for the management of epilepsy.***

Keywords: Epilepsy, *Centella asiatica*, Neuroprotection, Antiepileptic activity, Antioxidant enzymes, Wistar rats

1. Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent, unprovoked seizures arising from abnormal neuronal discharges in the brain. It affects over 50 million people globally and represents a major public health concern due to its long-term neurological, psychological and social consequences. Although conventional antiepileptic drugs (AEDs) are effective in controlling seizures in many patients, nearly one-third develop drug-resistant epilepsy or experience significant adverse effects such as sedation, cognitive impairment, hepatotoxicity and teratogenicity. These limitations have intensified interest in alternative and complementary therapies with improved safety profiles [1].

The pathophysiology of epilepsy involves complex mechanisms including oxidative stress, neuroinflammation, excitotoxicity, mitochondrial dysfunction and neuronal apoptosis. Recurrent seizures can lead to progressive neuronal damage, particularly in the hippocampus, contributing to memory deficits and behavioral disturbances. Therefore, agents possessing both antiepileptic and neuroprotective properties are considered ideal candidates for effective epilepsy management [2].

Centella asiatica (L.) Urban, commonly known as Gotu Kola, is a perennial medicinal herb belonging to the family Apiaceae and has been extensively used in Ayurveda and other traditional medical systems for centuries. It is well recognized for its neuroprotective, antioxidant, anti-inflammatory, anxiolytic and cognitive-enhancing effects. The therapeutic potential of C. asiatica is attributed to its major bioactive constituents such as asiaticoside, madecassoside, asiatic acid and madecassic acid [3].

Given the growing prevalence of drug-resistant epilepsy and the limitations of existing antiepileptic drugs, identifying plant-based alternatives with both antioxidant and anticonvulsant properties could provide safer, complementary options for long-term epilepsy management. Emerging experimental evidence suggests that *Centella asiatica* may play a significant role in epilepsy management by modulating neurotransmitter balance, enhancing γ-aminobutyric acid (GABA)ergic activity, reducing oxidative stress and protecting neurons from seizure-induced damage. Its ability to preserve neuronal integrity and improve cognitive function highlights its promise as an adjunct or alternative therapeutic agent. Thus, exploring the neuroprotective effects of *Centella asiatica* may provide valuable insights into developing safer and more effective strategies for epilepsy treatment [4], [5]. This study aims to evaluate the antioxidant and neuroprotective potential of *Centella asiatica* methanolic extract in a PTZ-induced rat model of epilepsy, focusing on its effects on SOD and CAT enzyme activities across various brain regions.

2. Materials and Methods

Procurement and Maintenance of Experimental Animals

Male adult Wistar rats weighing 150±25 grams were used as the experimental animals in the present investigation. The rats were purchased from the Indian Institute of Science (IISc), Bangalore, maintained in the animal house of the department in polypropylene cages under laboratory conditions of 28±2^{0}C temperature with photoperiod of 12 hours light and 12 hours dark and 75% relative humidity. The rats were fed with standard pellet diet (Hindustan Lever Ltd., Mumbai) and water ad libitum. The rats were maintained according to the ethical guidelines for animal protection and welfare bearing the CPCSEA 438/01/a/cpcsea/dt:17.07.2006. This animal study was approved by the resolution No:09/(i)/a/ CPCSCA/ IAEC/ SVU/ Dept. of Zoology/Dt. 04.03.2016.

2.1 Selection of Drug

Pentylenetetrazole (PTZ), an anticonvulsant drug, was selected for the present study. It was obtained as commercial grade chemical from Sigma chemicals, USA. Diazepam 2mg/kg body weight as reference control.

2.2 Induction of Epilepsy

Convulsions were induced by an intraperitoneal (i.p.) injection of Pentylenetetrazole (60mg/Kg body weight) in saline [6][7][8].

2.3 Experimental design for screening of PTZ –Induced Seizures

The rats were divided into 4 groups, each consisted of 6 rats and used for studying effects of PTZ. Group 1 consisted of normal saline-treated rats (SC), Group 2 consisted of rats treated with PTZ, Group 3 is epileptic rats pretreated with Methanol extract of CA (ME+PTZ) and Group 4 is epileptic rats pretreated with Diazepam (DP+PTZ).

2.4 Isolation of Tissues

After observed the seizures activity falling onto their backs, followed by episodes of rushing and jumping in all PTZ treated rats within an hour, the animals were sacrificed by cervical dislocation and different brain regions such as Cerebral Cortex (CC), Cerebellum (CB), Hippocampus (HC) and Pons Medulla (PM) were immediately isolated, frozen in liquid nitrogen and were stored at -80^{0}C until analysis.

2.5 Procurement of Chemicals

All chemicals used in the present study were Analytical Reagent (AR) grade and obtained from the following scientific companies: Sigma (St. Louis, MO, USA), Fisher (Pittsburg, PA, USA), Merck (Mumbai, India), Ranbaxy (New Delhi, India), Qualigens (Mumbai, India). In the present investigation Barnstead Thermoline water purification plant for nanopure water, Kubota KR centrifuge and Hitachi U-2000 Spectrophotometer and other standard equipments were used for biochemical/physiological analyses.

2.6 Biochemical assays:

2.61 Superoxide dismutase (SOD – EC: 1.15.1.6)

Superoxide dismutase activity was determined according to the method of Misra and Fridovich (1972) [9] at room temperature. The tissue was homogenized in ice cold 50 mM phosphate buffer (pH 7.0) containing 0.1 mM EDTA to give 5% homogenate (w/v). The homogenates were centrifuged at 10,000 rpm for 10 min at 40C in cold centrifuge. The supernatant was separated and used for enzyme assay. 100 µl of tissue extract was added to 880 µl (0.05 M, pH 10.2, containing 0.1 mM EDTA) carbonate buffer; and 20 µl of 30 mM epinephrine (in 0.05% acetic acid) was added to the mixture and measured the optical density values at 480 nm for 4 min on a Hitachi U-2000 Spectrophotometer. Activity expressed as the amount of enzyme that inhibits the oxidation of epinephrine by 50% which is equal to 1 unit.

2.62 Catalase (CAT-EC 1.11.1.6)

Catalase activity was measured by a slightly modified version of Aebi (1984) [10] at room temperature. The tissue was homogenized in ice cold 50 mM phosphate buffer (pH 7.0) containing 0.1 mM EDTA to give 5% homogenate (w/v). The homogenates were centrifuged at 10,000 rpm for 10 min at 40C in ice cold centrifuge. The resulting supernatant was used as enzyme source. 10 µl of 100% ethyl alcohol was added to 100 µl of tissue extract and then placed in an ice bath for 30 min. After 30 minutes the tubes were kept at room temperature followed by the addition of 10 µl of Triton X-100 RS. In a cuvette containing 200 µl of phosphate buffer, 50 µl of tissue extract and 250 µl of 0.066 M H_2O_2 (in phosphate buffer) were added. The decrease in optical density was measured at 240 nm for 60 s in a UV Spectrophotometer. The molar extinction coefficient of 43.6 M cm-1 was used to determine CAT activity. One unit activity is equal to the moles of H_2O_2 degraded / mg protein / min.

2.7 Statistical treatment of data

All assays were carried out with six separate replicates from each group. The mean, standard error (SE) and Analysis of Variance (ANOVA) were done using SPSS statistical software version 25 for different parameters. Difference between control and experimental assays was considered as significant at $P<0.01$.

3. Results

3.1 Superoxide dismutase (SOD):

The changes in the Superoxide dismutase levels in different regions of rat brain during PTZ-induced epilepsy and pre-treatment with methanol extract of *Centella asiatica* were represented figure 1.

A significant induction of SOD was recorded in all the regions of brain of epileptic animals after pre-treatment with methanol extract of CA and diazepam.

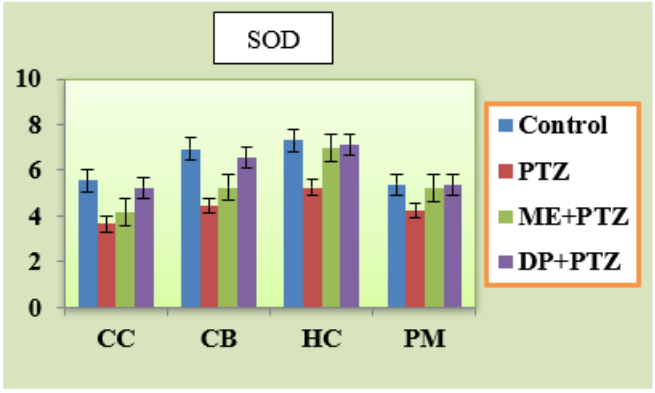

Figure 1

Experimental values are expressed in the amount of enzyme that inhibits the oxidation of epinephrine by 50% which is equal to 1 unit.

*ρ-value ≤0.01 is considered significant in one way ANOVA.
*Values shown on the bars represent mean differences between control and experimental groups

3.2 Catalase:

The changes in the Catalase levels in different regions of rat brain during PTZ-induced epilepsy and pre-treatment with methanol extract of *Centella asiatica* were represented in figure 2

The Catalase activity was markedly elevated in different regions of brain in PTZ-induced epileptic animals after pre-treatment with methanol extract of CA and diazepam.

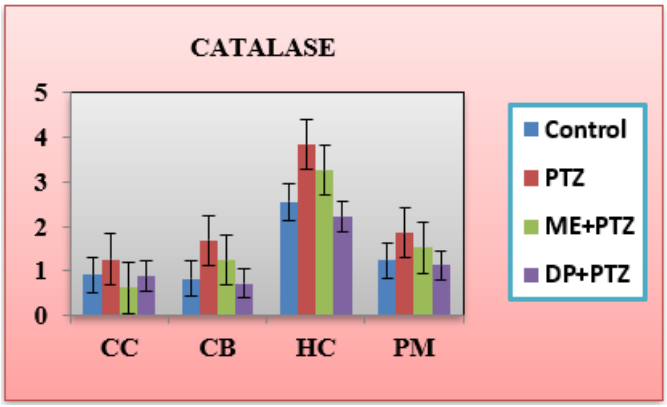

Figure 2

Experimental values are expressed in the unit activity is equal to the moles of H_2O_2 degraded / mg protein / min.

*ρ-value ≤0.01 is considered significant in one way ANOVA. *Values shown on the bars represent mean differences between control and experimental groups.

4. Discussion

The present observation that a significant induction of superoxide dismutase (SOD) activity was recorded in all brain regions of epileptic animals following pre-treatment with methanolic extract of *Centella asiatica* and diazepam highlights the critical role of oxidative stress modulation in epilepsy management. Epileptic seizures are known to generate excessive reactive oxygen species (ROS), leading to oxidative damage of neuronal membranes, proteins and DNA. Reduced antioxidant defense, particularly diminished SOD activity, has been consistently reported in experimental and clinical epilepsy, contributing to neuronal hyperexcitability and neurodegeneration [11].

Pre-treatment with methanolic extract of *Centella asiatica* significantly enhanced SOD levels across various brain regions, indicating its strong antioxidant and neuroprotective potential. This effect may be attributed to its rich content of triterpenoids such as asiaticoside, asiatic acid and madecassoside, along with flavonoids and phenolic compounds, which are known to scavenge superoxide radicals and upregulate endogenous antioxidant enzymes. By enhancing SOD activity, *C. asiatica* aids the conversion of superoxide anions into hydrogen peroxide, thereby reducing oxidative burden and protecting neurons from seizure-induced damage [12].

Diazepam, a well-established benzodiazepine anticonvulsant, also showed elevated SOD activity, which may be linked to its ability to enhance GABAergic neurotransmission and indirectly reduce oxidative stress by suppressing seizure severity. The comparable increase in SOD levels observed with *Centella asiatica* suggests that the plant extract may exert anticonvulsant effects through mechanisms similar to standard antiepileptic drugs, while also providing antioxidant neuroprotection [13].

The induction of SOD in all brain regions is particularly significant, as it indicates a widespread protective effect rather than a region-specific action. This broad antioxidant enhancement may help reduce neuronal loss. It also stabilizes neuronal membranes and supports better cognitive outcomes in epilepsy [14]. Overall, these findings support the potential use of *Centella asiatica* as an effective adjunct therapy in epilepsy, targeting oxidative stress–mediated neuronal damage alongside conventional anticonvulsant treatment [15].

The present findings demonstrate that catalase (CAT) activity was markedly elevated in different regions of the brain of pentylenetetrazole (PTZ)-induced epileptic animals following pre-treatment with methanolic extract of *Centella asiatica* (CA) and diazepam [16]. PTZ-induced seizures are widely recognized to generate excessive reactive oxygen species (ROS), leading to oxidative stress, lipid peroxidation, and neuronal damage. Catalase plays a crucial role in the antioxidant defense system by decomposing hydrogen peroxide into water and molecular oxygen, thereby preventing the formation of highly reactive hydroxyl radicals [11].

The significant elevation of CAT activity observed after CA pre-treatment suggests a strong antioxidant and neuroprotective effect of the plant extract. This enhancement may be attributed to the presence of bioactive triterpenoids such as asiaticoside, asiatic acid, and madecassoside, along with flavonoids and phenolic compounds, which are known to upregulate endogenous

antioxidant enzymes. By increasing catalase activity, *Centella asiatica* helps to maintain redox homeostasis and protect neuronal cells from seizure-induced oxidative injury [16].

Diazepam, used as a standard antiepileptic drug, also produced a marked increase in CAT activity, likely due to its ability to suppress seizure intensity through potentiation of GABAergic neurotransmission, thereby indirectly reducing oxidative stress. The comparable effects of CA and diazepam on catalase activity indicate that CA may exert anticonvulsant effects through antioxidant-mediated mechanisms in addition to neurotransmitter modulation [17].

The elevation of CAT activity across multiple brain regions highlights the widespread protective influence of CA against PTZ-induced oxidative damage. This broad enhancement of antioxidant defense is critical in preventing neuronal degeneration, preserving synaptic integrity and minimizing cognitive deficits associated with epilepsy. Collectively, these findings support the therapeutic potential of *Centella asiatica* as a neuroprotective adjunct in epilepsy management, particularly in oxidative stress–related seizure pathology. The findings demonstrate that methanol extract of *Centella asiatica* significantly enhances antioxidant enzyme activity in PTZ-induced epileptic rats. This indicates its potential role in mitigating oxidative damage associated with seizures. The comparable performance to diazepam further underscores its therapeutic promise. Future studies should explore its clinical applicability, optimal dosage and long-term safety in human populations.

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