

Evaluation of anticonvulsant and antioxidant properties of *Cyperus esculentus* Linn. in various types of experimentally induced seizures in rats

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Abstract

Purpose: The purpose of the study was to evaluate the anticonvulsant and antioxidant properties of ethanolic extract of *Cyperus esculentus* using three animal models maximal electroshock seizure (MES), pentylenetetrazole (PTZ), and strychnine nitrate (STN) for inducing seizures in rats. **Methods:** In the entire three animal models, MES, PTZ, and STN, each model was included four groups, in which albino rats ($n = 6$) were used in each group. The first group was considered as control, the 2nd group as standard where diazepam 4 mg/kg is administered, and the 3rd and 4th served as test groups which were treated with ethanolic extract of *C. esculentus* (EECE) 200 and 400 mg/kg, respectively. In all the three experimental animal models, all the groups were treated for 14 days. On the last day, that is, 14th day after completion of all drugs administration in all three animal models which is total 12 groups of rats, within 30–40 min seizures were induced by exposing them to a shock of 150 mA with convulsimeter using ear electrodes for 2 s in MES model, 75 mg/kg of intraperitoneal injection of PTZ model and 2 mg/kg of strychnine (STN) model. Anticonvulsant activity was appreciated better only after abolition of hindlimb tonic extension (HLTE) in MES model and by measuring the duration of seizures and latency-induced seizure threshold in the PTZ and STN experimental rat models. **Results:** In MES model, EECE at a dose of 400 mg/kg abolishes complete HLTE in the rats, similarly at the same dose observed prolonged latency in the onset of seizures in both PTZ and STN experimental animal models. **Conclusion:** It is concluded that EECE has shown effective anticonvulsant activity in these animal models as it abolishes HLTE in MES model and delayed the latency of seizure threshold in PTZ and STN models.

Key words: Anticonvulsant Activity, Antioxidant, Diazepam, Ethanolic Extract of *Cyperus Esculentus*, Maximal Electroshock Seizure, Pentylenetetrazole, Strychnine Nitrate

INTRODUCTION

Epilepsy a group of disorders characterized by recurrent spontaneous seizures that apparently result from complex processes involving several neurotransmitters, namely, the glutamatergic, cholinergic, and GABAergic systems.^[1] Alteration or changes exist in the nature of neuronal networks in the brain which causes seizures and also due to spontaneous expression of synchronized burst firing which interspersed by periods of normal electrical activity.^[2] Glutamate and γ -amino butyric acid (GABA) are quantitatively the most important excitatory and inhibitory neurotransmitters, respectively, in the mammalian brain.^[3] Hence, these two neurotransmitters are reported as important targets for producing antiepileptic

action. Approximately 30% of patients with partial epilepsy and 25% of patients with generalized epilepsy are not completely recovered with allopathic medications.^[4] These many patients very often take multiple medical treatments to control their seizures. Thus, there is an unmet need to identify newer molecules with antiepileptic properties. In our study, we have chosen herbal medication and it could be one of the sources for newer antiepileptic therapeutics.^[5]

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The plant we selected in our study is *Cyperus esculentus*, and it has many synonyms as like nut sedge, yellow nut grass, Zulu nut, earth nut, earth almond, nut grass, rush nuts, yellow nut sedge, and chufas. Chufa tubers are daily used ingredients by many people in their daily routine diet who lives in North Africa and Spain.^[6] The tubers of *Cyperus* species have been used traditionally as remedy for several diseases including hepatotoxicity (Mehta *et al.*, 1999; Hassanein *et al.*, 2011) and as antioxidative agent (Satoh *et al.*, 2004).^[7-9] Although many researchers have worked on *C. esculentus* tubers, the tubers are not well utilized due to limited information on their medicinal potential and nutritional benefits (Rita, 2009; Adejuyitan, 2011; Ukwuru and Oyedepo and Odoje, 2014).^[10] *Cyperus rotundus* has central nervous system (CNS) depressant activity and potentiated the sleep time of mice.^[11] Four sesquiterpenes and one triterpene were isolated from *C. rotundus* and tested for their ability to modulate GABAA-benzodiazepine receptor function. The results suggested that isocurcumenol (sesquiterpenes) act as a benzodiazepine receptor agonist [83].^[12] In mice brain, *C. rotundus* reduced intensity and duration of seizure and increased the level of superoxide dismutase and nitric oxide (NO) and decrease malondialdehyde level.^[13] Several therapeutically important natural compounds have been isolated from *C. esculentus* (such as alkaloids, flavonoids, carbohydrates, tannins, saponins, and steroids) and all these compounds can serve as very potent and reliable drug molecules for the treatment of various disorders. This study was undertaken to evaluate the possible anticonvulsant activity of *C. esculentus* extract using different *in vivo* models such as maximal electroshock seizure (MES), as well as pentylenetetrazole (PTZ) and strychnine nitrate (STN)-induced seizures.

Experimental Procedure

Source of plant material

C. esculentus Linn. plant was collected from Thirupathi hills, Andhra Pradesh, India, in the month of December 2016. It was shown to Prof. Dr. Madhavasetty, Department of Botany, University, Thirupathi, Andhra Pradesh, India, to be got identified and authentication. The voucher number is 2137 and the specimen was placed, maintained in our laboratory for further future reference.

Preparation of extract

The whole plant of *C. esculentus* Linn. was dried in shade and made it into dry powder. Powder was then sieved through the 40 mesh number. Dried powder was subjected to continuous hot extraction procedure in Soxhlet apparatus using ethanol as a solvent at temperature of 60–70°C. The extract was evaporated under reduced pressure using rotary evaporator until all the solvents have been removed to get a sample of extract. In the ethanolic extract of *C. esculentus* (EECE), preliminary phytochemical screening procedure identified the presence alkaloids, flavonoids, carbohydrates, glycosides, tannins, terpenoids, and phenols [Table 1].^[14]

Experimental animals

Adult male Wistar rats, weighing 150–180 g, were procured from the animal house of CES College of Pharmacy, Chinnatekur, Kurnool (Reg., no.1278/ac/09/CPCSEA). The animals were kept in polypropylene cages (six in each cage) under standard laboratory conditions (12 h light and 12 h dark day night cycle) and had free access to commercial pellet diet with water *ad libitum*. The temperature was maintained at $25 \pm 10^\circ\text{C}$ with relative humidity ($50 \pm 15\%$). The study was approved by the Institutional Animal Ethical Committee (IAEC/CESCOP/2017-14).

Acute toxicity study

The acute toxicity of 90% ethanolic extract of whole plant of *C. esculentus* Linn. (EECE) was determined as per the Organization for Economic Cooperation and Development guideline no. 423 (acute toxic class method). It is observed that the plant extract was not mortal even at the dose of 2000 mg/kg. Hence, 1/10th (200 mg/kg) and 1/5th (400 mg/kg) of this dose were chosen to further study.^[15] Acute oral toxicity→The obtained results were indicated that *C. esculentus* extract at oral doses up to 2000 mg/kg did not produce any symptoms of acute toxicity and none of the rats died till 72 h. On observation of rats up to 14 days, none of animal died.

Grouping of animals and parameters read

In each individual animal model, that is; MES, PTZ, and STN having four groups, and each group had six rats. This grouping was common to all three animal models. Group I rats received sodium carboxymethyl cellulose, Group II received diazepam, Group III received EECE 200 mg/kg, and Group IV received EECE 400 mg/kg. In MES model, animals exhibit hindlimb tonic extension (HLTE) and the percentage of animals protected against HLTE was considered when it is abolished in 10 s and hindlimb extension <90° with plane of body. In PTZ and STN models, latency of seizure threshold, duration of seizures, % of animals protected against seizures, and % of animals protected against lethality were recorded within a 30 min duration^[9] after intraperitoneal injection of PTZ and STN.

Table 1: Phytochemical constituents

Test	Inference
Lieberman's test	–
Salvoski test	–
Shinoda test	+
Ferric chloride	+
Dragendorff's test	–
Boritrager's test	–
Kedde's test	–
Legal's test	–

Animal model 1: MES-induced seizure				Animal model 2: PTZ-induced seizure				Animal model 3: STN-induced seizure			
Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)	(n=6)
MES 150 Mamp/2 s	Phenytoin 25 mg/kg i.p.	EECE 200 mg/kg p/o	EECE 400 mg/kg p/o	PTZ i.p., 75 mg/kg	Diazepam 4 mg/kg i.p.	EECE 200 mg/kg p/o	EECE 400 mg/kg p/o	STN 2 mg/kg i.p.	Diazepam 4 mg/kg i.p.	EECE 200 mg/kg p/o	EECE 400 mg/kg p/o
Total treatment duration time 14 days				Seizure induced by PTZ method				Seizure induced by STN method			
Seizure induced by MES method											
Readings taken											

MES: Maximal electroshock seizure, PTZ: Pentylene tetrazole, STN: Strychnine nitrate, EECE: Ethanolic extract of *Cyperus esculentus*

Induction of Seizures in Rats

MES model

Test was performed to induce seizures in albino rats of either sex. Rats were subjected to shock of 150 mA by convulsimeter through ear electrodes for 2 s on the 14th day after 30 min of administering the last dose of vehicle, diazepam, and extracts. The number of animals exhibiting HLTE seizures and the percentage of animals protected against HLTE was recorded [Table 2]. Animals in which HLTE response were abolished within 10 s after delivery of the electroshock and also if the hindlimb extension did not exceed, a 90° angle with the plane of the body was taken as protected rats which are free from seizures.

PTZ and STN models

Albino rats of either sex were used to induce seizures. On the last day, that is, 14th day, 30 min after administration of the last dose of the vehicle, diazepam, and the test extracts, seizures were induced in rats in both models by intraperitoneal injection of PTZ 75 mg/kg and STN-induced seizure with the dose 2.5 mg/kg. The latency to PTZ- and STN-induced seizures threshold, the duration of seizures, percentage of animals protected against seizures, and percentage of animals protected against lethality were recorded within a 30 min duration^[9] after intraperitoneal injection of PTZ and STN [Tables 3 and 4].

Statistical Analysis

Data were presented as percentage (%) protection and mean \pm SEM and were analyzed by one-way ANOVA followed by Dunnett's test for multiple comparisons using GraphPad Prism version 5.03. Results were considered significant at $P < 0.05$.

RESULTS

The percentage yield of ethanol extract of entire plant of *C. esculentus* Linn. was found to be 7.2%w/w, respectively.

Anticonvulsant Activity

The present study carries out the evaluation of protective effect of ethanolic extract (200 mg/kg, 400 mg/kg) of *cyperus esculentus* against seizure induced by MES, PTZ and STZ. Results shown there is abolition of HLTE in the MES induced animals, indicates the anticonvulsant activity of *cyperus esculentus* extract. In PTZ test, *cyperus esculentus* 400 mg/kg was found to be more effective than 200mg/kg.

DISCUSSION

The study results indicate that the EECE (200 and 400 mg/kg) has anticonvulsant property in an animal models MES- and

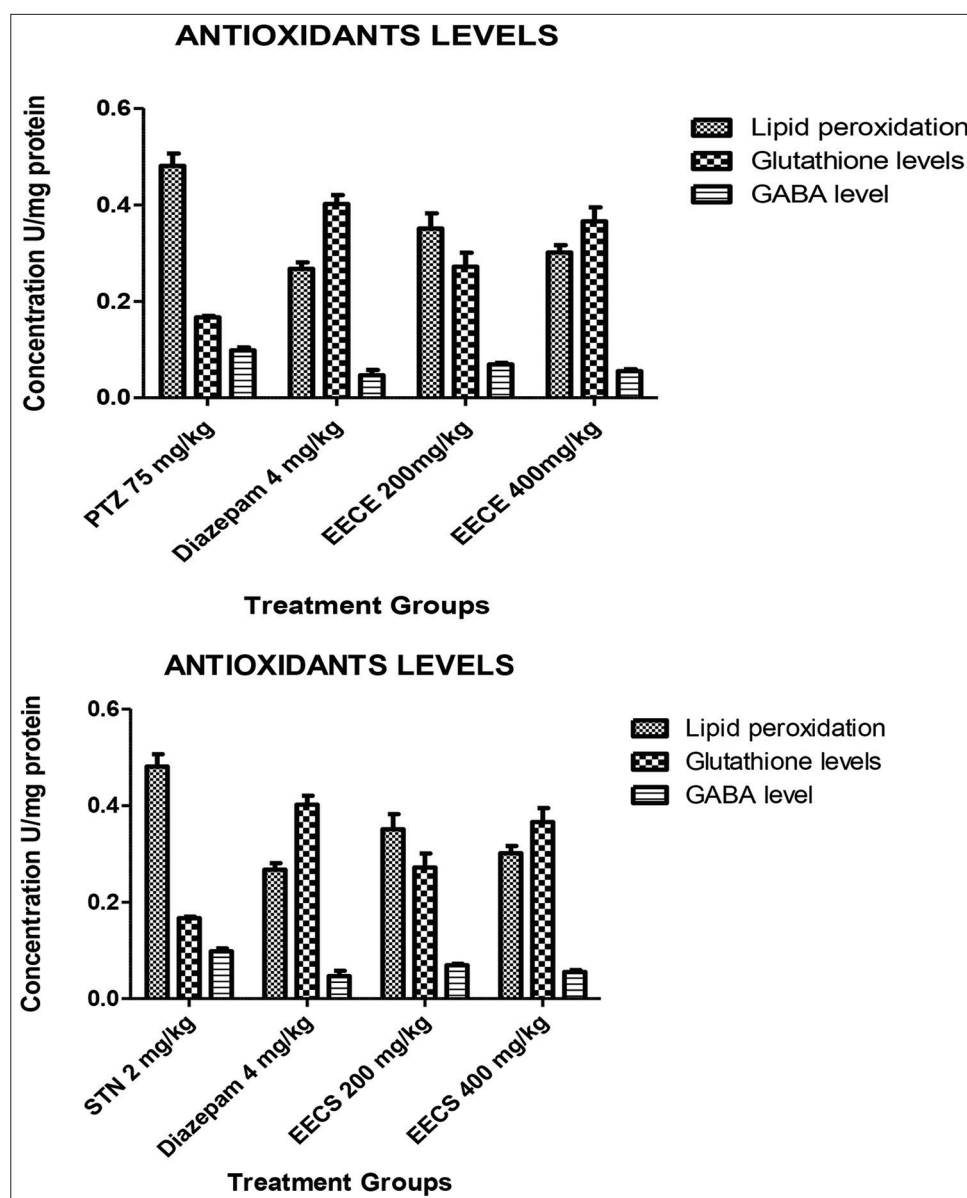


Figure 1: Antioxidants parameters

Table 2: Effect of EECE in MES-induced convulsions in albino rats

Groups	Drug treatment	Flexion (s)	Extensor (s)	Clonus (s)	Stupor (s)	Recovery (s)	Percentage protection
I	Control (3% w/v SCMC)	6.64±0.26	13.4±0.84	15.20±1.24	30.86±0.82	162.40	44
II	Diazepam (4 mg/kg/i.p.)	3.46±0.46a***	0	10.2±1.45a***	12.26±0.45 a***	112.64	100
III	EECE (200 mg/kg/p.o.)	4.68±0.34b***	4.17±0.16 b***	7.44±0.26 b***	18.34±2.34 b***	146.20	70
IV	EECE (400 mg/kg/p.o.)	3.88±0.38b***	2.19±0.24 b***	5.62±0.42 b***	15.24±1.72b**	122.46	92

Where $n=6$, the observation is Mean±SEM. * $P<0.05$, ** $P<0.01$, and *** $P<0.001$ as compared to control. All the data were analyzed using one-way ANOVA followed by Dunnett's test. MES: Maximal electroshock seizure, EECE: Ethanolic extract of *Cyperus esculentus*, SCMC: Sodium carboxymethyl cellulose

PTZ-induced seizure. Antiepileptic drugs which abolish tonic extension occurred by MES act by inhibiting spread of

seizures. Drugs that either prevent or delay seizure occurrence caused by PTZ, act by elevating the seizure threshold.^[16]

Table 3: Effect of EECE in PTZ-induced convulsions in albino rats

Groups	Drug treatment	Latency (s)	Jerky movements (s)	Straub's tail (s)	Clonic convulsions (s)	Status of animals	
						No. of animals alive	% inhibition
I	Control	82.17±3.953	17.83±1.014	13.00±0.8563	420.7±11.69	2	33%
II	Diazepam (4 mg/kg)	161.8±4.483***	7.000±0.6325***	6.167±0.7032***	247.2±17.86 ***	6	100%
III	EECE (200 mg/kg)	121.0±5.538***	14.67±0.8819*	10.00±0.5774*	325.0±16.45 **	4	66%
IV	EECE (400 mg/kg)	142.5±2.825***	8.333±0.4216***	7.667±0.4944***	268.8±17.20 ***	5	83%

Values are mean±SEM of six ($n=6$) observations comparison between: a – Group I and Group II, b – Group II versus Group III, Group IV. Statistical significant test for comparison was done by ANOVA, followed by Dunnett's "t"-test. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. MES: Maximal electroshock seizure, EECE: Ethanolic extract of *Cyperus esculentus*, SCMC: Sodium carboxymethyl cellulose

Table 4: Effect of EECE in strychnine-induced convulsions in albino rats

Groups	Drug treatment	Latency (s)	Jerky movements (s)	Clonic convulsions (s)	Status of animals	
					No. of animals alive	% inhibition
I	Control	80.00±4.502	27.00±2.206	42.17±1.740	2	33%
II	Diazepam (4 mg/kg)	150.5±9.309***	13.67±1.382***	21.00±0.9661***	6	100%
III	EECE (200 mg/kg)	117.5±6.339**	17.83±1.922**	26.50±1.839***	4	66%
IV	EECE (400 mg/kg)	136.7±2.963***	15.67±1.256***	23.33±0.8819***	5	83%

Values are mean±SEM of six ($n=6$) observations comparison between: a – Group I and Group II, b – Group II versus Group III, Group IV. Statistical significant test for comparison was done by ANOVA, followed by Dunnett's "t"- test. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. MES: Maximal electroshock seizure, EECE: Ethanolic extract of *Cyperus esculentus*, SCMC: Sodium carboxymethyl cellulose

In our study, in the MES test, 100% of the controlled rats exhibited HLTE seizure. The MES is a standard procedure which evaluates the ability of the testing materials to protect against HLTE. Ibrahim *et al.*^[17] stated that the seizure features in MES are similar for all laboratory animals and human except for the time scale. The standard drug diazepam (4 mg/kg) and the EECE (200 and 400 mg/kg) exhibited significant anticonvulsant activity and provided protection against electroshock-induced HLTE, respectively. In the MES, protection against HLTE predicts the anticonvulsant activity of the tested compounds. Moreover, protection against HLTE in MES-induced seizure indicates the efficiency of *C. esculentus* extract to either stop or to slow down the discharge of the seizure within the brain stem substrate.^[18] Seizure induced by MES can be blocked either by inhibiting the voltage-dependent Na⁺ channels or by blocking glutamatergic excitation mediated by the N-methyl-D-aspartate (NMDA) receptors.^[19] Since *C. esculentus* extract showed antiepileptic activity in the MES, it may act by the same mechanism of action.^[20] The significant anticonvulsant activities of *C. esculentus* extract may be due to the presence of many potent compounds or phytoconstituents such as flavonoids, phenols, and terpenes.^[21]

In PTZ test, diazepam (4 mg/kg), *C. esculentus* (200 and 400 mg/kg) extracts exhibited a significant anticonvulsant effect. *C. esculentus* 400 mg/kg was found to be more effective than 200 mg/kg. These results give us evidence that ethanolic extract possesses anticonvulsant activity. The ability of ethanolic extracts to delay the onset of convulsions and/or shorten the duration of convulsions was considered an evidence of anticonvulsant activity.

In studies, it is known that compounds which are effective in suppression of PTZ-induced clonic seizures partially overlapped with the group of compounds effective against MES.^[22] In this regard, diazepam was found to be more effective against PTZ than MES seizures. PTZ is a GABA-A receptor antagonist. Accordingly, PTZ produces seizures by blocking the major GABAergic inhibitory pathways in the CNS.^[23] Standard antiepileptic drugs such as diazepam are thought to produce their effects by enhancing GABA-mediated inhibition in the brain.^[24] Moreover, activation of the NMDA receptors is also involved in the initiation and propagation of PTZ-induced seizures. In this regard, drugs that block glutamatergic excitation mediated by NMDA receptors have demonstrated anticonvulsant activity against PTZ-induced seizures [Figure 1].^[25] Seizures induced by

PTZ can also be blocked by reducing T-type Ca^{2+} currents.^[26] Therefore, the anticonvulsant activities of *C. esculentus* extracts against PTZ seizures might be due to an enhancement in release of inhibitory neurotransmitter GABA in the CNS, inhibiting T-type Ca^{2+} currents or blocking the glutamatergic neurotransmission mediated by NMDA receptors, which were not tested in this study. Nitric oxide scavenges upon the O_2 free radical in the brain, thereby attenuating the damage due to the free radical induced oxidative stress (Sudha *et al.*, 2001).^[27] Probably, in PTZ rats, the reduced level of NO is resulted from free radicals production at seizure time and its consumption due to its cleaning effect. The enhanced level of NO in treated group with EECE extract is also due to its antioxidant effect by which eliminates O_2 - radicals and consequently prevents lipid peroxidation and oxidative stress-induced injury that leads to increased level of NO. STN directly antagonizes the inhibitory spinal reflexes of glycine (Chen *et al.*, 2007).^[28] EECE exhibits its anticonvulsant effect on STN-induced convulsions, thus indicating its glycine independent activity.

CONCLUSION

The present study evaluated protective effect against seizures induced by MES, PTZ, and STN and antioxidant activity of EECE. The observed antioxidant and anticonvulsant activities are due to the presence of considerable amount of flavonoids and phenolics in the extract of *C. esculentus*. Ethanolic extract of 400 mg/kg *C. esculentus* compared to 200 mg/kg showed good anticonvulsant activity in MES-, PTZ-, as well as STN-induced convulsions may be due to the involvement of GABAergic and glutaminergic transmission and through glycine inhibitory property. However, further studies are needed to develop the exact underlying mechanism of anticonvulsant action of possible constituents of the plant after isolation of bioactive compounds.

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