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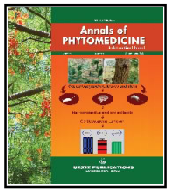

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Neurotransmitter modulation and stress hormone regulation of *Capparis zeylanica* L. in epilepsy induced mice models

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Abstract

Capparis zeylanica L. (Capparideaceae), is regionally known for its anticonvulsant activity in folk medicine and as an ingredient in various Ayurvedic preparations. This study was designed to screen the anticonvulsant activity of *C. zeylanica* stem bark ethanolic extract using strychnine (1 mg/kg) induced convulsions in Swiss albino mice. To screen its anticonvulsant activity, the extracts were assessed in comparison to standard diazepam treated group. The influence of stress hormone corticosterone was evaluated in maximal electroshock induced mice. Anxiolytic activity is assessed in other four groups where elevated pulse mazes (EPM) and open field are employed and anxiolytic activity is screened in comparison to standard drug. After behavioral assessments, the animals were sacrificed. Brains were isolated and homogenized, various neurotransmitter levels and antioxidant enzyme activities were measured.

C. zeylanica extract significantly increases the time in onset of seizure, decreased the duration of seizure and mortality in strychnine induced mice when compared to standard drug diazepam treated animals. The extract also showed significant anxiolytic activity on EPM and open field in comparison to diazepam, and the blood corticosterone and brain glutamate concentration were well attenuated. These reports suggest that the ethanolic extract could be a therapeutic agent for treating stress related convulsions and other epileptic convulsions.

1. Introduction

Epilepsy is an enduring brain condition categorized by repeated imbalance of the nervous system due to unexpected extreme discharge of electrical impulse from the cerebral neurons (Bartolini *et al*., 2022). It is the second most common neurological disorder and around 50 million peoples worldwide have epilepsy. The risk of death by premature ageing due to epilepsy is three times higher than in general population (World Health Organization, 2022). Seizures are inhibited and treated in nearly 70% of patients through drugs acting on ion channels or on gamma amino butyric acidergic (GABA) or glutamatergic transmission (Goldenberg, 2010). The hypothalamic-pituitary-adrenocortical (HPA) axis controls bodily responses to together physical and expressive stress. Well-organized activation of brain is also managed by the hormone corticosterone in a variety of CNS locations including hypothalamus, hippocampus and cerebral cortical regions. Stress and its cortisone regulation is important in seizure control and have influence on epilepsy conditions (Wulsin *et al.*, 2018). In many patients, the currently obtainable antiepileptic drugs (AEDs) are unable to regulate the seizures proficiently. Furthermore, the drug-related neurotoxicity and adverse effects associated with AEDs edge their clinical applications (Serafini, 2021). Many a times, natural drugs although given in the simple form, displayed reduced side effects, improved effectiveness and are economic. Out of the powerful natural drugs in herbal medicine and Ayurveda, *C. zeylanica*, is traditionally used to treat snake bite, testicle swelling, boils, small-pox, cholera, neuralgia and have central nervous depressant property (Balekari *et al*., 2015) and also studied in epilepsy induced rats (Mishra *et al*., 2012). The leaf extract of *C. zeylanica* with black pepper dust given for dysentery (Sunil Kumar Mishra; 2011). The root bark of *C. zeylanica* is used traditionally as stomachic, sedative, antihydrotic and also in cholera, neuralgia, hemiplegia and rheumatism.The seeds and fruits are used in urinary purulent discharges and dysentery (Padhan *et al*., 2010). In this study, the investigation of anticonvulsant activity of *C. zeyalinica* was carried out using epileptic animal model to evaluate the turnover of neurotransmitters and stress hormone corticosterone in the epileptic conditions.

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2. Materials and Methods

2.1 Plant material and extraction

The fresh entire plants of the *C. zeylanica* were collected from Khammam district of Telangana during the month of December. Plants were authenticated by Dr. V. Krishna Reddy, Assistant Professor, Department of Botany, Kakatiya University, Warangal. Fresh stem bark was isolated from the whole plant of *C. zeylanica* and subjected to shade dry for one week. The fully dried stem bark was coarsely powdered and extracted with ethanol (50-60°C) by Soxhlet extraction method. The extract was evaporated in rotary vacuum evaporator to yield the ethanolic extract.

2.2 Experimental design

The study encompassed the evaluation of behavioral and brain biochemical parameters, plasma corticosterone and determination of EECZ in strychnine induced convulsion. Animals were divided into three sets of four groups.The experimental protocol was approved by the animal ethics committee (Reference No: I/IAEC/LCP/025/2012/SAM/54). One set of animals contains 4 groups. In the first set, each group having 6 animals was treated for a period of 15 days with EECZ 200 mg/kg and 400 mg/kg. Diazepam is used as standard drug (1 mg/kg, i.p) and was treated only in the fourth group on the last day before 30 min of the behavioral experiment. After the treatment, the animals were subjected to behavioral studies. The biochemical estimations (neurotransmitters) were performed in the brain homogenates of vehicle, EECZ 200 and EECZ 400. In the second set, four groups of animals were used such as vehicle control, Maximal electroshock induced (Vyawahare and Bodhankar, 2009) and EECZ 200 and 400 treated with induction of MES on the end of the treatment before blood collection. Then, the animals were bled retro-orbitally and plasma was isolated for estimation of corticosterone. For determination of strychnine induced convulsion, the animals were injected with strychnine after two weeks of treatment and the percentage protection and mortality were assessed.

2.3 Behavioural studies (open field and plus-maze test)

The locomotor activity was assessed in an open field chamber consisting of 16 squares. The animals were allowed to explore and number of line crossings and head dippings were counted. In elevated plus-maze test the number of entries into open arm, number of entries into closed arm, time spent in the open arm, and time spent in the closed arm were studied (Jayasingh Chellammal *et al*., 2021).

2.4 Estimation of glutamate, GABA and glycine

The brains were isolated after cervical dislocation and homogenates were prepared at 20% concentration in phosphate buffered saline. Standard compounds of glutamate and GABA at a concentration of 2 mM are used. The amino acids were isolated using paper chromatographic methods and eluted with 0.005% $CuSO_4$ in 75% ethanol. After isolation, the absorbance is read at 515 nm and expressed as mmoles/g of wet weight tissue. For glycine, the sample was derivatized with dichlone in presence of sodium bicarbonate and read at 470 nm (Sunanda *et al*., 2000).

2.5 Estimation of antioxidant enzyme activity

Superoxide dismutase (SOD) enzyme was estimated by pyrogallol oxidation method. The brain catalase (CAT) was determined in 50 µl of sample. That is reacted with 32.4 mM ammonium molybdate and was added to the mixture and measured at 405 nm. Glutathione peroxidase was measured in brain homogenate. 1 ml of brain homogenate, was added with 4 ml of phosphate solution and DTNB (0.5 ml). The absorbance was noted at 412 nm (Singh *et al*., 2011).

2.6 Strychnine induced convulsions in mice

After 30 min of test, drug administration at 200 and 400 mg/kg b.wt. strychnine was injected (1 mg/kgi.p) and the onset of convulsion and duration was considered to calculate the percentage protection (Kar *et al*., 2014).

2.7 Estimation of corticosterone

The blood was collected retro-orbitally and plasma corticosterone is measured by HPLC/UV method using dexamethasone as standard (Singh *et al*., 2013). 50 µl of blood plasma was mixed to dexamethasone (1µg) and extracted by 5 ml of dichloromethane (DCM). Then, DCM was dried and made a solution in known amount of mobile phase. 20 µl was injected in HPLC using methanol: water (70:30) and detected at 250 nm.

3. Results

3.1 Effect EECZ on the open-field and plus-maze test

The Table 1 shows the significant decrease in locomotor activity, represented by nose poking and line crossing, in EECZ treatment when compared with vehicle treatment. The result of treatment groups was significant decrease ($p<0.001$) in line crossing and also significant decrease ($p<0.05$) in nose poking, respectively, at doses 200 mg/kg and 400 mg/kg. The EECZ high dose (400 mg/kg) exhibited significant increase in the number of entries into open arm ($p<0.05$) and time spent in open arm ($p<0.001$) when compared with vehicle control group and all these results were comparable with the reference drug diazepam and depicted in the table.

Table 1: Effect of *C. zeylanica* on exploratory behaviour and elevated plus-maze

Group	Line crossing	Head dips	Elevated plus maze	
	(counts/5 min)		No. of open arm entries	Time spent in open arm (sec)
Vehicle	159.8 ± 7.3	28.0 ± 4.1	5.0 ± 1.268	20.25 ± 3.7
EECZ 200	107.2 ± 2.5[a]	12.3 ± 4.3[c]	9.0 ± 1.852	35.38 ± 3.7[b]
EECZ 400	73.50 ± 4.1[a]	7.6 ± 1.8[c]	10.3 ± 1.322[c]	40.25 ± 1.6[a]
Diazepam	136.3 ± 4.0[c]	26.5 ± 3.4	11.3 ± 0.419[c]	41.25 ± 1.2[a]

EECZ 200 and 400 represent the low dose (200 mg/kg) and high dose (400 mg/kg) treatment in animals. Diazepam is the standard drug used in the study. [a] $p<0.001$, [b] $p<0.01$ and [c] $p<0.05$ is the significance in comparison with vehicle.

3.2 Effect of EECZ on glutamate, GABA and Glycine

The EECZ treatment exhibited a brief reduction in GABA and glycine levels; however, there were no significance noted. In case of the brain glutamate levels, there were significant decrease ($p<0.001$) when compared with the vehicle treated group. The results were indicated in the Table 2.

Table 2: Effect of *C. zeylanica*on neurotransmitters

Group	Glutamate	GABA	Glycine
	(mmoles/g wet tissue weight)		
Vehicle	359.4 ± 14.6	170.1 ± 5.1	7.98 ± 0.25
EECZ 200	267.3 ± 6.05[a]	174.4 ± 3.9	8.37 ± 0.27
EECZ 400	239.7 ± 4.54[a]	178.2 ± 0.9	9.42 ± 0.20

EECZ 200 and 400 represent the low dose (200 mg/kg) and high dose (400 mg/kg) treatment in animals. Diazepam is the standard drug used in the study. [a] $p<0.001$, [b]$p<0.01$ and [c]$p<0.05$ is the significance in comparison with vehicle

3.3 Effect of EECZ on antioxidant enzymes

The Table 3 shows the catalase levels in whole brain significantly ($p<0.01$), ($p<0.001$) increased in both low dose (200 mg/kg) and high dose (400 mg/kg) EECZ treated groups when compared to vehicle group. The SOD enzyme levels in whole brain were found to increase significantly at high dose with significant improvement in glutathione peroxidase. All the results are exhibited in Table 3.

Table 3: Effect of *C. zeylanica*on antioxidant parameters

Group	Catalase (U/mg protein)	SOD (U/min/mg protein)	GPx (U/min/mg protein)
Vehicle	1.05 ± 0.06	0.70 ± 0.07	16.07 ± 0.32
EECZ 200	1.44 ± 0.05[b]	0.75 ± 0.02	26.04 ± 1.37[a]
EECZ 400	1.89 ± 0.07[a]	1.04 ± 0.04[b]	29.24 ± 0.38[b]

EECZ 200 and 400 represent the low dose (200 mg/kg) and high dose (400 mg/kg) treatment in animals. [a]$p<0.001$ and [b]$p<0.01$ is the significance in comparison with vehicle.

3.4 The effect of EECZ on strychnine induced convulsions in mice

In strychnine epileptic model, the effect of EECZ at doses 400 mg/kg and 200 mg/kg replicated by the onset of convulsion was increased when compared to control group. However, the high dose of EECZ (400 mg/kg) was found to be identical with standard drug diazepam. Another parameter of efficacy, the mortality of EECZ treated animals was 0% and 33.30 % at doses of 400 mg/kg, 200 mg/kg, respectively, in contrast to 100% mortality in control group. However, Mortality of EECZ (400 mg/kg) was identical with that of standard drug. Protection of EECZ treated animals was 100% and 66.60 % at dose of 400 mg/kg and 200 mg/kg, respectively, against strychnine induced convulsions, whereas percentage protection of EECZ (400 mg/kg) was same as that of standard drug.

Table 4: Effect of *C. zeylanica*on strychnine induced convulsions in mice

Groups	Onset of seizures (min)	Duration of seizures (min)	% Mortality	% Protection
Vehicle	3.83 ± 0.30	2 ± 0.44	100	0
EECZ 200	4.33 ± 0.49	1.20 ± 0.06a	33.30	66.60
EECZ 400	6.00 ± 0.36[b]	0.73 ± 0.02[a]	0	100
Diazepam	6.33 ± 0.33[a]	0.70 ± 0.00[a]	0	100

Values are expressed as mean ± SEM of six animals. [a] $p<0.001$ and [b]$p<0.01$ indicate the comparison of vehicle with all other groups.

3.5 Effect of EECZ in corticosterone

In the MES induced (negative control group), induction of maximal electroshock increased the level of corticosterone significantly ($p<0.001$) when compared to the vehicle. In the treatment group, the administration of EECZ in 200 and 400 mg/kg significantly reduced the corticosterone level. The results were depicted in Table 5.

Table 5: Effect of *C. zeylanica* on corticosterone

Group	Corticosterone (ng/ml serum)
Vehicle	137.2 ± 9.07
MES induced	265.6 ± 37.87[a]
EECZ 200	174.4 ± 13.40 [b]
EECZ 400	144.3 ±11.82[c]

Values are expressed as mean ± SEM of six animals. [a]$p<0.001$ indicates the comparison of group vehicle with maximal electroshock induced (MES induce). [b]$p<0.01$ indicates the significant difference on comparing negative control with EECZ 400.

4. Discussion

Epileptic seizure often causes transient impairment of consciousness, leaving the patients at risk of bodily harm and often interfering with education and employment. Therapy is symptomatic in that available drugs, inhibits the seizures, but neither effective prophylaxis nor cure is available. Compliance with medication is a major problem because of the need of long-term therapy together with unwanted effects of many drugs (Dhossche *et al*., 2010). The mechanism of action of antiseizure drugs are classified into three major categories such as inactivation of voltage activated Na^+ channel, modification in numerous neurotransmitter levels in several regions of brain and increasing the gamma amino butyric acid. Gamma amino butyric acid (GABA) systems have an important role with reverence to anticon vulsive possessions. Dropping GABA levels in brain outcomes in the appearance of convulsion (Schmidt, 2009). Certain antiepileptic drugs enhance the synaptic action of GABA, decrease the glutamate, and limits the activation of voltage triggered Ca^{++} channel (Goldenberg, 2010). Benzodiazepines are hypothetical to act at specific binding sites on GABA receptors. Upsurge in glutamate levels in brain sources convulsions and some drugs act by blocking it. It was observed in the current studies are focused in herbal and complementary and alternative medicine (CAM) for the treatment of epilepsy and convulsions. The studies in this area have suggested that these drugs have least or no adverse effect and also provide effective control on seizures (Mesraoua *et al*., 2021). Corticosterone also plays important role in seizures and epileptic forms (van Campen *et al*., 2018). In our

study, there was no change in the brain GABA and glycine levels in EECZ treated group whereas, glutamate and corticosterone levels, which are known to be key role players in epilepsy, were significantly decreased as compared with vehicle treated group. Hence, the mechanism of action of EECZ is related to glutamate and stress hormone may be predicted. In present study, the behavioral parameters of EECZ pretreated animals by open-field and elevated pulse-maze (EPM) tests are investigated.

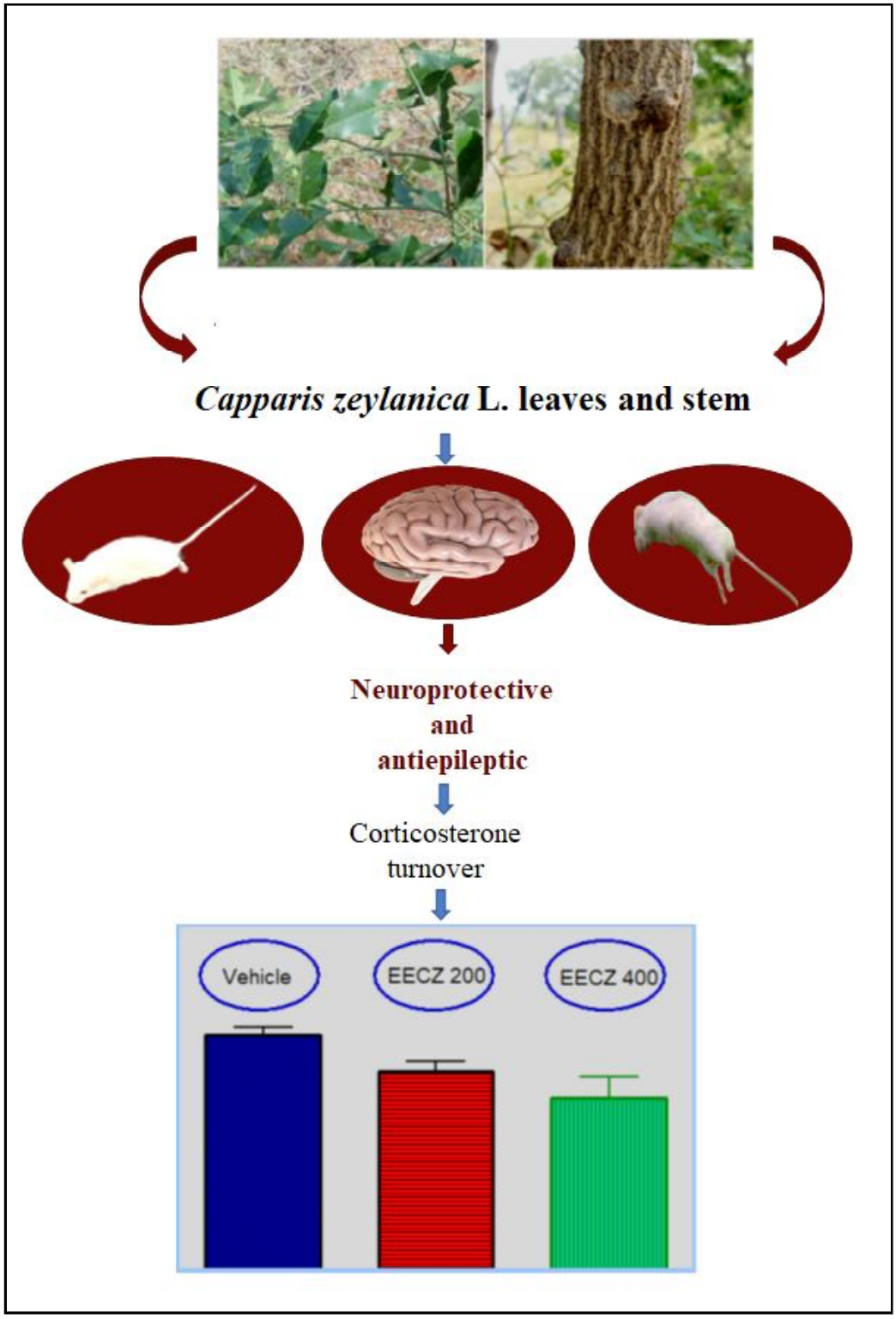

Figure 1: Representation of antiepileptic effect of *C. Zeylanica*.

Open field test is used for the evaluation of locomotor activity which is determined by observing the nose poking and line crossings. The elevated plus-maze (EPM) trial is one of the records used for behavioral memory to evaluate anxiety-related behavior in rodents. It was experiential that treatment with EECZ suggestively reduced the locomotor activity and upsurge in the open arm entries and time spent by mice in the EPM as comparison with vehicle treated group. It is generally believed that locomotor activity results from brain activation, which is manifested as an excitation of central neurons involving different neurochemical mechanism and an increase in cerebral metabolism (Khoo *et al.*, 2021). Anxiety may be characterized by an avoidance of the open arm and immovability of an animal placed in the EPM. Diazepam and other drugs with anxiolytic action augmented the time spent by animals in the open arm (Vyawahare and Bodhankar, 2009; Walia *et al.*, 2021). This finding suggests that the extract has anxiolytic activity. Oxidative stress is intricate in the pathogenesis of neurologic conditions and neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and epilepsy (Cao *et al.*, 2020; Shekh-Ahmad *et al.*, 2019). Several animal models of epilepsy showed the appearance of mitochondrial dysfunction, amplified reactive oxygen species, programmed cell death of neurons in many areas of brain, and numerous clinical studies also established that oxidative strain is intricated in the pathogenesis of epileptic seizures (Esih *et al.*, 2017; Upaganlawar *et al.*, 2021). Concerning epileptic seizures, glutamate over expression has been recognized to escort the generation of reactive oxygen species and reactive nitrogen species (Loshali *et al.*, 2021; Wang *et al.*, 2021) Currently, there has been an increasing interest in herbs possessing the antioxidant properties as they could be possible drugs for prevention of oxidative damage linked epileptic seizures. In the present study, EECZ produced a significant increase in catalase, SOD and glutathione peroxidase proving its antioxidant potential. Strychnine increases the spinal reflex and causes seizures and EECZ reduced the seizures and protected the mice from induction. In MES induced mice, it is also demonstrated that there were a reduction in plasma corticosterone indicates the potential role of EECZ in regulating the stress hormone and that it has been demonstrated to have a comprehensive mechanism of anticonvulsant action (Figure 1). The percentage protection (anticonvulsant effect) was found to be amplified dose dependently and reveals the neuromodulation and stress hormone regulation with antioxidant capacities.

5. Conclusion

In conclusion from our pharmacological screening, it is revealed that the treatment of *C. zeylanica* extract exerted anticonvulsant property. It was understood from the behavioral studies, that the extract possessed antianxiety effect, which was prominent on open field test and elevated pulse-maze test. Moreover, in biochemical parameters, the ability to inhibit glutamate and turnover in the levels of stress hormone corticosterone in brain indicated that the drug remarkably attenuated the property of NMDA-receptor function with renewed antioxidant effect and stress modulation.To conclude it is revealed that the drug *C. zeylani*ca could be a therapeutic agent for prevention and the treatment of epilepsy. Further, studies are required to reveal the molecular aspects of stress hormone and glutamate receptor interactions.

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Conflicts of interest

The authors declare no conflicts of interest relevant to this article.

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