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Anticonvulsant Study of *Capparis zeylanica* Linn. Root in Wistar Rats

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ABSTRACT

The phytochemical screening reveals the presence of phenol, tannins, flavonoids, fatty acids, saponins etc. in ethanolic extracts of *Capparis zeylanica* root which was confirmed by the used of various reagents and TLC chromatography. The aim of this study was to evaluate the effects of the ethanol extract of *Capparis zeylanica* roots (EECZ) in animal models of epilepsy. The ethanolic extract of *Capparis zeylanica* Linn. (EECZ) was subjected to acute toxicity and then screened for anticonvulsant activity on Maximal Electroshock (MES) and Pentylenetetrazole (PTZ) induced seizures models in albino Wistar rats. The extract was found non toxic up to the recommended dose 2000 mg kg⁻¹ b.wt. orally as per OECD guidelines No. 423. For the acute study, in the maximal electroshock seizure model, the administration of 100 mg kg⁻¹ of EECZ resulted in the complete abolition of seizures in 33.65% of the rats and this was increased to 82.51% with the administration of 400 mg kg⁻¹. In the pentylenetetrazole-induced seizure model, 20% protection from mortality was obtained by administration of 100 mg kg⁻¹ and 36% from 200 mg kg⁻¹ EECZ whereas, 80% rats were protected with the administration of 400 mg kg⁻¹. For the chronic study, in the maximal electroshock seizure model, the administration of 100 mg kg⁻¹ EECZ resulted in the complete abolition of seizures in 12.76% of the mice and in 80%, with the administration of 400 mg kg⁻¹. In the pentylenetetrazole-induced seizure model, 15% of the mice were protected from mortality with 100 mg kg⁻¹ EECZ and 85%, with 400 mg kg⁻¹ EECZ. These findings indicate that EECZ consists of anticonvulsant effect and is comparable to clinically used antiepileptic drugs (diazepam and phenytoin).

Key words: *Capparis zeylanica*, PTZ, MES, epilepsy, Capparidaceae, anxiolytic

INTRODUCTION

Epilepsy is a major neurological disorder and up to 4% of the world population develops epilepsy in their lifetime. A substantial number, approximately 20-30%, of epileptic patients continue to have seizures inspite of adequate treatment with antiepileptic drugs (AEDs) (Jeub *et al.*, 2002). Traditional systems of medicine are popular in developing countries and up to 80% of the population relies on traditional medicines or folks remedies for primary health care needs (Akerele, 1988). The modern conventional antiepileptic drugs (AEDs) are effective in approximately 50% of patients, many cases still remain resistant to AED treatment (Heinemann *et al.*, 1994). These drugs are associated with vast array of side effects including chronic toxicity,

teratogenicity, adverse effects on cognition and behavior among others (Raza *et al.*, 2001). Moreover, medicinal plants are believed to be an important source of new chemical compounds with potential therapeutic effects and have been used in the discovery and developed of new drugs (Farnsworth, 1994; Cragg *et al.*, 1997). Thus, due to aforementioned reasons and others, it is pertinent to look for affordable and conventional alternative medicine with view to providing a better protection and activities-particularly from medicinal plants. A great number of scientists and organizations turn their attention to traditional therapies in order to find and conserve important resources. However, the medicinal plants have been an important source of new drugs with biological activity (Carlini, 2003), the selected plant *Capparis zeylanica* Linn. (*C. horrida* Linn., *Capparis brevispina* DC.) is known as Indian caper belonging to family Capparidaceae. In Sanskrit it is known as vyakhranakhi, kinkani, tapasapriya, granthila, karambha (Satyanarayana *et al.*, 2008). It is a rigid, wiry and much branched shrub and is widely distributed in Bangladesh, India, Sri Lanka and Malaysia (Hooker, 1875). It grows in moist habitat and is found throughout the major parts of India. In different parts of India it is known with different names like asadhua in Orissa, kathotti in Tamil Nadu etc. (Muthu *et al.*, 2006). Almost all the parts i.e., root, bark, fruits, leaves, fruits, seeds are used for different purposes. The root bark of *C. zeylanica* is used traditionally as stomachic, sedative, antihydrotic and also in cholera, neuralgia, hemiplegia and rheumatism. The roots of *C. zeylanica* were reported to have antibacterial, antioxidant activities; it also found to act as endothelin receptor antagonists (Duke, 2000). The roots of *C. zeylanica* contain alkaloid, phytosterol, acids and mucilage etc. (White, 1997). A new fatty acid E-Octadec-7-en-5-yonic acid has been isolated from the roots of chloroform extract of *C. zeylanica* (Haque *et al.*, 2004). The *Capparis zeylanica* root bark in particular is also recommended traditionally for CNS problems and CNS depressant effect (Chaudhary *et al.*, 2004; Upaganlawar *et al.*, 2008). It is also reported to possess anti-inflammatory and analgesic activity in its root in general and bark portion of root in particular (Chaudhary *et al.*, 2004; Upaganlawar *et al.*, 2008). Therefore, the purpose of this study consisted of investigating the effects of the EECZ in animal models of epilepsy. Since epilepsy is a chronic disease that requires long-term management, oral administration of the investigational drug daily over a period of time may be more appropriate in determining its efficacy than a single dose.

Hence, this study aimed to evaluate the anti-epileptic effect of EECZ based on chronic (repeated doses) in addition to acute (single dose) administration.

MATERIALS AND METHODS

The following drugs and chemicals were used and all the reagents and chemicals used were of analytical grade:

- Pentylenetetrazole (Ranbaxy, India) (80 mg kg⁻¹ i.p.) was used as standard convulsion producing agent
- Phenobarbitone (Sigma, St. Louis, USA) (60 mg kg⁻¹ p.o.) was used as standard anticonvulsant drug
- Diazepam (Ranbaxy, India) (1 mg kg⁻¹ i.p. and 3 mg kg⁻¹ p.o.) was used as the standard anxiolytic agent

Plant and extract: Roots of *Capparis zeylanica* Linn. (*C. horrida* Linn., *Capparis brevispina* DC., were collected from Medicinal Plant garden of Banaras Hindu University campus and specimen (H.P.L. 512) has been deposited in the herbarium of the Laboratory of Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi, Uttar Pradesh, India. The roots were oven-dried at 40°C, pulverized in a room temperature and extracted with 95% ethanol in water for 72 h. The extract was dried at 60°C using rotavapor and the yield was approximately of 10.8% for obtaining the ethanol extract of *Capparis zeylanica* Linn. roots (EECZ).

Preliminary phytochemical screening: The phytochemical examination of the methanolic extract of *Capparis zeylanica* Linn. was performed by the standard methods (Harbone, 1973).

Animals: Adult Charles Foster albino rats (150±20 g) and Wistar mice (25±5 g), of either sex were obtained from the Central Animal House, Institute of Medical Sciences, Banaras Hindu University and were randomly distributed into different experimental groups. The animals were kept in six groups in a cage (polypropylene) at an ambient temp. of 25±1°C and 45-55% relative humidity. The cycle of light/dark was maintained for 12:12 h. for each period. Animals were acclimatized to laboratory conditions for at least one week before the start of experiment. The experiments were conducted between 9.00 and 14.00 h. The animals were subjected for experiment only once and principal for laboratory animal care (NIH publication number 85-23, revised 1985) guidelines were fully followed.

Drug treatment

Treatment of animal: The standardized extract of *Capparis zeylanica* L. with 60% ethanol was prepared, filtered, evaporated and dried. The yield of effective extract was quantified (10.8% w/w) further it was kept in controlled condition of light and temperature (-4°C) until its use. The extract was solubilised in 0.3% CMC solution before experimental study and administered orally at different dose level for seven consecutive days. Control animals were treated with 0.3% CMC solution. The acute effect was studied in mice in single doses of 100, 200 and 400 mg kg⁻¹ of EECZ and the chronic effect was studied in doses of 100, 200 and 400 mg kg⁻¹ (administered daily for 21 days) using the maximal electroshock seizure and pentylenetetrazole-induced seizure models of epilepsy. Standard drugs were used in each set of experiment as mentioned below accordingly and were administered either orally or intraperitoneally to rodents 1 h or 30 min. before experiment for comparison, respectively:

- Phenobarbitone (Sigma, St. Louis, USA) (60 mg kg⁻¹ p.o.) was used as standard anticonvulsant drug
- Diazepam (Ranbaxy, India) (1 mg kg⁻¹ i.p.) was used as the standard anxiolytic agent

Acute toxicity study: The acute toxicity of EECZ was determined as per the OECD guideline No. 423 (acute toxic class method). It was observed that the test extract was not mortal even at 2000 mg kg⁻¹ dose. Hence, 1/20th (100 mg), 1/10th (200 mg kg⁻¹) and 1/5th (400 mg kg⁻¹) of this dose were selected for further study (OECD, 2002).

Antiepileptic activity: The anticonvulsant profile of EECZ (acute and chronic effects) was evaluated in two conventional experimental models of epilepsy: The Maximal Electroshock Seizure (MES) test and the Pentylenetetrazole (PTZ)-induced seizure test in albino Wistar rats. In bred feed albino Wistar rats of both genders weighing 150-230 g were used for the study. The rats were housed in groups of three to five in clean polypropylene cages in the laboratory environment at a temperature of 24-27°C, with cross-ventilation, a natural day/night cycle and free access to food and water. The rats were screened 24 h prior to the study. Only the rats that showed all phases of convulsion with the maximal electroshock current were selected. In total, 30 rats were included in the acute experimental model. These were distributed into five groups of six rats each, of which three were males and three were females. Of the five groups, Group I served as a control while Groups II, III and IV received the ethanolic extract of *Capparis zeylanica* Linn. (EECZ) (100, 200 and 400 mg kg⁻¹ b.wt.) and Group V received (phenytoin, 30 mg kg⁻¹) as a standard drug. A total of 50 rats were included in the chronic experimental model. These were distributed into five groups, each containing ten rats, of which five were male and five were female. Among these, Group I served as the control group while Groups II, III and IV received the ethanolic extract of *Capparis zeylanica* Linn. (EECZ) (100, 200 and 400 mg kg⁻¹ b.wt.) and Group V received a standard drug.

Effect on Maximal Electroshock (MES) induced seizures: MES was induced in the rats using an electroconvulsimeter (Techno India Ltd. Ambala, Haryana, India). MES stimuli, comprising 0.2 sec of rectangular positive pulses (48 mA at 60 Hz; pulse width 0.4 msec) were delivered through ear clip electrodes (Balakrishnan *et al.*, 1998). Each rat of either sex were divided into five groups of six animals each. The first group received vehicle control (0.3% w/v CMC) whereas, Group-V received standard drug (Phenytoin, 30 mg kg⁻¹) intraperitoneally, Group II, III and IV received ethanolic extract of *Capparis zeylanica* Linn. (EECZ) (100, 200 and 400 mg kg⁻¹ b.wt.) p.o., respectively for 14 days. On 14th day the seizure was induced by using electroconvulsimeter in all the rats. In the chronic study, the EECZ was administered orally at once a day for 21 days. The rats were subjected to the test procedure one hour after the last dose on the 21st day. Each rat was administered the EECZ or normal saline (control) 30 min prior to receiving an electroshock. The anticonvulsant activity of the EECZ was evaluated based on its ability to protect (%) against MES and decrease the duration of tonic hind limb extension, flexion and clonus in unprotected animals (i.e., only in animals in which seizures were not abolished).

Effect on Pentylenetetrazole (PTZ) induced seizures: Albino Wistar rats of either sex weighing 150 to 230 g were divided into five groups of six animals each. The first group received vehicle control (0.3% w/v CMC) whereas, Group-V received standard drug (diazepam, 1 mg kg⁻¹) intraperitoneally, Group II, III and IV, received ethanolic extract of *Capparis zeylanica* Linn. (EECZ) (100, 200 and 400 mg kg⁻¹ b.wt.) p.o., respectively for 14 days. On the 14th day, Pentylenetetrazole (PTZ) (80 mg kg⁻¹ b.wt., i.p.) was administered to all the groups to induce clonic convulsions (Dhir *et al.*, 2006). In the chronic study, the drugs were administered orally at once a day for 21 days. The mice were subjected to the test procedure one h after the last dose on the 21st day. The anticonvulsant effect was evaluated based on the ability of the drug to prolong the duration of the latent period (i.e., the time taken for the onset of clonus with a loss of the righting reflex or tonic hind limb extension whichever appeared first after the administration of PTZ) and its ability to decrease mortality.

Statistical analysis: The data were expressed as Mean±Standard Error Mean (SEM). The Significance of differences among the groups was assessed using one way and multiple way Analysis of Variance (ANOVA). The test followed by Dunnet's test $p > 0.05$ were considered as significance.

RESULTS

Phytochemical screening: The results of preliminary phytochemical screening of the ethanolic extract of *Capparis zeylanica* Linn. revealed that presence of tannins, fatty acids, phenols and saponins etc.

Acute effects of EECZ on MES induced epilepsy: For the acute study, in the MES model (Table 1), complete abolition of seizures was observed in 33.65, 74.83 and 82.51% of rats in the groups administered 100, 200 and 400 mg kg⁻¹ EECZ, respectively. In unprotected animals, a significant decrease in the duration of tonic hind limb extension was observed in the dosages of 100, 200 and 400 mg kg⁻¹ EECZ (4.00±0.12, 2.92±0.16 and 2.10±0.13 sec, respectively as compared to 12.21±0.03 sec in the control group at $p < 0.05$). A significant decrease in clonus was observed in the dosage of 200 and 400 mg kg⁻¹ (14.81±0.36, 12.82±0.85 sec at $p < 0.05$ as compared to 18.78±0.32 sec in the control group). The significant effect in the flexion was also observed at 200 and 400 mg kg⁻¹ dosage (6.72± 0.51, 4.09± 0.22 sec as compared to 8.9±0.32 sec at $p < 0.05$). The effect observed with EECZ (400 mg kg⁻¹) was significant and is comparable to the standard drug of phenytoin in all of the above parameters.

Acute effect of EECZ on PTZ induced epilepsy: In the PTZ-induced seizure model (Table 2), complete protection from PTZ-induced mortality was observed in 20% of the mice in the groups administered 100 mg kg⁻¹ and 36% of the rats in the groups administered 200 mg kg⁻¹ EECZ and in 80% of the mice in the group administered 400 mg kg⁻¹ EECZ. In unprotected animals, a significant increase in the latent period was observed in all the dosages of 100, 200 and 400 mg kg⁻¹ EECZ (245.83±1.51, 495.83±1.51, 684.36±1.22 as compared to 82.00±7.36 sec in the control group, at $p < 0.05$). The effect observed with EECZ (400 mg kg⁻¹) was significant and is comparable to the standard drug diazepam in all of the above parameters.

Chronic effects of EECZ on MES induced epilepsy: For the chronic study, in the MES model (Table 3), complete abolition of seizures was observed in 12.76, 68.29 and 80.00% of rats in the

Table 1: Acute study for the effect of ethanolic extract of *Capparis zeylanica* Linn. (EECZ) on MES induced seizures in rats

Treatment group	Dose (mg kg ⁻¹)	Mean±SEM (sec)			Abolition of seizure [†] (%)
		Flexion	THLE	Clonus	
Vehicle control (GI)	8.9±0.32	12.21±0.03	18.78±0.32	0.00
EECZ (GII)	100 p.o.	8.03±0.34	4.00±0.12**	16.62±0.33	33.65
EECZ (GIII)	200 p.o.	6.72±0.51*	2.92±0.16**	14.81±0.36*	74.83
EECZ (GIV)	400 p.o.	4.09±0.22**	2.10±0.13**	12.82±0.85**	82.51
Phenytoin (GV)	25 i.p.	3.9±0.33**	0**	8.91±0.54**	100.00

Values are expressed as Mean±SEM of six observations. * $p < 0.05$; ** $p < 0.01$. Comparison between Group I vs. Group II, III, IV and V,

[†]Denotes the abolition of the tonic hind limb extension and is considered as the end point of the test. Statistical significant test for comparison was done by ANOVA followed by Dunnet's test

Table 2: Acute study for the effect of ethanolic extract of *Capparis zeylanica* Linn. (EECZ) on PTZ induced seizures in rats

Treatment group	Dose (mg kg ⁻¹)	Mean latent period± SEM (sec)	Mortality (%)
Vehicle control (G I)	187.75±0.66	100
EECZ (G II)	100 p.o.	245.83±1.51**	80
EECZ (G III)	200 p.o.	495.83±1.51**	64
EECZ (G IV)	400 p.o.	684.36±1.22**	20
Diazepam (G V)	4 i.p.	705.31±1.13**	0

Values are expressed as Mean±SEM of six observations. *p<0.05; ** p<0.01. Comparison between Group I vs. II, III, IV and V. Statistical significant test for comparison was done by ANOVA followed by Dunnet's test

Table 3: Chronic study for the effect of ethanolic extract of *Capparis zeylanica* Linn. (EECZ) on MES induced seizures in rats

Treatment group	Dose (mg kg ⁻¹)	Mean±SEM (sec)			Abolition of seizure [†] (%)
		Flexion	THLE	Clonus	
Vehicle control (G I)	9.21±0.22	12.0±0.30	18.83±0.21	0.00
EECZ (GII)	100 p.o.	8.99±0.12	10.30±0.43	16.53±0.12	12.76
EECZ (GIII)	200 p.o.	7.02±0.24*	3.78±0.12**	13.89±0.26*	68.29
EECZ (GIV)	400 p.o.	3.98±0.42**	2.23±0.23**	11.92±0.58**	80.00
Phenytoin (GV)	25 i.p.	3.67±0.32**	0**	8.56±0.24**	100.00

Values are expressed as Mean±SEM of six observations, *p<0.05; **p<0.01. Comparison between Group I vs. II, III, IV and V, [†]Denotes the abolition of the tonic hind limb extension and is considered as the end point of the test. Statistical significant test for comparison was done by ANOVA followed by Dunnet's test

Table 4: Chronic study for the effect of ethanolic extract of *Capparis zeylanica* Linn. (EECZ) on PTZ induced seizures in rats

Treatment group	Dose (mg kg ⁻¹)	Mean latent period± SE (sec)	Mortality (%)
Vehicle control (GI)	134.25±0.36	100
EECZ (GII)	100 p.o.	215.38±1.36**	85
EECZ (GIII)	200 p.o.	393.87±1.47**	63
EECZ (GIV)	400 p.o.	654.48±1.12**	15
Diazepam (GV)	4 i.p.	693.03±1.013**	0

Values are expressed as mean±SEM of six observations. *p<0.05; **p<0.01. Comparison between Group I vs. II, III, IV and V Statistical significant test for comparison was done by ANOVA followed by Dunnet's test

groups administered 100, 200 and 400 mg kg⁻¹ EECZ, respectively. In unprotected animals, a significant decrease in the duration of tonic hind limb extension was observed in the dosages of 200 and 400 mg kg⁻¹ EECZ (10.30±0.43 at p<0.05 and 2.23±0.23 sec at p<0.05, respectively, as compared to 12.0±0.30 sec in the control group). A significant decrease in clonus was observed in the dosages of 1 and 4 mg kg⁻¹ (13.89±0.26 at p<0.05 and 11.92±0.58 sec at p<0.05, respectively as compared to 18.83±0.21 sec in the control group). The decrease in the duration of flexion was significant only at the dosage of 200 mg kg⁻¹ and 400 mg kg⁻¹ EECZ (7.02±0.24 and 3.98±0.42 sec as compared to 9.21±0.22 sec in the control group, at p<0.05). The effect observed with EECZ (400 mg kg⁻¹) was significant and is comparable to the standard drug of phenytoin in all of the above parameters.

Chronic effects of EECZ on PTZ induced epilepsy: In the PTZ-induced seizure model (Table 4), complete protection from PTZ-induced mortality was observed in 15, 37 and 85% of the rats in the groups administered 100, 200 and 400 mg kg⁻¹ EECZ, respectively. In unprotected animals, a significant increase in the latent period was observed at all the dosage of 100, 200 and

400 mg kg⁻¹ EECZ (215.38±1.36, 393.87±1.47 and 654.48±1.12 sec at p<0.05, as compared to 134.25±0.36 sec in the control group). The effect observed with EECZ (400 mg kg⁻¹) was significant and is comparable to the standard drug of diazepam in all of the above parameters.

DISCUSSIONS

The aim of this study was to evaluate the anticonvulsant effects of EECZ using the MES and PTZ-induced seizure models. The MES test is the most frequently used animal model for identification of anticonvulsant activity of drugs for the generalized tonic-clonic seizures "grand mal" (Loscher and Schmidt, 1988; Oliveira *et al.*, 2001). This model based on observation of the stimulation by repeated electrical pulses induce in different neuronal structures one characteristic standard of epileptic activity (Quintans-Junior *et al.*, 2002). In the MES model, complete abolition of seizure (protection) was observed in 82.51% of animals that were administered the highest dose (400 mg kg⁻¹) in the acute study which was comparable to that of Phenytoin. Eighty percent of the animals were protected in the chronic study compared to 100% for Phenytoin. In unprotected animals, EECZ decreased the duration of tonic hind limb extension and clonus in a dose-dependent manner in the acute study. The same type of trend of effect was observed in both acute and chronic study. This finding suggests that the extract having good effect in both type of convulsions. The MES model is used to identify compounds which prevent seizure spread, corresponding to generalized tonic-clonic seizures in humans (Stables and Kupferberg, 1995; White, 1997). Currently used anticonvulsant drugs (e.g., phenytoin, carbamazepines) effective in therapy of generalized tonic-clonic and partial seizures have been found to show strong anticonvulsant action in MES test (White, 1997; Macdonald and Kelly, 1993). Since, EECZ significantly inhibited generalized tonic-clonic seizures in MES test; it suggests the presence of anticonvulsant compounds.

In the acute study of the PTZ-induced seizure model, EECZ increased the latent period in a dose dependent manner in all the doses. The same type of trend of effect was observed in both acute and chronic study. This finding suggests that the extract having good effect in both types of convulsions. Despite this, the protection from mortality with the highest dose remained at 85% which is comparable to diazepam. Demonstration of the anticonvulsant effect of EECZ in all the above doses experimentally, as in this study, is in our view, a very significant finding. We found that treatment with EECZ on PTZ induced rats significantly reduce the duration of convulsion and delayed the onset of clonic convulsion. Although animal models based on pentylenetetrazole (e.g., pentylenetetrazole threshold and acute convulsions) have still been widely used for drug screening, the mechanism by which pentylenetetrazole elicits its action has not been completely understood. One generally accepted mechanism by which pentylenetetrazole exerts its action is by acting as an antagonist at the picrotoxin sensitive site of the GABAA receptor complex (Ramanjaneyulu and Ticku, 1984). Since PTZ has been shown to interact with the GABA neurotransmission (Loscher and Schmidt, 1988; De Deyn *et al.*, 1992) and PTZ induced seizures can be prevented by drugs that enhance gamma amino butyric acid type A (GABAA) receptor-mediated inhibitory neurotransmission such as benzodiazepines and phenobarbital (Coulter *et al.*, 1989; Macdonald and Kelly, 1995), the antagonism of PTZ- induced seizures suggests the interaction of the EECZ with the GABA-ergic neurotransmission. Prior administration of EECZ has resulted in significant protection against MES as well as PTZ-induced seizures in both the acute and chronic studies. However, the maximal effect was also comparable to that of standard drug (phenytoin and diazepam) at 400 mg kg⁻¹ BW. Hence, EECZ can be considered as a good alternate anticonvulsant

drug from plant origin. The study concluded EECZ possesses an anticonvulsant effect which results from the potentiation of the activity of GABA. However, more precise mechanisms of EECZ anticonvulsant activity and the relationship between the seizure and GABAA receptor subunits and the other neurotransmitter systems which may explain how EECZ produce anticonvulsant effect must be investigated further.

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