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ANTICONVULSANT ACTIVITY OF FLOWER EXTRACT OF *COSTUS SPECIOSUS (COASTACEAE)* IN EXPERIMENTAL ANIMALS

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ABSTRACT

Objective: The main objective of the work was to evaluate the anticonvulsant activity of *Costus speciosus* **Methods:** The anticonvulsant activity of methanolic and aqueous extract of *Costus speciosus* flowers was evaluated using *Pentylenetetrazole* (PTZ) induced convulsions in mice and maximal electro shock (MES) induced Convulsions and *lithium-pilocarpine* induced status epilepticus in rats. **Results:** methanolic and aquoeus extract of *Costus speciosus* (100 and 200 mg/kg) and (200 mg/kg) delayed onset of PTZ- induced convulsions and also prolonged the onset of tonic convulsions in mice. Both the extracts failed to protect the rats from MES induced convulsions. The extracts also protected rats against seizures induced by *lithium-pilocarpine*. In *Lithiumpilocarpine* model the methanolic extract (100 and 200 mg/kg) and aqueous extract (200 mg/kg) delayed the latency to rearing with forelimb clonus significantly. **Conclusion:** The results indicate that which are active in case of *Pentylenetetrazole* (PTZ) and *lithium pilocarpine* induced status epilepticus, which support the ethnomedicinal application of the plant as an anticonvulsant agent.

KEYWORDS: *Costus speciosus*, Anticonvulsant, *Pentylenetetrazole*, Maximal electroshock, *Lithium-pilocarpine*,

INTRODUCTION

Epilepsy is a common neurological disorder that demands immediate medical attention and, often,long-term therapy.[1] Synthetic antiepileptic drugs are associated with side-effects, including teratogenicity, chronic toxicity and adverse effects, on cognition and behaviour.[2] An ideal antiepileptic drug should suppress all seizures without causing any untoward effect.Unfortunately, the drugs available in the modern medicine not only fail to control the seizure activity in some patients, but quite frequently cause unwanted effects that range in severity from minimal impairment of the CNS to death from aplastic anemia or hepatic failure.[3] *Costus speciosus* is popularly known as kemuka, Kushta, Kashmira, Shura, Katar katar in Sanskrit, pushpamoola in Kannada, kashmeeramu in Telugu[4], keukand, Keu in Hindi and Bengali, Chengalva Koshta' in Telegu and Kannada, 'Kottam' or 'Koshtam' in Tamil and 'Penava' or 'Pushkarmula' in Marathi[5], Jom lakhuti in Assamese, Crepe ginger in English.[6] It is mainly cultivated in rainy seasons.[7] It grows well on rich moist soil or clayey loam soil in shady area under mixed deciduous forests of South India.[8] It grows well in the climate with high humidity and low temperature. *Costus speciosus* is propagated by different methods such as vegetative methods using rhizome pieces[9], This plant is used as food and medicine by the Kannikars, the primitive hill tribes of South India.[10] Recently it is used in drug industry as a natural source of diosgenin which is a steroidal sapogenin used for synthesis of sex hormones, cortisone and oral contraceptives.[11,12,13] Diosgenin content up to 3.37% has been reported in rhizome of *Costus speciosus.*[14] The plant parts has many medicinal uses, juice of rhizome is applied to head for cooling and relief from head-ache, bruised leaves are applied in fever, decoction of stem is used in fever and dysentery, patients with high fever mostly utilize leaf infusion or decoction as a sudorific or in a bath, sap from leaves, young stems are use against diarrhea[15] cough, cuts, wounds, scabies,

antidote for snake bite, jaundice, arthritis[16], burning sensation, constipation, leprosy, skin diseases, asthma, bronchitis, inflammations, anemia[17], intestinal warms, worm infection, rash, nose pain, to stop vomiting[18] spermatorrhoea, used as antivermin and for abortion.[19] The rhizomes of *Costus speciosus* are bitter, astringent, acrid, cooling, aphrodisiac, purgative, anthelminthic, depurative, febrifuge, expectorant, tonic[20], improve digestion[21], and is a stimulant herb that clears toxins. The rhizomes have anti-fertility, anabolic properties.[22] The rhizomes are generally consumed in the form of decoction. An alkaloid extract from rhizomes had papaverine like smooth muscle relaxant and enhances antispamodic activities. Rhizomes are also given in pneumonia,rheumatism, dropsy, urinary diseases, jaundice, and leaves are given in mental disorders. *C. speciosus* rhizomes' extract stimulate the uterine contraction due to non-estrogenic effects.[23] The plant is also used for eye and ear infections. Rhizomes have also been seen to exhibit cardiotonic, hydrochloretic, diuretic and CNS depressant activities, formerly used in Malaysia for small pox.[24] It is used as an ingredient in a cosmetic to be used on eyelashes to increase sexual attractiveness, as mentioned in Kama Sutra. But, its anticonvulsant activity is not yet validated scientifically as on date. Hence in the current dissertation the anticonvulsant activity of methanol and aqueous extract of leaf of *Costus speciosus* in experimental animals is evaluated.

MATERIALS AND METHODS

Plant Introduction

Costus speciosus, an important medicinal and ornamental plant cultivated in India belongs to family Costaceae. Leaves powder was purchesed in chaudapudi shop at warangal (500gm). for further extraction process.

Preparation of methanol and Aqueous extract: The powder of *Costus speciosus* leaf powder was charged in to the Successive cold extraction process by using of methanol and Water.

Animals

Albino mice of either sex weighing between 20-30g And albino rats of either sex weighing between (180-220) gm were procured from Mahavir enter priceses hyderabad. The animals were acclimatized to laboratory conditions for 7 days. The animals were supplied with commercially available standard diet. Water was allowed ad libitum under hygienic conditions. All animal studies were performed in accordance to guideline of CPCSEA.

Drugs

Phenytoin (Shreeji Pharma International, Vadodara,India), *Pentylenetetrazole* (Sigma,USA), *Diazepam* and *Clonazepam*(Campose injection, Ranbaxy, India), *Lithium carbonate* (Glenmark Pharmaceuticals, India), and *pilocarpine* (FDC Limited, India) were used in the study. All other chemicals were of analytical grade. *PTZ, Phenytoin, Diazepam inj., Lithium carbonate, pilocarpine nitrate* were dissolved in distilled water just before administration.The extracts were suspended in CMC (0.5 %). A gastric catheter was used for oral drug administration. The extracts did not show any sign of toxicity till the oral dose of 2000 mg/kg hence the extracts were used in the range of 100–300 mg/kg orally assuming that LD50 dose is 2000 mg/kg.

Determination of LD50 of Leaf Extract of *Costus speciosus*

The acute toxicity of leaf extracts of *Costus speciosus* was determined by using albino mice of either sex weight between (20-25 g), maintained under standard conditions. The animals were fasted for 3 hr prior to the experiments. Animals were administered with single dose of either Methanol or aqueous leaf extract of *Costus speciosus* and observed for its mortality up to 48 hr study period (short term toxicity). Based on the short-term toxicity profile,the next dose was decided as per OECD guidelines No 425. Since no mortality was observed upto dose 2000mg/kg From the LD50 dose, 100 mg/kg and 200 mg/kg doses were selected and considered as low and high doses respectively.

Assessment of anticonvulsant activity

Treatment schedule

Albino rats and mice were used to evaluate anticonvulsant activity. Rats were used in the Maximal electroshock induced seizures and *Lithium pilocarpine* induced status-epilepticus and mice were used in *pentylenetetrazole*-induced convulsions. Animals were divided in six groups. One group received vehicle, two groups received MECS (100 & 200 mg/kg), two groups received AQECS (100 & 200 mg/kg) and the sixth group received the reference standard.

Pentylenetetrazole(PTZ) induced seizures

60 min after above mentioned drug treatment Clonic seizures were induced in mice by subcutaneous injection of 80mg/kg *Pentylenetetrazole*. The latency to the onset of clonic convulsions in non-protected mice and lethality during the following 24 hour was recorded and compared with those of vehicle treated control mice to assess the anticonvulsant activity.[25,26,27] One group received *clonazepam* 0.1 mg/kg - i.p. as a reference standard 30 min before *PTZ.* The animals were observed for onset of convulsion up to 30 min after *PTZ.* Each animal was then placed into individual plastic cages and were observed initially for 30 min and later up to 24 hrs. The following parameters were recorded during test session of initial 30 min and up to 24 hrs respectively: Latency (onset of clonus), Onset of tonic-clonic convulsions, Status of animal after 1hr Status of animal after 24 hrs, Percent protection.

Maximal Electro Shock Induced seizures (MES)

One group received *phenytoin* (20 mg/kg- p.o.) as a as a reference standard.Tonic clonic convulsions were induced by giving maximal electroshock seizures (MES) (150 mA for 0.2sec) using an electroconvulsometer (INCO, Ambala, India) via crocodile ear clip, 60 minutes

after administration of either vehicle or test drug dosese and 90 minutes after *Phenytoin* (20mg/kg-p.o.). sabolition of tonic hind limb extension within 10 sec after delivery of the electroshock was considered as protected rat) and duration of observed tonic hind limb extension seizure (HLTE) was recorded in each dose group.[25,28] For recording various parameters, rats were placed in clear rectangular plastic cages with an open top, permitting full view of the animal's motor responses to seizure. In the pilot study various phases of convulsions, viz., tonic flexion, extension, clonus, stupor and mortality due to convulsions were selected as the parameters.

***Lithium pilocarpine* induced status-epilepticus**

Status epilepticus was induced by administration of *pilocarpine* (30mg/kg i.p) 24 h after *lithium carbonate* (3 mEq/kg i.p). The effect of MECS & AQECS (each 100 & 200 mg/kg, p.o) was studied on the rearing with forelimb clonus by administering both extracts 30 min. Before injection of pilocarpine(29). *Diazepam* was used as a reference standard in a dose of 1 mg/kg i.p.

RESULTS

Acute toxicity study

Both the petroleum ether and methanol extracts did not produced any sign of toxicity.

Assessment of Anticonvulsant Activity of *Costus speciosus* Leaf powder.

***PTZ* - Induced seizures**

Costus speciosus leaf powder were screened for anticonvulsant activity using *PTZ* induced convulsion model in mice. Study was conducted using low, and high doses of MECS & AQECS (100 & 200 mg/kg respectively). The above mentioned doses were administered as mentioned earlier. It was observed that both low and high doses of MECS while only high dose of AQECS exhibited a significant anticonvulsant exhibited a significant anticonvulsant effect. The mathanol extract was found to be more effective than aqueous extract. The standard drug *clonazepam* (0.1 mg/kg-i.p.) exhibited a significant anticonvulsant activity and offered 100% protection. The observations are given in Table 1.

Table 1: Effect of methanol and aqueous extracts of *Costus speciosus* Leaf powder on PTZ (80mg/kg-s.c.) Induced Convulsions in mice

Treatment(mg/kg)	Onset of firstclonus(second)	No. of animals survived/used	Percent mortality (%)
Vehicle Control	200.04 ± 0.57	0/6	100 %
MECS-100	201.07 ± 0.17*	2/6	66.66 %
MECS-200	223.14 ± 0.27**	3/6	50 %
AQECS-100	199.14 ± 0.91	1/6	84.43 %
AQECS-200	190.01 ± 0.18*	1/6	83.33 %
Clonazepam - 0.1	NIL	6/6	0.00 %

Values are mean ± SEM; n=6; One way analysis of variance (ANOVA) followed by Dunnetts test. Where, *P<0.05, **P<0.01,***P<0.001, MECS: methanol extract of *Costus speciosus* leaves, AqECS: aqueous extract of *Costus speciosus* leaves, PTZ: *Pentylenetetrazole.*

MES Induced seizures

Costus speciosus leaf powder extracts were screened for anticonvulsant activity using MES induced convulsion model in rat. Study was conducted using low and high doses of MECS & AQECS (100 & 200mg/kg) respectively. The above mentioned doses were administered as mentioned earlier. It was observed that both the low dose and high doses of MECCSS & AQ failed to protect the rats and to produce anticonvulsant effect as compared to control by reducing the duration of tonic extensor phase and tonic-clonic seizures. The standard drug *phenytoin* (20 mg/kg- p.o.) exhibited a significant anticonvulsant activity and offered 100% protection. The observations are given in Table 2.

Table 2: Effect of methanol and aqueous extracts of *Costus speciosus* Leaf powder on MES Induced Convulsions in rats

Treatment(mg/kg)	Duration of hind limb extension (second)	convulsed/Rats used
Vehicle Control	21.45 ± 0.15	6/6
MECS-100	27.77 ± 0.21*	6/6
MECS-200	29.11 ± 0.99**	6/6
AQECS-100	22.48 ± 0.81	6/6
AQECS-200	23.01 ± 0.14*	6/6
Phenytoin-20	05.14 ± 0.55**	6/6

Values are mean ± SEM; n=6, One way analysis of variance (ANOVA)followed by Dunnettstest,Where, *P<0.05, **P<0.01,***P<0.001, MECS: methanol extract of *Costus speciosus* leaves, AqECS: aqueous extract of *Costus speciosus* leaves, MES: Maximal electro shock.

Table 3: Effect of methanol and aqueous extracts of *Costus speciosus* Leaf powder on *Lithium pilocarpine* induced statusepilepticus

Treatment (mg/kg)	Latency to rearing with forelimb clonus (min)
Vehicle Control	20.95 ± 0.88
MECS-100	48.19 ± 0.51*
MECS-200	67.42 ± 0.49**
AQECS-100	22.18 ± 0.76
AQECS-200	38.01 ± 0.47*
Diazepam – 1	69.24 ± 0.88**

Values are mean ± SEM; n=6, NS non significant, One way analysis of variance (ANOVA) followed by Dunnetts test, Where, *P<0.05, **P<0.01,***P<0.001, MECS: methanol extract of *Costus speciosus* leaves, AqECS: aqueous extract of *Costus speciosus* leaves,

***Lithium pilocarpine* induced status-epilepticus**

Costus speciosus leaves were screened for anticonvulsant activity using *Lithium pilocarpine* induced status epilepticus model in rat. In vehicle treated group latency to forelimb clonus was observed at 18.17±0.7491 min after *pilocarpine*. Study was conducted using low, and high doses of MECS & AqECS (100 & 200 mg/kg-p.o. respectively). The above mentioned doses were administered as mentioned earlier. It was observed that both low and high doses of MECS while only high dose of AqECS exhibited a significant anticonvulsant effect by showing significant delay in latency to rearing with forelimb clonus when compared to control group. The petroleum ether extract was found more effective than methanol extract. The standard drug *diazepam* (1mg/kg-i.p.) exhibited a significant anticonvulsant activity. The animals were normal in behaviour after 180 min. The observations are given in Table 3.

DISCUSSION

There are a number of synthetic anticonvulsant drugs currently available for use in the management, control and treatment of individuals with epilepsy. However, most of the synthetic drugs are not only inaccessible and unaffordable, but also possess many toxic adverse effects. Therefore, there is a great need for the development of cheap, effective and safe anticonvulsant agents from plants and other sources. GABA is the primary inhibitory neurotransmitter in the central nervous system (CNS). Diminution of brain GABA level has been reported after PTZ. Diminution of brain GABA level has been reported after subconvulsive dose of PTZ.[30] Many plants having anticonvulsant activity are known to inhibit GABA transaminase activity thereby increasing brain contents of GABA.The MES test predicts activity against generalized tonic clonic and cortical focal seizures and the PTZ test against absence seizure, while Lithium-pilocarpine was found useful in status epilepticus.[31] Pretreatment of *lithium* initiates limbic seizures after administration of subconvulsant doses of *pilocarpine* and other cholinergic agonist; Still *lithium* does not have proconvulsant activities.[32] If *lithium* and *pilocarpine* administred concurrently it results in an accumulation of inositol monophosphate and reduction in cortical inositol that are about 10 times greater than the effects obtained with either drugs alone.[32, 33] *Lithium-pilocarpine* induced convulsion have used to study the effect of *fluoxetine* on post- status epilepticus induced depression in rats.The study has shown that depression in epilepsy may have specific mechanisms and not only altering serotonergic pathways. serotonergic or cholinergic mechanisms may be responsible for inhibition of *lithiumpilocarpine*- induced convulsion.[34] *Phenobarbitone, sodium valproate, diazepam* and *trimethadione* prevent the limbic seizures induced in rats by *pilocarpine,* however, *phenytoin* and *carbamazepine* are ineffective.[35] *Lithium-pilocarpine*induced seizures were inhibited by blocking of serotonergic transmission and inhibition of post-synaptic 5-HT receptors.[36] The anticonvulsant activity may be due to the presence of flavonoids and sterols in the extracts. From the above data it is concluded that *Costus speciosus* leaves possesses significant anticonvulsant activity against *pentylenetetrazole, Lithiumpilocarpine* and not against MES induced convulsions.

CONCLUSION

The methanolic extract of *Costus speciosus* leaves is more potent for showing the anticonvulsant activity than aqueous extract.The extracts showed dose dependent effect.Further studies are required to find and isolate active principles and determine the mechanism of their anticonvulsant action, also our study suggests the application of *Costus speciosus* leaves in the treatment ofconvulsive disorders as a need of modern health science.

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