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Original Article

EVALUATION OF ANTIEPILEPTIC ACTIVITY OF ETHANOLIC EXTRACT OF *AZIMA TETRACANTHA* ROOT IN MICE

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ABSTRACT

Objective: To evaluate the antiepileptic activity of ethanolic extract of *Azima tetracantha* root (EEATR) against Maximal electroshock (MES) and Pentylenetetrazole (PTZ) induced seizures in mice.

Methods: 48 adult male mice were used and 4 groups with six in each were allocated to each model. 4 Groups are divided into control, standard and two test groups. The control group received normal saline, standard group, Sodium valproate-200 mg/kg and the two test groups received an ethanolic extract of roots of Azima tetracantha (EEATR) 250 and 500 mg/kg respectively. Antiepileptic activity was assessed based on hind limb tonic extension duration, the onset of convulsions and mortality. The results were compared with control and standard.

Results: In MES model EEATR reduced the duration of hind limb extension (HLE) and seizure protection was 50% and 66.6% with 250 and 500 mg/kg respectively. In PTZ model both the doses of EEATR delayed the onset of clonic phase and prevented death in 50% of animals in the group treated with 500 mg/kg EEATR, similar to sodium valproate. Results were analysed by ANOVA with $p<0.05$ considered as significant.

Conclusion: EEATR has shown anticonvulsant activity in both MES and PTZ models. 500 mg/kg of EEATR has better protection than 250 mg/kg against seizure in MES model and equally efficacious as sodium valproate standard in PTZ model.

Keywords: Antiepileptic activity, Maximal Electroshock (MES), Pentylenetetrazole (PTZ), Azima tetracantha root, Sodium Valproate

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INTRODUCTION

Epilepsy, a disorder of brain function which is defined clinically as a syndrome of two or more unprovoked or recurrent seizures on more than one occasion [1].

Epilepsy accounts for 0.5% of global health burden. Approximately 80% of incidence is reported from developing countries [2]. It is accounted that one out of 21 men and one out of 28 women will develop epilepsy during their lifetime [3]. The incidence is high in the pediatrics age group, decreasing through adulthood until approximately 60 y and the incidence again increases [4].

The unpredictable nature of epilepsy causes psychological stress to the individual even if the disease is well controlled. People with epilepsy may have poor health, suffer from unemployment, inability to work and higher mortality compares to non-epileptics [5]. It has been reported that there is a higher risk of suicide in epileptic individuals [6]. A low socioeconomic status has been shown to be a risk factor for developing epilepsy [7, 8].

Currently, the treatment of epilepsy is by pharmacological agents such as phenytoin, sodium valproate, carbamazepine, which control the excess abnormal electrical activity of brain neurones. These agents act by blocking sodium/calcium channels and balancing the inhibitory and excitatory neurotransmitter system in central nervous system. Research is going on identifying new targets and new molecules. The limitation of the use of available drugs is that they can only offer remission but not cure of epilepsy. In addition, the long term side effects and cost of especially recently introduced drugs such as levetiracetam and compliance to lifelong therapy imposes the necessity to develop new drugs.

None of the antiepileptic drugs, including those that act on newly identified targets, can be considered as an ideal drug that reliably cures epilepsy [9].

Temkin NR, reviewed many clinical trials on epilepsy and found that the use of antiepileptic drugs suppressed seizures in the short-term, but not long-term [10].

The outcome of antiepileptic treatment is also not the same in all individuals which could be due to genetic variation which has led to personalised therapy [11].

Hence in this scenario, there is a need to search for alternative drugs with lesser adverse effects and equal efficacy.

Limitations with the currently existing drugs made the researchers search for an alternative therapy from natural resources. A review on the plants having antiepileptic activity was done by Saba Hasan *et al.*, Malvi Reetesh K *et al.* and Lucindo J *et al.* Many Plants were evaluated for antiepileptic activity. Some of them are *Allium sativum*, *Artemesia* spp,*Cissus sicyoides*, *Ocimum sanctum, Brahmi grihta, Dorstenia arifolia,Withania somnifera, Citrus sinensis, Datura stramonium, Terminalia glaucescens, Caesalpinia crista, Mentha cardifolia, Tetrapleura tetraptera, Ricinus communis, Taxus wallichiana, Senna singuena, Jatropha gossypiifolia, Glycerrhiza glabra, Catharanthus roseus,* Passion flower etc [12-14].

Azima tetracantha Lam. (AT) is a herb used in Indian traditional medicine. *Azima tetracantha* is commonly called needle brush in English, *mulluchangu* in Ayurvedha and Kundali in sidha. It belongs to salvadoraceae family. *Azima tetracantha* has been traditionally used for many diseases especially root part. In Zimbabwe, root paste has been used for Snake bites, Stem juice for a headache, fever, chronic dysentery in South Africa, root and Stem juice for Rheumatism and sprain and leaf juice for a toothache, chronic diarrhea, acidity, venereal diseases, cough and cold in India andSouth Africa. Root decoction has been used Stomach disorders (diarrhea, dysentery) in Kenya, India [15].

Pharmacological actions reported for AT are anti-inflammatory, analgesic, antipyretic, antimicrobial, antifungal, antiulcer, diuretic, anticancer, anti-snake venom, and hepatoprotective and antioxidant activities [16-18]. The nephroprotective effect in acute renal failure has been recently reported [19].

Phytochemical composition

It contains alkaloids, flavonoids, glycosides, terpenoids and fatty acids. Dimeric piperidine alkaloids are azimine, azcarpaine and

carpaine present in the whole plant. Glucosinolates and glucosinolate-derived compounds present in root and fruit are 3-indolylmethylglucosinolate N-hydroxyl-3-indolylmethyl-glucosinolate N-methoxy-3-indolylmethyl-glucosinolate and neo-ascorbigen. Flavonoids, quercetin, myricetin, rutin, are present in root and stem. Leaf contains an important terpenoids are freidelin and beta-sitosterols [20-22].

Considering the presence of phytochemicals such as alkaloids, flavonoids and terpenoids which are reported to have antiepileptic activity AT has been chosen in this study for evaluation of its antiepileptic activity in animal models. The root part was chosen for this study because it is traditionally more commonly used part and also it contains all basic nutrients and phytochemicals. There is no study reported for azima tetracantha for its action in central nervous system disorders.

MATERIALS AND METHODS

The study was initiated after getting approval from Institutional Animal Ethics Committee. Letter No. IAEC2/Desp. No.50/Dt. 29.07.2013.

Animals

The study was initiated after getting Institutional animal ethical committee approval. A total of 48 healthy male Swiss albino mice weighing between 25-30 grams were used for this study. Animals were obtained from the Central Animal House of CHRI. The animals were divided into 8 groups with six in each. 4 groups were allocated for each experiment. Each group was housed in clean polypropylene cage and maintained in the proper environment. All these animals had free access to food and water. The animals were acclimatized for these conditions for one week.

Drugs and chemicals used in the experiment

PTZ was purchased from Sigma Chemicals and Sodium valproate of Sanofi Synthelabo (India) was purchased from the pharmacy of Chettinad Hospital and Research Institute.

Preparation of ethanolic extract of azima tetracantha roots (EEATR)

Azima pyracantha roots were purchased from RN Rajan and Co, exporters of Herbal raw products, Chennai. Roots were milled into a coarse powder and this powder was subjected to continuous extraction with 95% v/v ethanol in Soxhlet apparatus for 15 cycles. The extract was then dried in a flash evaporator. 55.03 g of green coloured, thick and sticky residue was obtained. It was reconstituted in distilled water so that concentration obtained was 1 gm/ml.

Acute toxicity study

Acute toxicity study was conducted as per OECD-423 guidelines. A total of 12 female mice divided into 4 groups with 3 in each were used for this study. ATR extract at doses 5, 50, 300 and 2000 mg/kg of was given orally in overnight fasted animals. All these animals were observed for their general behaviour, mortality and convulsions for the first 2 h and then hourly for the next 6 h and after 24, 48, and 72 h.

The extract was found to be safe as there is no change in behaviour or mortality was observed up to the dose of 2000 mg/kg. Doses, 250 and 500 mg/kg of the ethanolic extract were selected for this study based on acute toxicity test.

Route of administration

All the drugs were given through intraperitoneal route

Methodology

All the drugs required were freshly prepared before starting the experiment. The test group received the drugs calculated according to the body weight and the control group received the same volume of vehicle (distilled water) through intraperitoneal route. No food or water was given during the experiment.

Experimental design

Four groups of 24 mice with six in each were allocated to each model used Groups in each model

Group 1: Control group received distilled water, 2 ml/kg, i. p.

Group 2: Standard group received Sodium valproate, 200 mg/kg, i. p.

Group 3: Received test drug (Test group I) 250 mg/kg of EEATR, i. p

Group 4: Received Test drug (Test group II) 500 mg/kg of EEATR, i. p

Maximal electroshock (MES)-induced seizures test

The effect of the Azima tetracantha on generalised seizures was evaluated by the maximal electroshock (MES) method as described by Schmutz M *et al.* [23]. Four groups of six animals in each group were selected for this model. The control (distilled water–2 ml/kg), standard (sodium valproate-200 mg/kg) and test drugs Iand II (Azima tetracantha 250 and 500 mg/kg) were administered intraperitoneally before inducing seizures. Generalised seizures were induced half an hour later with electroshock through a pair of ear electrodes which delivered an alternating current of constant frequency (60Hz) and 50mA for 0.2 sec. The control group had a convulsive pattern having a tonic flexor phase, a tonic extensor phase with characteristic hind limb extension followed by clonic phase. An animal was considered to be protected if the characteristic seizure pattern is absent or there is a reduction in the duration of hind limb extension. The duration of hind limb extension, number and percentage of animals protected in each group was determined.

Pentylenetetrazole (PTZ)-induced seizures test

PTZ was used to induce seizures according to the method described by Swinyard EA *et al.* [24]. The mice were divided into four groups of 6 animals each. The control (distilled water–2 ml/kg), standard (sodium valproate-200 mg/kg) and test drugs IandII (Azima tetracantha 250 and 500 mg/kg) were administered intraperitoneally half an hour before induction of convulsions. Typical convulsions began in control group with jerking movements of the body followed by clonic convulsions within 2-3 min. The treated groups were compared with that of control for the delay or latency of onset convulsions as well as protection from death which were considered as indicators of anticonvulsant activity.

Statistical analysis

Statistical analysis was done using one-way ANOVA. P valve of<0.05 was considered significant

RESULTS

MES model

All the animals in control group treated with electric shock developed convulsions. The standard drug sodium valproate (200 mg/kg) protected 83.3% (5 out of 6) of animals from seizures.

In group III, treated with 250 mg/kg of EEATR, 3 out of 6 animals did not develop convulsion and the percentage of protection was 50%. In group IV, treated with 500 mg/kg of EEATR 4 out of 6 (66.6%) animals did not develop seizures and in the remaining 2 animals, there was a decrease in the duration of hind limb tonic extension. In this model EEATR has significantly decreased the duration of hindlimb extension in both 250 mg/kg (P<0.01), and 500 mg/kg (p<0.001). The effect of test drug at 500 mg/kg was comparable to the effect of the standard drug (fig. 1 table 1).

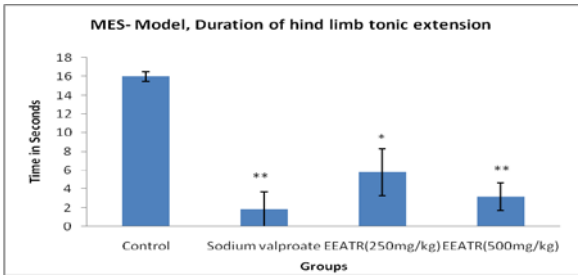

Fig. 1: Effect of EEATR on duration of hind limb extension in MES model, N=6, Values were expressed as MEAN±SEM *p<0.01, **p<0.001

Table 1: Percentage of seizure inhibition in MES model

Group (n=6)	Hind limb tonic extension (HTLE)		Protection against seizure (%)
	Present (+)	Absent (-)	
G-1(Control)	6	0	0
G-2(Standard)	1	5	83.3
G-3(Test drug I)	3	3	50
G-4(Test drug II)	2	4	66.6

Table 2: Percentage of animals protected from death in PTZ model

Group (n=6)	No of animals		Percentage of animals protected from death (%)
	Dead (+)	Alive (-)	
G-1(Control)	6	0	0
G-2(Standard)	3	3	50
G-3(Test drug I)	4	2	33.3
G-4(Test drug II)	3	3	50

PTZ model

Convulsions were induced in all the animals by giving PTZ in the dose of 80 mg/kg. 100% mortality was observed in control group. Sodium valproate and EEATR (500 mg/kg) significantly ($p<0.05$) increased the threshold for the onset of convulsions and had imparted 50% protection. In the group treated with EEATR (250 mg/kg) 4 out of 6 animals died.

Thus in PTZ model the EEATR 500 mg/kg effectively increased the seizure onset time and found to have 50% protection from death similar to Sodium valproate (fig 2 and table 2).

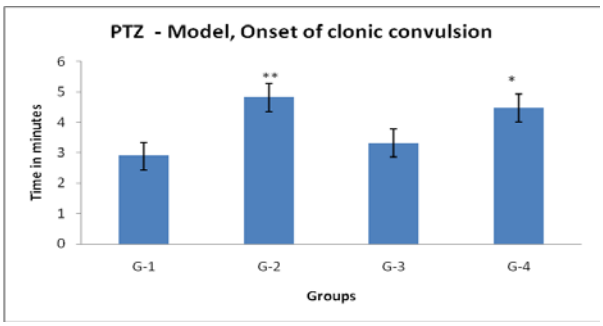

Fig. 2: Effect of EEATR on onset of convulsions in PTZ model, N=6, Values were expressed as MEAN±SEM *p<0.05, **p<0.01

DISCUSSION

The present study has evaluated the antiepileptic activity of EEATR in both MES and PTZ mice models.

The antiepileptic activity was measured by duration of hind limb extension in MES model and onset of convulsions and prevention of death in PTZ model. The MES model is the most frequently used as an animal model for identification of anticonvulsant activity of drugs for the generalised tonic-clonic seizures (GTCS). In this model, animals are stimulated with a same supramaximal current strength which induces seizures [25]. The mechanism reported for convulsions induced by MES is antagonism of GABA activity.

In our study, the percentage of seizure prevention was 83.3% in sodium valproate-treated group whereas it was 50% ($P<0.01$) and 66.6% ($p<0.001$) in groups treated with EEATR 250 and 500 mg/kg respectively.

PTZ induces seizures by antagonizing the inhibitory GABAergic neurotransmission and calcium channel blockade. and also increasing the excitatory neurotransmitters level causing neuronal excite toxicity leading to seizure development. This model is commonly used for screening of drugs for petit mal/absence seizures. In our study Sodium valproate and EEATR (500 mg/kg) significantly ($p<0.05$) increased the threshold for convulsions and had shown to protect 50% of the animals from death and 33.3 % in the group treated with EEATR 250 mg/kg.

In both the models, EEATR showed antiepileptic activity. The extent of antiepileptic activity varied between MES and PTZ models. The antiepileptic activity of EEATR was found to be lower than sodium valproate in MES model whereas it was found to be equal in PTZ model. Between the two doses of EEATR, 500 mg/kg offered higher protection in MES model. In PTZ model, there was no difference between EEATR 500 mg/kg and sodium valproate. This indicates that EEATR has antiepileptic activity equal to that of sodium valproate in MES model and PTZ model. The antiepileptic activity of EEATR could be due to facilitating the GABAergic inhibitory system (MES model) or calcium channel blockade (PTZ model).

Phytochemical compounds present in Azima tetracantha root are alkaloids, flavonoids, terpenoids, sterols and glycosides. It has been reported that alkaloids [26], flavonoids [27], saponins [28], and terpenoids [29] have antiepileptic activity. It is reported that flavonoids modulate GABA receptors, may reduce the glutamatergic transmission and having a neuroprotective effect [30].

The antiepileptic activity of Azima tetracantha root proven in this study could be due to the presence of these phytochemicals. A similar study conducted by Karunakar Hegde *et al.* by using root part of Carissa carandas Linn reported that the antiepileptic activity of the plant root could be due to the presence of phytochemicals especially triterpenic steroids and triterpenoidal saponins against MES and PTZ models and alkaloids, monoterpenes, flavonoids against PTZ induced convulsions [31].

Rajasree *et al.* did the similar study by root extract of Moringa oleifera in which they estimated the biogenic amines such as noradrenaline, serotonin and dopamine in the brain. They observed that there was an increase in these amines in the forebrain region [32]. It is reported that low level of dopamine has an inhibitory effect on glutamate and increase in the same can inhibit the seizure activity [33].

Oxidative stress has been implicated as a cause for epilepsy. Menon B in her study showed that antioxidant status was low in untreated epileptic individuals and not improved with antiepileptic treatment with classical drugs [34]. Most of the plant products evaluated for antiepileptic activity are reported to have antioxidant activity due to their phytochemical content. The *in vitro* antioxidant activity of Azima tetracantha root extract and *in vivo* activity of kidney tissue has been reported by konda *et al.* 2015[19]. Hence it can be inferred that the antiepileptic activity of EEATR could be not only due to its effect GABAergic transmission and calcium channel blockade but also could be due to antioxidant activity.

Further studies are required to find an exact mechanism and exact chemical compound responsible for its antiepileptic activity using genetic models which closely resemble idiopathic epilepsy in humans.

CONCLUSION

The present study on Azima tetracantha root extract has shown that it has anticonvulsant activity in both MES and PTZ induced seizure in mice. EEATR in the dose of 250 and 500 mg/kg was found to be safe and effective in preventing seizures in both the models. In MES model 250 and 500 mg/kg of EEATR effectively decreased the duration of tonic hind limb extension. The anticonvulsant activity was significant with 500 mg/kg of EEATR compared to control. In PTZ model EEATR 500 mg/kg protected 50% of animals from death which was comparable to sodium valproate. The antiepileptic activity of Azima tetracantha root extract could be due to its phytochemical compounds. The probable mechanism could be due to the modulatory effect on central neurotransmitter system as well as antioxidant activity. Further studies are required to explore its mechanism of action and the active principle responsible for its action. These findings can be taken forward to develop new antiepileptic drug with less side effects.

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CONFLICT OF INTERESTS

Declare none

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