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Madhuca longifolia water extract revealed protective effect against MES, PTZ and Li-pilocarpine induced epilepsy

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ABSTRACT

Objective: Present study was designed to screen the antiepileptic property of aqueous extract of Madhucalongifolia (AqML) in laboratory animals. **Materials and methods:** Rat and mice were divided in different groups. Antiepileptic activity was tested by using maximal electric shock (MES), Pentylenetertrazole (PTZ) and lithium pilocarpine (Li-Pilocarpine) models. Treatment group of animals were received AqML at 100, 200 and 400 mg/kg p.o. for 7 days. At the end of treatment period, different parameters related of antiepileptic action were observed. **Result:** Preliminary phytochemical investigation revealed the presence of carbohydrate, protein, amino acid and alkaloids. Animals treatment with AqML showed significant ($p<0.05$) antiepileptic activity in MES, PTZ and li-pilocarpine screening models. In all the screening models AqML showed dose dependant prevention in seizure was observed and of them dose 400mg/kg p.o. was found to be very significant ($p<0.05$) antiepileptic effect. **Conclusion:** The result revealed that AqML at 400 mg/kg p.o. possesses antiepileptic activity in MES, PTZ and Li-pilocarpine models.

Keywords: Antiepileptic, PTZ, Lithium-pilocarpine.

INTRODUCTION

Epilepsy is a chronic disorder of central nervous system affecting about approximately 50 million people of the world population with prevalence rate around 30 to 50 per 100000 populations per year [1]. A large part of the problem is that epilepsy is very difficult to diagnose and treat effectively. Currently available drugs are to control and prevent epilepsy with side effects and addiction liabilities associated with long term administration. Only 40-60% of patients are control by currently available drugs; another 20-30% attains partial control, while rest remain resistant [2]. Severe side effects and addiction liabilities associated with widely prescribed synthetic drugs indicates need of new drugs as alternative.

Medicinal plants can be used as alternative drug therapy for the management of this disease [3]. Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown activity when screened for the antiepileptic activity [4]. The knowledge of traditional medicine gives the path on the discovery of new and potent medicine but scientifically sound data are missing for many medicinal plants in India.

Madhucalongifolia (Koen.) Macb. Family- *Sapotaceae* is medium to large sized deciduous tree, also known as a *Bassialongifolia Koenig* and commonly known as mahua [5]. Whole plant is being employed for the treatment of various ailments in the indigenous system of medicine. Several bioactive compounds recognised in the β-carotene, xanthophylls, erthrodiol, palmitic acid, myricetin, quercetin, oleanolic acid, β-sitosterol and stigmasterol [6]. It possesses stimulant, anthelmintic, analgesic, diuretic, aphorodisiac, helminths, tonsillitis, pharyngitis, bronchitis, diabetis, rheumatism, ulcer and antiepileptic activity [6]. Traditional claims about *M. longifolia* suggest its potential in treatment of epilepsy [7]. There was no scientific report prescribed on the antiepileptic activity of aqueous extract of *M. longifolia* wood. Hence study was planned to explore the possible antiepileptic potential of aqueous extract of *M. longifolia* (AqML) in experimental animals.

MATERIALS AND METHODS

Plant material

M. longifolia wood was collected from area of Pimpalner, Sakri city, Dist. Dhule, Maharashtra, India in between the month of October to December 2014. The plant specimen was authenticated by A. Benniamin, Scientist 'D', Botanical Survey of India, Western regional centre, Pune-411001

(No. BSI/WRC/Tech./2014/CVT-2).

Preparation of Extract

The wood was washed using water and shade dried at room temperature to retain its vital phytoconstituents and then subjected to size reduction for further extraction process. About one kg of the dried plant material was powdered with mechanical grinder and sieved to get uniform particle size. The powder material was extracted with solvent water by maceration method for 24 hrs. The extract was concentrated for further studies on water bath at 40 ºC. The extract was finally air dried then stored in an air tight container till used.

Experimental Animals

Albino rats of wistar strain (180–220 g) and Swiss albino mice of either sex (25– 30 g) were used in the study and maintained under standard laboratory conditions, which include a temperature of 20-24ºC, relative humidity of about 50-60% and a 12-h light cycle beginning early in the morning. The animals allowed free access to food (Golden Feed, New Delhi) and water *ad libitum* except during the short time they are removed from their cages for testing. All the animals were acclimatized for a week before the study and randomized into different groups. Extract and standard prototype drugs (diazepam, phenytoin) were administered once daily (0900) in the morning for a period of 07 days. Food, but not water was withdrawn 3-4 h before the experiment. Protocol of the study approved from the Institutional Animal Ethics Committee (No. IAEC/ABCP/09/2014-15 Date 17/10/2014) and conducted according to CPCSEA guidelines.

Chemicals and Drugs

Diazepam, PTZ and lithium sulphate were procured from Merck, India. Pilocarpine and phenytoin were obtained from Sigma-Aldrich, Germany. The plant extract, phenytoin, diazepam were dissolved in water for administration to animals.

Preliminary Phytochemical investigation of extracts

A preliminary phytochemical analysis of aqueous extract of *M. longifolia* wood was carried out for the presence of various phytoconstituents like alkaloids, carbohydrates, reducing sugars, proteins and Amino acids [8].

Acute Oral Toxicity Study

Albino mice of either sex weighing 25-30 g selected by random sampling technique was performed as per OECD-423 guidelines. The animals were fasted for 3-4 hr, provided only water, after which the extract was administered to the respective groups at the dose level of 5 mg/kg p.o.. If mortality was observed in 2 or 3 animals, then the same dose was repeated. If mortality was observed in one animal, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed, the procedure was repeated for further higher doses such as 5, 50, 300 and 2000 mg/kg p.o.. The animals were observed for 72 hr.

Screening of antiepileptic activity

Maximum electroshock induced seizures

The maximal electroshock (MES) method was performed to induce the seizures in order to screen for antiepileptic activity. Albino Mice were randomly divided into five groups of six animals each. Vehicle, standard drug and extract dose pretreated once daily for 7 days. Group I served as disease control group (Vehicle treated MES induced), Group II served as reference standard (received Phenytoin sodium 25 mg/kg i.p. body weight); Group III to V were treated with extract dose 100, 200, 400mg/kg p.o.. The test extract were administered orally, 1hr prior to induce the convulsion and standard drug (Phenytoin sodium 25 mg/kg i.p.) was administered 30 min before to induce the epilepsy. Electroconvulsive shock (50 mA for 0.2 sec) (Scientech, India) was delivered through corneal electrode to induce epilepsy to five groups of mice (n=6). The various phases of epilepsy were produced Flexion, Extension, Clonus and stupor. Prior to delivery of electric shock, current output was checked by multimeter. After the electric stimulation occurrence, the duration of phases were noted. [9]

Pentylenetetrazol-induced seizures

Albino Mice were randomly distributed in to five groups of six animals each. Vehicle, standard drug and extract dose pretreated once daily for 7 days. Epilepsy was induced by subcutaneous injection of PTZ (80 mg/kg s.c.) and the animals were observed for onset of myoclonic spasm, clonicepilepsys and duration of epilepsy. Group I served as disease control group (Vehicle treated PTZ induced), Group II served as reference standard (received diazepam 5.0 mg/kg, i.p.); Group III to V were treated with extract Dose 100, 200, 400mg/kg p.o.. The test extract were administered orally, 1hr prior to induce the epilepsy and standard drug was administered i.p.30 min before to induce the epilepsy. The animals were observed for onset of epilepsy upto 30 min after PTZ. [10]

Lithium-pilocarpineinduced seizures

Albino Wistar rats were randomly distributed in to five groups of six animals each. Vehicle, standard drug and extract dose pretreated once daily for 7 days. Status epilepticus was induced by administration of pilocarpine (30 mg/kg, *i.p.*) 24 h after lithium sulphate (3 meq/kg, *i.p.*). The effect of extract was studied on the status epilepticus by administering extract 1 hr before injection of pilocarpine nitrate. Group I served as disease control group (Vehicle treated Li-pilocarpine induced), Group II served as reference standard (received diazepam 5.0 mg/kg, i.p.); Group III to V were treated with extract Dose 100, 200, 400mg/kg p.o.. The test extract was administered orally, 1hr prior to induce the epilepsy and standard drug was administered i.p.30 min before to induce the epilepsy. The severity of status epilepticus was observed every 15 min till 90 min and then every 30 min for next 90 min using the scoring system as described: stage 0- no response, stage 1- fictive scratching, stage 2- tremors, stage 3-head nodding, stage 4- forelimb clonus, stage 5-rearing and falling back [10].

Statistical Analysis

The data were expressed as mean±SEM. Difference between the groups was statistically determined by one-way ANOVA followed by Bonferroni t-test. Level of significance was set at $p< 0.05$.

RESULTS

Phytochemical screening

In preliminary investigation, AqML extract revealed the presence of alkaloids, carbohydrate, proteins and amino acids.

Acute Toxicity

AqML was exposed to acute toxicity study. For the LD_{50} dose determination, extract was administered up to dose 2000 mg/kg p.o. and extract did not produce any sign of toxicity and mortality. Hence one twentieth, one tenth and one fifth dose tested, i.e. 100, 200, 400 mg/kg p.o. was selected for the study.

MES induced seizure

MES produced various phases of epilepsy i.e. hind limb extension, flexion, clonus and stupor. Fig. 1 show, AqML extract at dose 400mg/kg p.o. significantly reduced all phases of epilepsy as compared with diseased control group. Decrease in the duration of hind limb extension was considered as protective action. AqML extract at dose 100, 200 and 400 mg/kg p.o. were significantly ($p<0.05$) reduced duration of hind limb extension. Standard drug phenytoin at a dose 25 mg/kg i.p. reduced all the phases of epilepsy significantly ($p<0.05$) as compared with disease control. (Table 1)

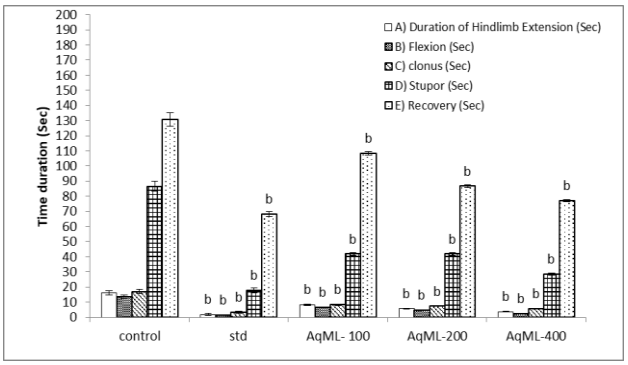

Figure 1: Effect of AqML on duration of hind limb extension, Flexion, clonus, stupor and recovery (Sec) in MES induced seizure test; a: $p<0.005$ b: $p<0.001$ with control group (one-way ANOVA is followed by Bonferroni test

PTZ Induced seizure

Administration of PTZ to mice produced myoclonic seizures in all animals.Onset of myoclonic spasm, onset of clonic seizure was significantly ($p<0.05$) delayed in all doses of AqML extract in comparison with disease control group. Duration of seizure was significantly ($p<0.05$) reduced at all selected dose as compared with diseased control group (Fig. 2, Table 2). Standard drug diazepam 5 mg/kg i.p. was completely abolishes the seizures and offered 100% protection. There was incidence of mortality in the group of animals treated with extracts excluding 400 mg/kg p.o. dose showed 50% survival. (Table 2)

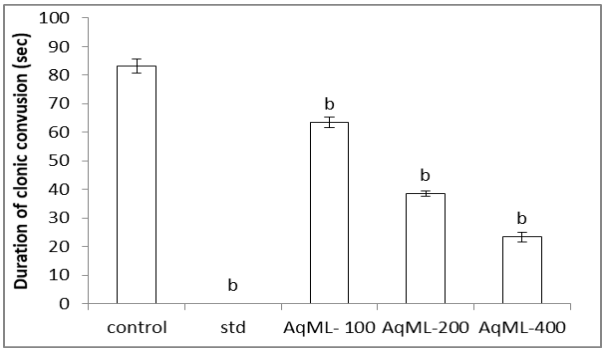

Figure 2: Effect of AqML on duration of clonic convulsion (Sec) in PTZ induced seizure test; a: $p<0.005$ b: $p<0.001$ with control group (one way ANOVA is followed by Bonferroni test)

Table 1: Effect of AqML against MES induced epilepsy

Treatment	Duration of HLE (Sec)	Flexion (Sec)	Clonus (Sec)	Stupor (Sec)	Recovery (Sec)
Disease control	16.00±1.367	13.67±1.256	17.00±1.582	86.50±3.233	130.83±4.400
Standard Phenytoin(25mg/kg)	1.83±0.601*[a]	1.33±0.211*[a]	3.33±0.843*[a]	17.83±1.493*[a]	68.33±1.606*[a]
AqML 100 mg/kg	8.33±0.422*[a, #a]	6.67±0.211*[a, #a]	8.33±0.422*[a, #a]	58.33±1.054*[a, #a]	108.33±1.054*[a, #a]
AqML 200 mg/kg	5.67±0.211*[a, #a]	4.67±0.211*[a, #a]	7.33±0.211*[a, #a]	41.83±0.749*[a, #a]	86.67±1.085*[a, #a]
AqML 400 mg/kg	3.67±0.211*[a, #a]	2.50±0.224*[a, #a]	5.67±0.211*[a, #a]	28.50±0.563*[a, #a]	77.17±0.703*[a, #a]

Values are Mean± SEM n= 6 in each group.
Statistical significant test for comparison was done by One-way ANOVA followed with Bonferroni t- test ($p<0.05$)
Plant extract treated groups are compared against disease control- *
Plant extract treated groups are compared against standard- #
a: $p<0.05$, NS- Non-significant

Table 2: Effect of AqML against PTZ induced epilepsy

Treatment	Onset Of Myclonic spasms After PTZ (sec)	Onset Of Clonic seizure After PTZ (sec)	Duration Of seizure (sec)	Mortality	% servival
Disease Control	98.50±3.373	116.67±4.543	83.17±2.548	6/6	0
Standard Diazepam(5 mg/kg)	0±0*[a]	0±0*[a]	0±0*[a]	0/6	100
AqML 100 mg/kg	172.17±2.414*[NS, #a]	189.67±2.813*[a, #a]	63.50±1.335*[a, #a]	6/6	0
AqML 200 mg/kg	246.17±4.483*[a , #a]	263.67±3.964*[a, #a]	38.50±0.847*[a, #a]	6/6	0
AqML 400 mg/kg	301.33±3.565*[a, #a]	318.83±3.208*[a, #a]	23.33±0.803*[a, #a]	3/6	50

Values are Mean± SEM n= 6 in each group.
Statistical significant test for comparison was done by One-way ANOVA followed with Bonferroni t- test (P<0.05)
Plant extract treated groups are compared against disease control- *
Plant extract treated groups are compared against standard- #
a: p<0.05, NS- Non-significant

Table 3: Effect of AqML against Li-pilocarpine induced epilepsy

Time after Pilocarpine(Min)	Disease Control	Standard Diazepam (5 mg/kg)	AqML 100mg/kg	AqML 200mg/kg	AqML 400mg/kg
15	1.67±0.211	0.50±0.224^{*a}	1.33±0.211$^{*NS, \#a}$	1.33±0.211$^{*NS, \#a}$	0.83±0.167 $^{*NS, \#a}$
30	2.83±0.167	0.50±0.224 ^{*a}	2.17±0.167$^{*a, \#a}$	1.83±0.167 $^{*NS, \#a}$	1.00±0.000 $^{*a, \#a}$
45	3.33±0.211	0.83±0.167 ^{*a}	2.67±0.211$^{*a, \#a}$	2.33±0.211 $^{*a, \#a}$	1.50±0.224$^{*a, \#a}$
60	3.67±0.211	1.33±0.334^{*a}	3.17±0.167$^{*NS, \#a}$	3.00±0.258 $^{*a, \#a}$	2.00±0.258 $^{*a, \#a}$
75	4.17±0.167	1.50±0.342^{*a}	3.67±0.211$^{*NS, \#a}$	3.33±0.211$^{*a, \#a}$	2.33±0.211$^{*a, \#a}$
90	4.50±0.223	1.67±0.334^{*a}	3.83±0.167$^{*a, \#a}$	3.67±0.211$^{*a, \#a}$	2.50±0.224$^{*a, \#a}$
120	4.67±0.211	1.17±0.307 ^{*a}	3.33±0.211$^{*a, \#a}$	2.83±0.167$^{*a, \#a}$	1.83±0.307$^{*a, \#a}$
150	3.83±0.167	0.50±0.224^{*a}	2.33±0.211$^{*a, \#a}$	2.00±0.258 $^{*a, \#a}$	1.33±0.211$^{*a, \#a}$
180	2.67±0.211	0.33±0.211^{*a}	1.67±0.211$^{*a, \#a}$	1.50±0.223$^{*a, \#a}$	0.83±0.167$^{*a, \#NS}$

Values are Mean± SEM n= 6 in each group.
Statistical significant test for comparison was done by One-way ANOVA followed with Bonferroni t-test (P<0.05)
Plant extract treated groups are compared against disease control- *
Plant extract treated groups are compared against standard- #
a<0.05, NS- Non-significant

Li-Pilocarpine induced seizure

Vehicle treated disease control group showed stage 4 and stage 5 seizures after 45 and 75 min respectively. The AqML at 400mg/kg p.o. significantly reduced the intensity of seizures as compared with disease control group and none of the animal exhibited stage 4 seizure. The standard drug diazepam 5mg/kg i.p. significantly diminished the intensity of seizures as compared with disease control and none of the animals exhibited stage 2 seizure and the animals were normal in behaviour after 180 min. The observations are given in Table 3.

DISCUSSION

Epilepsy is chronic disorder of central nervous system. Severe side effects and addiction liabilities associated with prescribed synthetic drugs that provoked the consideration of researchers towards natural sources. Traditional medicinal plants are considered as readily available, economical and effective medication sources. Medicinal plants can be used as alternative therapy for the management of epilepsy but scientifically proven data are lacking for activity of traditionally claimed plants. *M. longifolia* has been claimed to be traditionally useful in the treatment of epilepsy. Hence in the present study traditional claim about *M. longifolia* in treatment epilepsy was selected and screened for antiepileptic activity in animal models.

Seizures are occurred mainly due to imbalance of neurotransmitters in brain. Seizure take place whenever there is an imbalance or defects in Na+/Ca+2 ion conductance of the neuronal membrane, inhibition of GABA neuronal circuits, excitation of neurotransmitters glutamate, glycine and involvement of excitatory mechanism of NMDA, AMPA receptor channels for depolarisation [11]. Difficult to find out common neurochemical basis for human or experimental epilepsy but animal screening models are efficient tools to identify new antiepileptic compounds with clinical potential. Several animal models of epilepsy have been developed but MES and PTZ models are useful in early stage of AED discovery [12]. Hence, the aim of study was to assessment of the possible antiepileptic effects of *M. longifolia* in MES, PTZ and Li-pilocarpine in rodents.

The MES method is the first important investigational step for assessment of antiepileptic drugs in generalised tonic-clonic seizure because success rate is high for detection of clinically effective AEDs [13]. In MES test, mice received an electrical stimulus of sufficient intensity to induce maximal seizures of their hind limbs, with tonic extension as the end point of test [14, 15]. Phenytoin and Carbamazepine inhibit maximal electroshock induced hindlimb extension and are therefore effective in the treatment of generalised toniclonic seizure. Phenytoin and carbamazepine have mechanism to inhibit voltage gated Na+ channels or inhibition of glutaminergic excitation mediated by NMDA receptors [15,16].

The PTZ induced seizures are similar to the symptoms observed in the absence seizures, hence model represents valid model for generalized absence seizures [15]. Ethosuximide, Velproic acid, Diazepam, phenobarbitone drugs effective in PTZ induced seizure and its activity due to inhibition of the T-type of Calcium channels or mimicking GABA mediated neurotransmission in brain [15].

Status epilepticus is a medical emergency, resulting from continuous or repetitive grand mal seizure. The status epilepticus induced by lithium-pilocarpine increases brain contents of acetylcholine. Cholinomimetic convulsant pilocarpine is having high potency of producing sequence of behavioural alterations, which is followed by hippocampal damage and development of spontaneous recurrent seizures [17]. Diazepam drug is clinically effective drug and first choice of drug in status epilepticus.

In MES induced seizure, extract was able to produce dose dependant decrease the duration of hind limb extension, from which the extract at 400 mg/kg p.o. possesses significant (p<0.05) antiepileptic activity as compared with disease control. In PTZ model, extract at dose 400mg/kg p.o. significantly (p<0.05) reduces duration of convulsion and 50% survivality. In lithium-pilocarpine induced seizures, extract dose 400mg/kg p.o. showed significant (p<0.05) decrease in seizures

as compared with disease control group. 100, 200 and 400 mg/kg p.o. dose were used during screening, from that 400mg/kg p.o. dose showed potent antiepileptic activity against seizures induced in all screening models.

Since AqMLextract protects animals in MES, PTZ and lithium-pilocarpine induced seizure. It represents, AqML extract may showed activity against grandmal, petit mal epilepsy and status epilepsy. Probable protective action against epilepsy may be due to sodium channel blockage, NMDA blockage, Calcium channel blockage or may be due to mimicking action of neurotransmitter GABA. Moreover, MES and PTZ induced seizure models are associated with oxidative damage [18]. Hence antiepileptic activity may also be due to antioxidant property of *M. longifolia* [19].

Various plant origin chemical constituents particularly alkaloids, flavonoids, terpenoids, saponins and coumarins are reported to have antiepileptic activity in experimental animal models [20]. Since antiepileptic activity of *M. longifolia* may be due to presence of various phytochemicals like alkaloids, protein amino acids.

In further studies, there is need of investigation of the active compounds which are responsible for activity and their exact mechanism of actions responsible for antiepileptic activity of *M. longifolia*.

The world health organisation is encouraging to developing countries for use of herbal medicines, which they have been traditionally used [21]. Hence, our study provide base to develop herbal medicine and investigation of active compounds against convulsion.

CONCLUSION

In conclusion, AqML possess antiepileptic activity in screening models and these findings authenticate the traditional claim about use of *M. longifolia* in treatment of epilepsy. However, the exact mechanism and the active constituent involved in these effects need to be clarified in future studies, which could be a good alternative in treatment of epilepsy.

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