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Evaluation of Anti-Epileptic Activity of Leaves of Leucas Cephalotes

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ABSTRACT

Epilepsy is a neurological disorder characterized by recurrent seizures, affecting millions of people worldwide. Despite advancements in therapeutic interventions, there remains a need for novel and effective treatments with fewer side effects. This study aimed to evaluate the anti-epileptic potential of *Leucas cephalotes* leaves through experimental models. The leaves of *Leucas cephalotes* were collected, dried, and subjected to extraction using suitable solvents. The obtained extract was then evaluated for acute toxicity using standard guidelines. Subsequently, anti-epileptic activity was assessed using chemically induced seizure models in rodents. Behavioral observations, seizure latency, duration, and severity were recorded to determine the extract's efficacy. Preliminary phytochemical analysis of the extract revealed the presence of alkaloids, flavonoids, terpenoids, and phenolic compounds, which are known for their neurological effects. Acute toxicity testing indicated the safety of the extract at tested doses. In seizure models, the extract demonstrated a significant increase in seizure latency, reduction in seizure duration, and alleviation of seizure severity compared to control groups. These findings suggest that the leaves of *Leucas cephalotes* possess anti-epileptic properties, possibly attributed to the presence of bioactive compounds. Further studies are warranted to elucidate the underlying mechanisms and optimize dosage regimens for clinical application. *Leucas cephalotes* could emerge as a promising natural source for developing anti-epileptic agents with improved safety profiles.

KEYWORDS: Epilepsy, Leucas Cephalotes, Phytochemical Analysis, Bioactive Compounds.

INTRODUCTION

Epilepsy: A Neurological Disorder

Epilepsy is a neurological condition marked by unpredictable seizures and often co-occurs with depressive disorders. While pharmacotherapy for epilepsy has advanced with new drugs, treating depression in epilepsy remains challenging due to concerns about lowering seizure thresholds with antidepressants **[1].** Current treatments are limited to trial-based antidepressants, and there's a lack of specific drugs for this purpose. Antidepressants may lower seizure thresholds, while antiepileptic drugs can cause central nervous system depression [2]. Electroconvulsive therapy can help with depression but has limitations. Additionally, epilepsy drug therapy is hindered by side effects, teratogenic effects, and drug resistance in some patients [3]. This highlights the need for new remedies for depression in epilepsy without affecting

seizures. Traditional medicine, particularly plant-based remedies, may offer solutions with fewer side effects and antagonistic properties that could address both conditions effectively [4].

Types of Epilepsy and its Symptoms

Based on the type of behaviour and brain activity, seizures are divided into two broad categories:

- Generalized (local) seizures that are produced by electrical impulses from throughout the entire brain.
- Partial (focal) seizures that are produced (at least initially) by electrical impulses in a relatively small part of the brain [5].

Epidemiology of Epilepsy

Epilepsy is a significant neurological disorder, affecting about 50 million people worldwide and leading to substantial morbidity and mortality [6]. The prevalence of epilepsy ranges from 0.5-1% [7], with higher rates in developing countries due to factors like poor obstetric services and increased risk of brain infections and injuries. Access to treatment is challenging for many epileptic patients in developing nations [8]. Studies suggest a slightly higher incidence of epilepsy in males compared to females. Mortality among epileptic patients is notably higher, with sudden unexpected death in epilepsy (SUDEP) being a major cause [9]. SUDEP occurs in 1-3 per 1,100 epileptic patients per year and is more common in males, individuals aged 20-40, those with generalized seizures, and those resistant to medication.

Leucas cephalotes

Leucas cephalotes (Roth) Spreng. synonym *Phlomis cephalotes* belongs to family *Labiatae* or *Lamiaceae*. It is commonly known as Spiderwort and Dronapushpi (in Sanskrit). *L. cephalotes* is an annual herb that grows widely in India. According to Ayurveda, it is considered to be a stimulant, diaphoretic, insecticidal and emmenagogue. It is used in psoriasis, scabies, chronic skin eruptions as a blood purifier and eye diseases. It is used a homeopathic drug in the diagnosis of chronic malaria and asthma in many parts of India mainly in North India [10].

Material and method

Collection and authentication: - Fresh plants of Leucas cephalotes were collected from Varanasi near G.T road Rajatalab, it was found in waste agricultural lands, in month of October to February. The material was authenticated by taxonomist Dr. K.S. Negi (Principal Scientist) from N.B.P.G.R., Niglat, Bhowali, Uttarakhand having specimen no.P.S.01. The leaves of the plant were shade dried and grinded to powder and stored in airtight container.

Preparation of ethanolic extract of leaves of Leucas cephalotes: - 400gm of powder (shade dried) and powdered of L. cephalotes was first defatted with petroleum ether at room temperature for 72 h i.e. 3 days [11] and deffated materials was extracted with 70%v/v ethanol for another 72 hrs by maceration process. Then, extract allowed standing for 72 hrs with occasional shaking. Then, extract were filtered by whatman filter paper. The resultant ethanolic extract was concentrated using rotatory evaporator at 40°C under reduced pressure and dried at water bath (45^0c) finally the extracts were weighed and stored at -20°C till their usage in different tests [12].

Preliminary Phytochemical Screening

The freshly prepared ethanolic extract were subjected to preliminary phytochemical screening for the detection of various phytoconstituents, the chemical investigation with reagents showed the presence of

flavanoids, phenol, phytosterol, terpens and tannins [13]. Phytochemical examinations were carried out for all the extracts as per the standard methods

1) Tests for Glycosides:

About 2 ml of each extract was taken and subjected to the following tests:

Borntrager's test: In 3 ml extract, dilute H_2SO_4 was added then boiled and filtered, after cooling of filtrate equal volume of benzene and chloroform was added and then 0.5 ml of dilute ammonia solution was added. Ammonical layer turned reddish pink or red colour indicated the presence of anthraquinone glycosides.

Legal test: Aqueous and alcoholic extract was taken in separate test tube and then freshly prepared sodium nitroprusside (1ml) and pyridine (1ml) solution was added to the solution and observed for the formation of pink to red colour indicating the presence of cardiac glycosides. [14].

Foam Test: 0.5 gm of extract was shaken with 2 ml of water. If foam produced persists for ten minutes it indicates the presence of saponin glycosides.

2) Tests for Alkaloids:

The aqueous, alcoholic and chloroform extracts were evaporated separately. To residue, dilute HCl was added and shake well, then filtered.With filtrate,perform following tests:

Dragendroff's reagent: To 2-3 ml of filtrate was taken, few drops of Dragendroff's reagent were added. It was given orange brown precipitate [14].

Mayer's reagent (potassium mercuric iodide reagent): Few drops of Mayer's reagent when added in plant extract, formed yellow coloured precipitate which showed the presence of alkaloids **(Tiwari et al., 2011).**

Wagner's reagent (Iodine-potassium iodide): 2-3 ml of plant extract mixed with few drops of Wagner's reagent formed reddish brown precipitate, indicated the presence of alkaloids.

3) Test for Flavonoids

Shinoda test: A small quantity of test residue was dissolved in 5 ml ethanol (95% v/v) and reacted with few drops of concentrated hydrochloric acid and 0.5 g of magnesium turnings. Orange, pink, red to purple colour appeared the presence of flavonoids was indicated [14].

Sulphuric acid test: On addition of sulphuric acid into plant extract, flavones and flavonols dissolved into it, given a deep yellow solution.

Lead acetate Test: Extract was treated with few drops of lead acetate solution. Formation of yellow coloured precipitate indicated the presence of flavonoids **(Tiwari et al., 2011).**

Zinc Test: The test solution was heated with zinc and HCl, pink to red colour observed.

4) Tests for Tannins and Phenolic compounds:

Few drops were added of following reagents into few ml of plant extract indicated tannins and phenolic compound.

Ferric chloride test: Extract was treated with 3-4 drops of ferric chloride solution, formation of bluish black colour showed the presence of phenols **(Tiwari et al., 2011).**

Lead acetate solution: Extract gave white precipitate.

Acetic acid solution: Red colour solution appeared [14].

5) Test for Proteins

Biuret test (General test): To 3 ml of extract 1 ml of 4% sodium hydroxide solution was added and few drops of 1% solution of copper sulphate were also added. Violet colour was obtained and indicated the presence of proteins.

Millon's test (Mercuric nitrate solution): Mixed 3 ml plant extract with few drops of Million's reagent white precipitate observed that slowly turned pink after warming.

6) Test for Fats and Oils

Solubility test: Oils are soluble in ether, benzene and chloroform but insoluble in 90% ethanol and water [14].

Filter paper gets permanently stained with oils.

7) Tests for Steroids

Salkowaski reaction: 2 ml of extract was taken in 2 ml of chloroform and 2 ml of concentrated sulphuric acid were added from the side of the test-tube. The test tube was shaken for few minutes. Development of red colour in the chloroform layer and greenish colour in acid layer indicated the presence of sterols.

8) Test for Sugars and Carbohydrates

Molish's test (General test): 2-3 ml of aqueous extract was taken and added into few drops of α-naphthol solution in alcohol then shaken and added 1ml of concentrated sulphuric acid from the sides of the test tube. A violet ring is formed at junction of two liquids indicated the presence of sugars.

Barfoed's test: Mixed equal volume of plant extract and Barfoed's reagent. Red precipitate of cuprous oxide was formed indicating the presence of monosaccharides, after boiling on water bath and cooled.

Fehling's solution test: 1ml Fehling's solution A and 1ml B were mixed and boil for 1 minute. Then added equal volume of plant extract and boiled on water bath for 5 minute firstly yellow and then brick red precipitate was observed [14].

In-Vivo animal studies

Animals

Albino mice of male sex weighing 25-50gm were used for study. They were housed in standard cages under room temperature (24 ± 2°C), relative humidity (60% -70%) and exposed to 12:12 h light: dark cycle. The mice were fed with standard diet and water ad libitum [15].

Then animals were acclimatized to the laboratory conditions one week before the experiment.

Experimental protocols were approved by the Institutional Animal Ethics Committee and IAEC was approved by CPCSEA.

Drugs

The chemicals and drugs were used in experimental study as follows-

Carboxymethylcellulose (CMC), diazepam, pentylenetetrazole and test compound: The drug was natural plant extract. The extract was weighed 0.01 g and 0.02 g for 100 mg/kg or 200 mg/kg p.o respectively suspended in 0.2% CMC in distilled water.

Pharmacological Evaluations

Antiepileptic activity (Pentylenetetrazole-induced seizure test)

The method has been described previously [16]. Male albino mice were divided into four groups (n=6). The extract (100 and 200mg/kg p.o.) was administered to two groups while diazepam (2 mg/kg i.p) was given standard group and the control group administered 0.2% CMC. After 1 hour and 30 minutes of treatment with drugs orally and intraperitoneally respectively, each mouse was administered pentylenetetrazole, (40mg/kg) intraperitoneally. Then, animals were placed individually in clear plastic cages and observing onset of seizures, duration of seizure and intensity of seizure.

The animals in the various groups were treated as follows: -

a) **Control Group:** 0.2% aqueous suspension of CMC in distilled water (1 ml/100 gm) was given as vehicle orally, after 1hr pentylenetetrazole administered intraperitoneally.
b) **Test Group (T_1):** Aqueous suspension of ethanolic extract of L. cephalotes 100 mg/kg (1 ml/100 gm) with 1% gum acacia as 2% suspension in distilled water, orally after 1hr pentylenetetrazole administered intraperitoneally.
c) **Test Group (T_2):** Aqueous suspension of ethanolic extract of L. cephalotes 200 mg/kg (1 ml/100 gm) with 1% gum acacia as 4% suspension in distilled water, orally after 1hr pentylenetetrazole administered intraperitoneally.
d) **Standard Group:** Aqueous diazepam 2mg/kg (1 ml/100 gm) with 1% gum acacia as 0.4% suspension in distilled water, i.p after 30 min pentylenetetrazole administered intraperitoneally.

Rota rod test: - This was performed after observing seizure intensity using rotarod. All animals are previously given training on rotating rotarod at 10rpm for 5mins before commencements of treatment. The animals were placed on the rotating rota rod and latency to fall in seconds from the rotarod was noticed.

Forced swimming test: - After motor coordination test, animals were subjected for forced swimming test to assess depressive behaviour. In this test, animals were placed individually in glass cylinder ($25\times12\times25cm^3$) containing water at room temperature upto a level of 15cm for 5min and total immobility period in seconds was noted. The animals were judged to be immobile when they stopped struggling and remained floating motionless in water, making only those movements necessary to keep their head above water.

Phytochemical Analysis

The plant *Leucas cephalotes* was collected, authenticated and extracted with 70% v/v ethanol. The percentage yield of the extract was found to be 17.36% w/w. The preliminary phytochemical studies revealed the presence of flavonoids, carbohydrates, tannins, glycosides, steroids and phenolic compounds in hydro-ethanolic extract of *Leucas cephalotes*.

Table 1. Phytochemical screening of hydro-ethanolic extract of *Leucas cephalotes*

S.No.	Phytoconstitutents	Present/Absent
1.	Carbohydrates	+
2.	Glycosides	+
3.	Flavonoids	+
4.	Steroids	+
5.	Alkaloids	-
6.	Proteins	-
7.	Saponins	-
8.	Tannins	+
9.	Phenolic Compounds	+

(+) Present; (-) Absent

Recent investigations have proved that free radical scavenging activity of the plants is due to their flavonoids content. As far as the present research work is concerned, free radicals play a major role in lipid peroxidation, brain edema, dysfunction, leading to seizures in epilepsy. So, an investigational herb should possess flavonoids in order to combat the same. In the phytochemical screening carried out for *Leucas*

cephalotes, presence of flavonoids and phenolic compounds was confirmed and only then *L. cephalotes* was investigated further for its antiepileptic activity.

Antiepileptic activity

For the antiepileptic study, pentylenetetrazole was used to induce seizures in mice. Onset of seizures and duration of hind limb extension was recorded to assess the antiepileptic efficacy of *L. cephalotes*.

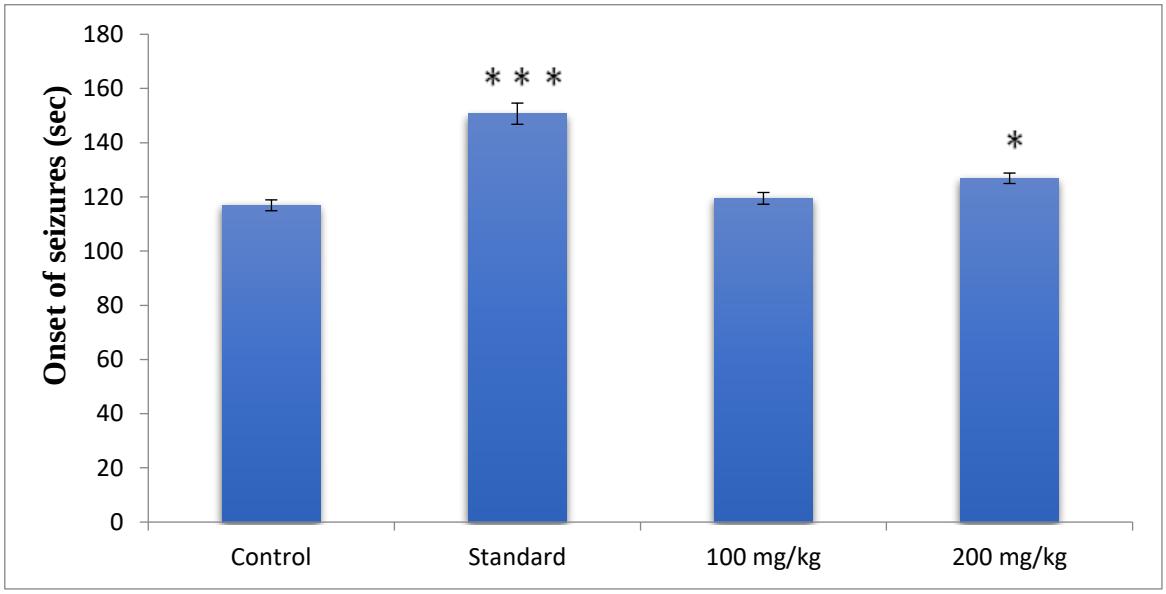
Table 2. Effect of hydro-ethanolic extract of *Leucas cephalotes* and diazepam on PTZ induced seizures in mice

Groups	Onset of seizures (sec)	Duration of hind limb extension (sec)
Control	116.893 ± 2.003	134.593 ± 10.787
100 mg/kg	119.465 ± 2.168	107.43 ± 11.92
200 mg/kg	126.87 ± 1.935*	98.595 ± 11.64*
Diazepam(2mg/kg)	150.713 ± 3.918***	45.751 ± 3.054***

Values are expressed as mean ± SEM, (n=6), symbols * corresponds to $p<0.05$ and *** corresponds to $p<0.001$ compared to control.

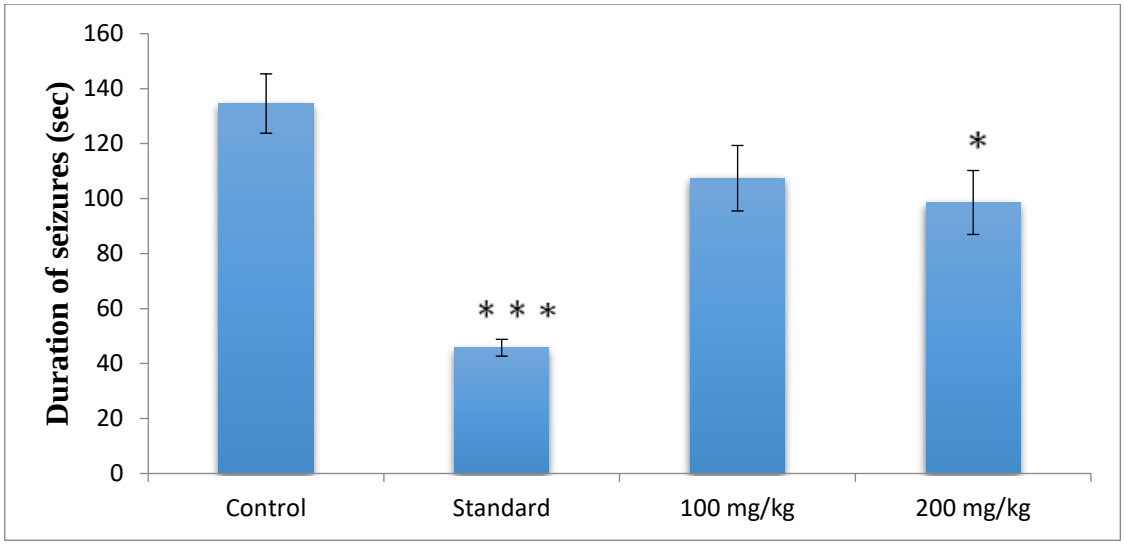
In the diazepam treated group, significant ($p<0.001$) delay in the onset of seizures was observed as compared to control group. Delay in the onset of seizures was also observed in the treatment groups that showed antiepileptic efficacy of hydro-ethanolic extract of *L. cephalotes*. Higher dose (200 mg/kg) of the extract showed significant ($p<0.05$) efficacy in delaying the onset of seizures.

Figure 1. Effect of *Leucas cephalotes* hydro-ethanolic extract on onset of seizures. Values are expressed as mean ± SEM, (n=6), symbols * corresponds to $p< 0.05$ and *** corresponds to $p<0.001$ compared to control.



In control group, hind limb extension was found to be more possibly due to more free radicals produced in the brain by pentylenetetrazole as compared to the other groups. Significant ($p<0.001$) decrease in the duration of hind limb extension was observed in the standard (diazepam treated) group that showed the already established highly potent antiepileptic efficacy of diazepam. Reduction in the duration of hind limb extension was also observed in the treatment groups that showed antiepileptic efficacy of *L. cephalotes* hydro-ethanolic extract as well. Although, lower dose (100 mg/kg) of *L. cephalotes* extract did produced reduction in the duration of hind limb extension, but only the higher dose (200 mg/kg) of the extract showed significant ($p<0.05$) effect.

Figure 2. Effect of *Leucas cephalotes* hydro-ethanolic extract on duration of hind limb extension. Values are expressed as mean ± SEM, (n=6), symbols * corresponds to p<0.05 and ***corresponds to p<0.001 compared to control.



Intensity of Seizures

For recording the intensity of seizures, a scoring system was generated and scoring of each animal was done in accordance with the under mentioned scores:

Score 0: No response
Score 1: Ear and facial twitching
Score 2: Hind limb extension
Score 3: Turn over side position
Score 4: Deat

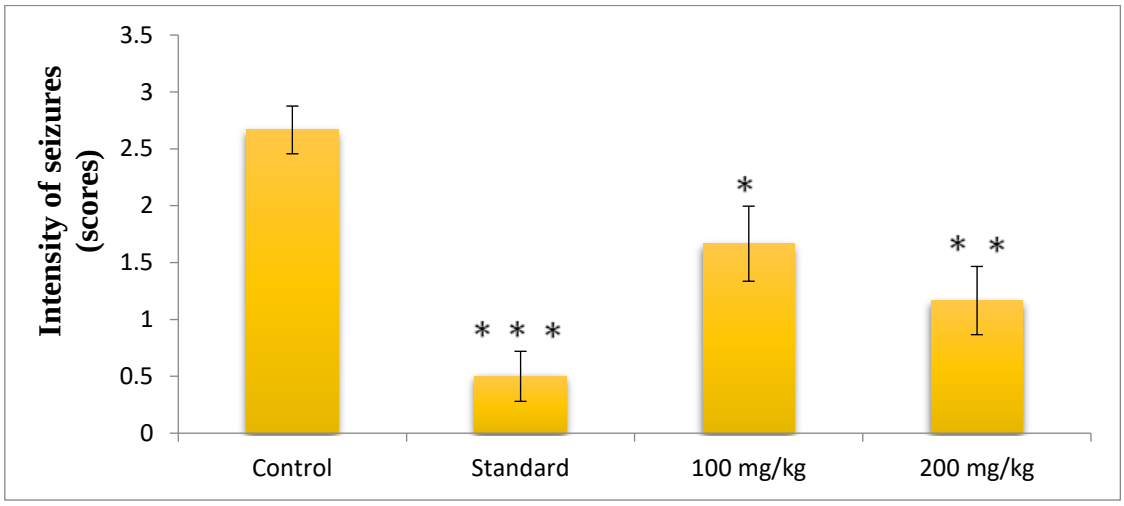
Table 3. Effect of hydro-ethanolic extract of *Leucas cephalotes* and diazepam on intensity of seizures

Groups	Intensity of seizures (scores)
Control	2.66 ± 0.21
100 mg /kg	1.66 ± 0.33 *
200 mg/kg	1.16 ± 0.30 **
Diazepam (2 mg/kg)	0.5 ± 0.22 ***

Values are expressed as mean ± SEM, (n=6), symbols *corresponds to p<0.05, ** corresponds to p<0.01 and *** corresponds to p<0.001 compared to control.

On the basis of the scores allotted to each group, the animals treated with *L. cephalotes* extract were found to be with reduced score of intensity of seizures as compared to the control group. *L. cephalotes* extract showed dose dependent efficacy in reducing the intensity of seizures of mice as compared to the control group, the higher dose (200 mg/kg) being more significant (p<0.01) in reducing the score of intensity of seizures as compared to the p<0.05 significance level of the lower dose (100 mg/kg). But, the potential of reducing the intensity of seizures was less as compared to the standard drug, diazepam that showed highly significant (p<0.001) reduction in the intensity of seizures in pentylenetetrazole treated mice.

Figure 3. Effect of *Leucas cephalotes* hydro-ethanolic extract on intensity of seizures. Values are expressed as mean ± SEM, (n=6), symbols * corresponds to p< 0.05, ** corresponds to p<0.01 and ***corresponds to p<0.001 compared to control.



Test for depressive behaviour and motor in-coordination

The major drawbacks associated with most antiepileptic drugs are their tendency to cause depression and motor in-coordination. In order to rule out this disadvantage, antidepressant and motor coordination activities of hydro-ethanolic extract of *L. cephalotes* were evaluated using forced swimming test and rota rod test, respectively.

Antidepressant activity: Forced swim test

Antidepressant activity was performed using forced swim test and observations were recorded as immobility time in seconds.

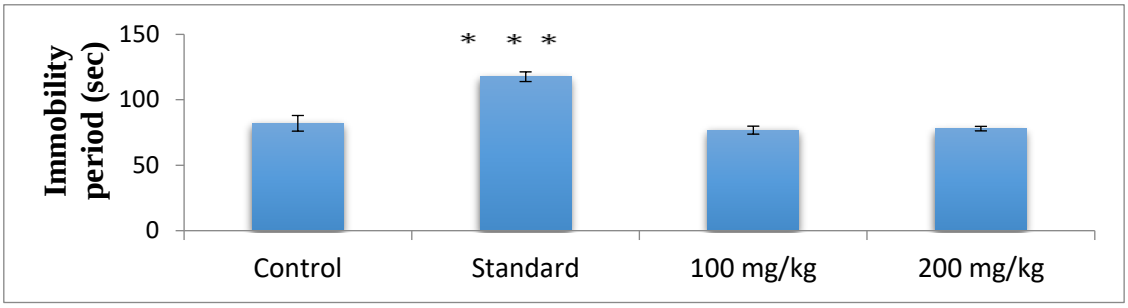
Table 4. The protective effect of hydro-ethanolic extract of *Leucas cephalotes* on immobility tim

Groups	Immobility time (sec)
Control	82.0533 ± 5.966
100 mg /kg	76.845 ± 3.049
200 mg/kg	77.978 ± 1.733
Diazepam (2 mg/kg)	117.651 ± 3.690***

Values are expressed as mean ± SEM, (n=6), symbol ***corresponds to p<0.001 compared to control.

The animals treated with *L. cephalotes* extract were found to be with increased alertness unlike the diazepam treated group that showed depressive behaviour. Significant increase in the immobilization time was observed in diazepam treated group as compared to the control group indicating the depressive behaviour of the drug. Both the doses of the *L. cephalotes* extract exhibited non-depressive behaviour which was evident from their very less immobility time that was comparable to the control group.

Figure 4. Effect of *Leucas cephalotes* hydro-ethanolic extract on immobility period (sec). Values are expressed as mean ± SEM, (n=6), symbol * corresponds to p<0.001 compared to control.**



Motor coordination activity: Rota rod test

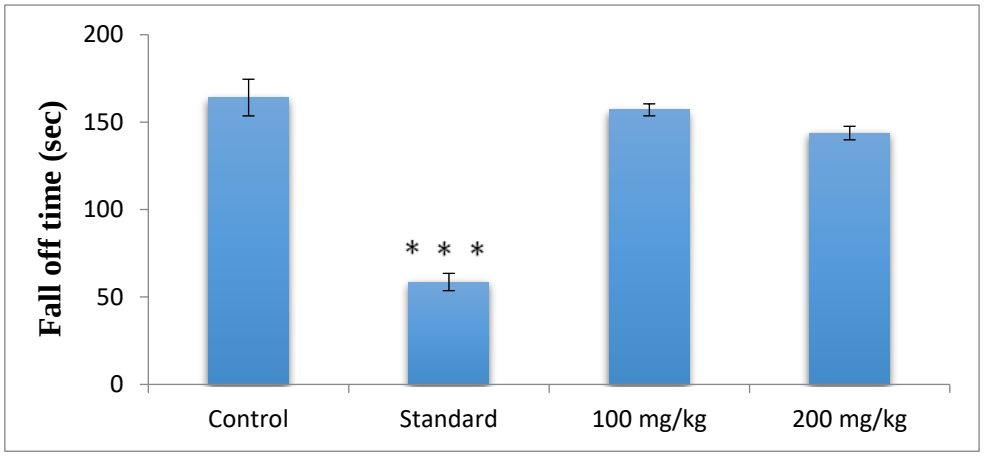
Motor coordination activity was performed using rota rod apparatus and observations were recorded as fall off time of mice from rota rod apparatus in seconds.

Table 5. The protective effect of hydro-ethanolic extract of *Leucas cephalotes* on motor coordination

Groups	Rota rod (Fall off time) sec
Control	164.03 ± 10.497
100 mg /kg	157.003 ± 3.427
200 mg/kg	143.748 ± 3.878
Diazepam (2 mg/kg)	58.561 ± 4.95***

Values are expressed as mean ± SEM, (n=6), symbol *** corresponds to p<0.001 compared to control. Both the doses of *L. cephalotes* extract protected the animals from impairment of motor coordination as was evident from their fall off time from rota rod apparatus which was comparable to that of control group. On contrary, diazepam significantly (p<0.001) reduced the fall off time of rats as compared to control group.

Figure 5. Effect of *Leucas cephalotes* hydro-ethanolic extract on motor coordination. Values are expressed as mean ± SEM, (n=6), symbol * corresponds to p<0.001 compared to control.**



CONCLUSION

From the antiepileptic study of hydro-ethanolic extract of *Leucas cephalotes* in Albino mice it was demonstrated that hydro-ethanolic extract of *L. cephalotes* possesses protective efficacy against pentylenetetrazole (PTZ) induced seizures. Pentylenetetrazole induced seizures mimic the increased oxidative stress in brain by altering membrane phospholipid metabolism and ultimately results in the release of free radicals. Oxidative stress is one of the underlying mechanisms of epilepsy. The protective effect of the extract may be due to its flavonoids and phenolic contents, presence of which was confirmed during the phytochemical evaluation. Duration of hind limb extension was found to be more and onset of seizures was found to be fast in control group which may be due to no protection offered against the free radicals produced in the brain by PTZ as compared to other groups that received treatment. Reduction in duration of hind limb extension and delay in onset of seizures were observed in *L. cephalotes* treated groups, but the higher dose produced significant effect. *L. cephalotes* showed dose dependent efficacy in reducing intensity of seizures of mice as compared to the control group, the higher dose being more significant in reducing the intensity of seizures as compared to the lower dose. Being potential free radical scavengers, flavonoids and phenolic contents in *L. cephalotes* extract might have protected the mice from oxidative damage and hence a decrease in the duration of hind limb extension, intensity of seizures and delay in the onset of seizures was observed.

Depression and motor in-coordination are the most reported side effects of antiepileptic drugs, therefore antidepressant and motor coordination activities were carried out using forced swim test and rota rod test, respectively to evaluate the depressive behaviour and motor coordination impairment of the extract as well. In forced swim test, hydro-ethanolic extract of *L. cephalotes* showed non depressive behaviour which was clearly evident from their immobility time which was comparable to the control group, but in the standard group increase in the immobility time was observed which clearly indicates its depressive behaviour. In rota rod test, hydro-ethanolic extract of *L. cephalotes* protected the animals from motor in-coordination side effects which were evident from their fall off time from rota rod apparatus, but in diazepam treated group the fall off time was highly reduced as compared to the control group. Both these favourable results show that the *L. cephalotes* extract has potential to cure epilepsy without inducing depression and without impairing motor coordination. Hence, it can be concluded that *L. cephalotes* possesses potential antiepileptic activity and requires further investigation for determining its mechanism of action and for it to be established as a treatment for epilepsy.

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