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Original Research Article

The antiepileptic promise of Vigna unguiculata (L.) Walp (Cowpea): A preclinical investigation in rats

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Abstract

Background: Epilepsy is the common neurological disorder that affects the quality of life and poses a health hazard as well as an economic burden on society. Approximately 50 million individuals globally are afflicted with epilepsy, with 5 million new diagnoses annually. Patients with epilepsy, especially the 20-30% whose seizures are not fully controlled with available drugs (drug-resistant epilepsy) have a significantly increased risk of death, as well as psychiatric and somatic comorbidities and adverse effects from antiepileptic drugs. Herbal remedies may offer a viable approach to controlling and treating epilepsy, often with fewer adverse effects compared to synthetic medications. A well-known medicinal plant named *Vigna unguiculata* (L.) Walp have a rich history of usage, demonstrating various pharmacological properties such as CNS depressant, antioxidant, anthelmintic, antifungal, antibacterial, and antimicrobial effects.
Objectives: The primary aim of this study is to propose an approach integrating traditional medicinal practices with experimental pharmacology to explore potential remedies for treating epilepsy.
Materials and Methods: The evaluation of antiepileptic activity of AEVU in Wistar albino rats was done by using Maximal Electro Shock (MES) and Isoniazid (INH)-induced convulsions models. Through histopathological analyses, we aimed to reassess its potential for managing epilepsy.
Results: Examination of the MES and INH-induced convulsions models showed a reduced onset time of convulsions and significantly increased recovery rates. This suggests a potential improvement in GABAergic transmission. The AEVU demonstrated the neuroprotective action addition to histological analysis.
Conclusion: The results of this study indicate that aqueous seed extracts of *Vigna unguiculata* (L.) Walp exhibit antiepileptic activity.

Keywords: Epilepsy, *Vigna unguiculata* (L.) Walp, *In-vivo* study, Histopathology.

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1. Introduction

Epilepsy is the most common and chronic neurological disorder that damages brain cells.[1] It is marked by sudden recurrent episodes of sensory disturbance, loss of consciousness or convulsions which are associated with abnormal electrical activity in the brain.[2-4]

Epilepsy can be caused by any of the following, according to the International League Against Epilepsy (ILAE): (1) At least two unprovoked (or reflex) seizures happening more than 24 hours apart; (2) one unprovoked (or reflex) seizure and a likelihood of subsequent seizures equal to the general recurrence risk (at least 60%) following two unprovoked seizures occurring during the next 10 years; 3) An epileptic syndrome's identification.[5,6]

The World Health Organization estimates that over 80% of the global population continues to rely primarily on conventional medicine for their healthcare needs.[7] Nonetheless, there is a rising interest in exploring natural sources which are presenting a valuable avenue for discovering new medicinal agents.[8] While many complementary and herbal remedies currently widely utilized require rigorous evidence of efficacy and safety from well-controlled scientific trials.[9]

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Many people with active epilepsy do not receive appropriate treatment for their condition, leading to a large treatment gap. It has also been observed that the presently available antiepileptic drugs are associated with serious side effects.[10] The traditional system is believed to be an important source of chemical substances with potential therapeutic effects. There is mounting evidence that a number of herbal remedies, including *Ginkgo biloba* (Ginkgo trees),[11] *Withaniasomnifera* (Ashwagandha),[12] *Bacopa monnieri* (Bramhi), *Hypericum perforatum* (St. Jhon's wort), and *Piper methysticum* (Kava strub) may be effective in the treatment of seizure problems.[13]

Vigna unguiculata (L) Walp is one of the plants in the Fabaceae/Papilionaceae family. It is an African native that is widely cultivated around the world.[14] The seeds of this plant are rich in saponins, thiamine, riboflavin, niacin, vitamin B_6, glycosides, foliate, glycosides, and steroids, along with trace minerals such as iron, sodium, zinc, selenium, manganese and copper.[15] In various regions of India, these seeds are utilized for various purposes and have demonstrated therapeutic properties including antidepressant, antioxidant, antipyretic, diuretic, antidiabetic and antibacterial effects.[16] Considering the documented therapeutic uses of these seeds, this study aimed to assess their antiepileptic potential through an experimental pharmacology.[17,18]

2. Materials and Methods

2.1. Preparation of aqueous extract of seeds

Identification and authentication of the brown seeds of *Vigna unguiculata (L)* Walp were done by Dr Harsha Hedge ICMR Belgaum; India, with accession number RMRC-1660; which were collected from the nearby location. Further, the seeds were cleaned and washed with tap water. Drying wad done under the shade and later processed for grinding into coarse powder. Extraction process conducted using cold maceration method. For this 5g of powder was weighed and macerated with 250 ml of distilled water in an airtight container for 3 days with vigorous shaking. After 3 days, the extract was taken and kept for evaporation at room temperature, corresponding to a 13.8% yield. The dried extract was collected and kept at -4°C in an airtight container.[19]

2.2. Experimental animals and management

The study was approved by the Institutional Animal Ethical Committee (IAEC) under the registration number 2102/PO/ReBi/S/20/CPCSEA. A total of 30 Wistar albino rats, of either sex and weighing approximately 180-200 grams, were sourced from Adita Biosys Private Limited, located on Madhugiri Road, Tumakuru, Karnataka. The experimental study was conducted under the CPCSEA's guidelines for the use and care of experimental animals. Throughout the study, the animals were housed in good condition with a 12-hour day-night pattern with a room temperature of 20°C (±3°C) and a relative humidity of 44–60%, respectively. Animals were fed standard rodent pellet feed and water ad libitum.[20]

2.3. Physicochemical and phytochemical analysis

To analyse the purity and the presence of active compounds, the crude extract and its aqueous fractions underwent quantitative and qualitative preliminary phytochemical screening for their organoleptic characteristics, loss of drying, percentage extract yield, ash value, and presence of active phytoconstituents by following and the standard procedures.[21,22]

2.4. Acute oral toxicity study

The acute oral toxicity study was conducted according to the Organization for Economic Co-operation and Development (OECD) guideline number 425.[23] The AEVU was tested in three female Wistar albino rats at a dose of 5000 mg/kg body weight for its toxicity screening. Animals received single dose of extract and observed for its potential harmful effects during 24 hours and later for continue 14 days. The toxicity screening was conducted under the 5th category dose with special relevance to animal and human safety.[24]

2.5. Evaluation of antiepileptic activity: In-vivo study

Five groups were taken to evaluate antiepileptic activity using the MES and INH-induced convulsion models. Each group consists of six rats. The study started with introducing respected doses into the treatment groups of AEVU for 14 days before going for the main study.[25] After 15 days, of course, the other groups received respected treatments at the time of the main study.

Group I (Control group) - received normal food and water.
Group II (Toxic control) - received normal saline p.o.
Group III (Standard control) - received phenytoin 25 mg/Kg p.o.
Group IV (Test I control) - received the AEVU at doses of 200 mg/Kg p.o.
Group V (Test II control) - received the AEVU at doses of 400 mg/Kg p.o.

2.5.1. Maximal electro shock (MES)-induced convulsions model

After giving the respected treatment to each group, convulsions were induced in all groups except the control group using an electroconvulsio meter after 30 and 60 min (p.o. and i.p., respectively) using ear electrodes. A 60 Hz alternating current of 150 mA strength caused MES seizures that lasted for 0.2 seconds of shock time. The different phases of convulsions (tonic flexion, tonic extension, clonic and stupor) were observed and tabulated.[26]

2.5.2. Isoniazid (INH)-induced convulsions model

Clonic tonic convulsions were induced with the help of Isoniazid 300 mg/kg body weight i.p. after 30 and 60 min (p.o. and i.p., respectively of receiving the standard and test treatment). Every animal from each group was closely

watched for 30 minutes to see whether any convulsions occurred. The proportion of protection was computed, and the latency of convulsions was noted. Following cervical dislocation, the whole brain was removed from each animal and preserved separately in 10% formalin for histological analysis.[27]

2.6. Statistical evaluation

The results were expressed as mean ± S.E.M. and analyzed using GraphPad Prism software, version 8.0.1. Statistical comparisons were conducted using Dunnett's t-test. Significance levels were denoted as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ns for non-significant results.

2.7. Histopathological evaluation

The goal of histological methods is to produce sections of high quality that may be utilized for a light microscopic analysis of alterations in human or animal tissue in either naturally occurring or triggered disorders. For this study, extracted brain tissues were preserved initially with 10% neutral formalin, later covered with paraffin, and manually sectioned using a microtome in order to produce 4-5 µm-thick paraffin slices. Then de-waxed sections were stained with hematoxylin and eosin (H&E) for histopathological evaluation. All the clarification was made via 40x magnification.[28,29]

3. Results

3.1. Physicochemical and phytochemical evaluation

The extracts, characterized by their brown colour, aromatic odor, solid consistency, and slightly bitter taste, were subjected to further physicochemical and phytochemical evaluations. The physicochemical analysis of the dried seed powder revealed its purity, with a total ash value of 9.5%, water-soluble ash of 1.33%, and acid-insoluble ash of 2.33%. Additionally, the water and alcohol-soluble extractive values were found to be 13.8% and 6.5%, respectively. Based on these findings, water was selected as the extractive solvent. A comprehensive physicochemical examination of the aqueous extracts of *Vigna unguiculata* (L.) Walp revealed the presence of carbohydrates, amino acids, steroids, glycosides, saponins, flavonoids, and tannins. The study highlighted that certain amino acids, glycosides, and steroids possess central nervous system (CNS) depressant properties, which informed the basis of this study.

3.2. Acute toxicity study

The acute toxicity study conducted in accordance with OECD Guideline 425 demonstrated that *Vigna unguiculata* (L.) Walp seed extract did not induce any toxicological signs or mortality in female Wistar albino rats over the 14-day observation period, even at the highest administered dose of 5000 mg/kg body weight. As such, the estimated LD_{50} for the extract is predicted to exceed 5000 mg/kg body weight.

3.3. MES induced convulsions

Table 1 compared to the toxic control group, both the Test I and Test II control groups exhibited a significant reduction in convulsion duration, accompanied by an increase in the protection rate. The standard group, receiving phenytoin at 25 mg/kg body weight, showed no tonic convulsions and a high protection rate. Notably, the Test II control group demonstrated a promising effect when compared to the standard treatment group.

Table 1: Effect of AEVU in MES induced convulsions model

S. No.	Animal Groups	Time in Second				Recovery rate in %
		Flexion	Extension	Clonus	Stupor	
1.	Toxic control	3.500±0.2236	14.83±0.945	15.83±1.046	129.7±5.308	33.3
2.	Standard	0.0±0.0***	0.0±0.0***	9.00±0.3651***	32.17±2.08***	100
3.	Test I	1.667±0.5578*	8.50±1.979*	12.83±0.7032*	104.2±4.498*	50
4.	Test II	1.333±0.614**	6.667±2.171**	10.83±0.702**	49.83±0.833**	83.33

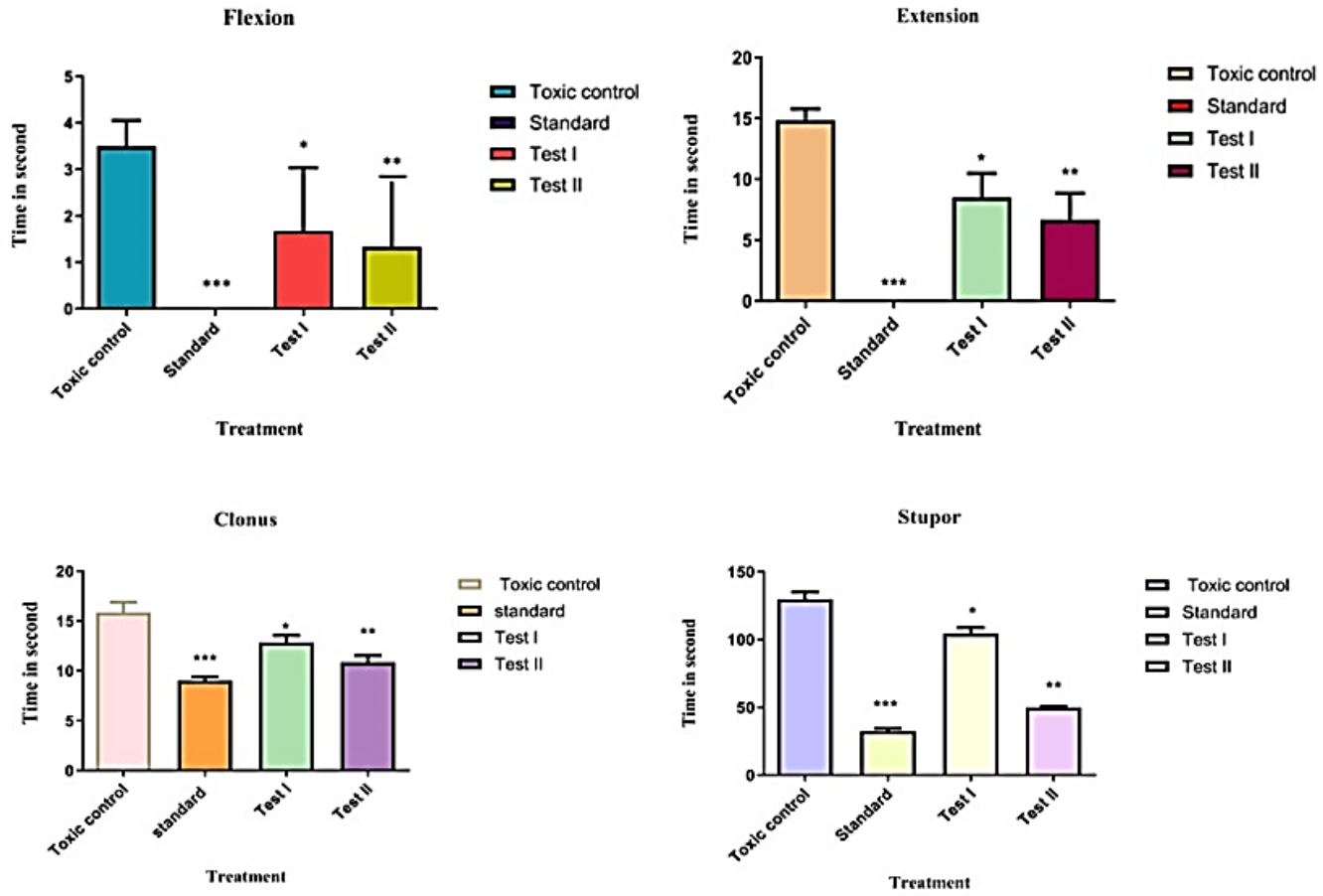

Figure 1: The values are expressed as the mean ± SEM for all four groups at the different phases of convulsions. Statistical comparisons were performed using one-way ANOVA, followed by Dunnett's t-test. The significance levels are denoted as: *p < 0.05, p < 0.01, *p < 0.001*, with "ns" indicating non-significant differences. The results demonstrated that AEVU produced a dose-dependent and statistically significant reduction in various stages of epileptic seizures

Table 2: Effect of AEVU in INH induced convulsions model

S. No	Animal groups	Time in second		Recovery rate in %
		Onset of Convulsions	Duration of Convulsions	
1	Toxic control	95.33±3.887	77.17±1.424	16.66
2	Standard	469.8±95.45***	9.333±6.173***	100
3	Test I	287.3±18.91*	57.50±2.997*	66.66
4	Test II	352.2±33.74**	23.17±7.490**	83.33

3.4. INH induced convulsions model

Table 2 compared to the toxic control group, pretreatment of rats with 200 mg/kg (Test I) and 400 mg/kg (Test II) of AEVU results in a substantial increase in recovery rate, while the standard group exhibits a higher recovery rate with a shorter period of convulsions. Significantly, the Test II control group showed a noteworthy effect when compared to the standard treatment group.

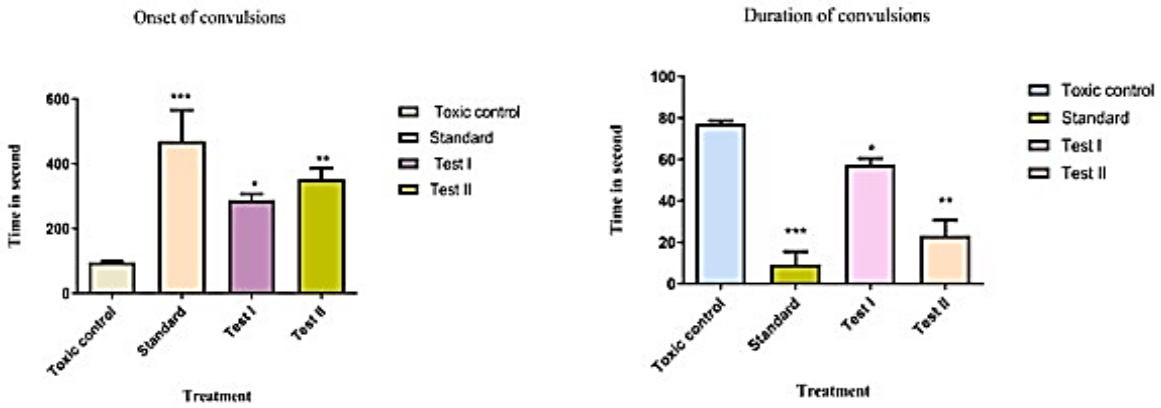

Figure 2: The values are expressed as the mean ± SEM for all four groups at the different phases of convulsions. Statistical comparisons were performed using one-way ANOVA, followed by Dunnett's t-test. The significance levels are denoted as: *p < 0.05, p < 0.01, *p < 0.001*, with "ns" indicating non-significant differences. The results demonstrated that AEVU produced a dose-dependent and statistically significant reduction in various stages of epileptic seizures

3.5. Histopathological evaluation

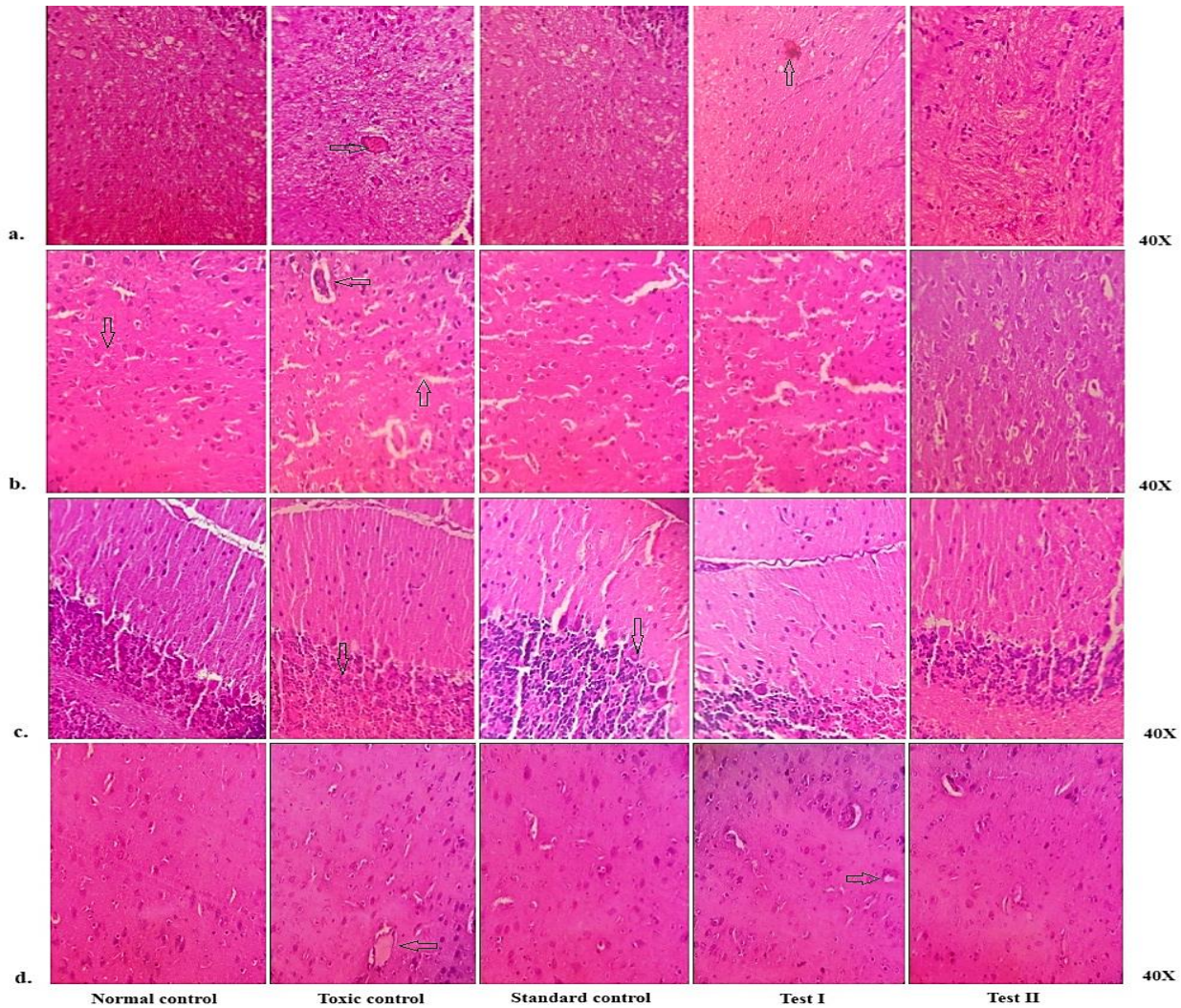

Figure 3: In the hippocampal region (**a**), both edema and pyknosis were observed in the toxic and Test I group. In the cerebral cortex (**b**), normal neuronal densities were evident across all groups; however, the toxic group exhibited signs of necrosis accompanied by inflammatory infiltration. The cerebellum (**c**) demonstrated normal granular cell and overall neuronal density in all groups, although a significant reduction in pyramidal cell density was noted in the toxic group relative to the normal control. In the hypothalamus (**d**), edema and necrosis were observed in the toxic and Test I groups, whereas the normal control, standard, and Test II groups showed no such abnormalities

4. Discussion

The present study demonstrates the potential antiepileptic activity of AEVU in Wistar albino rats. Acute oral toxicity assessments revealed that AEVU has an LD50 greater than 5000 mg/kg in female rats, with no observable signs of toxicity. To further investigate its therapeutic potential, a series of experimental animal models were utilized to assess the antiepileptic effects of AEVU.

The maximal electroshock (MES)-induced convulsion model, widely used to evaluate drugs for generalized tonic-clonic seizures, was employed. MES disrupts neuronal signal transmission, likely by inducing cellular alterations that facilitate the influx of cations such as Na^+ and Ca^{2+} into neurons, thereby promoting prolonged convulsions and cellular damage. AEVU, at a dose of 400 mg/kg body weight, significantly delayed the onset of convulsions, exhibiting protective effects comparable to the standard drug, phenytoin sodium (25 mg/kg).

In the isoniazid (INH)-induced convulsion model, INH, an antitubercular agent, induces seizures by inhibiting pyridoxal-5-phosphate, a cofactor essential for glutamic acid decarboxylase (GAD), the enzyme responsible for synthesizing GABA from glutamic acid. Treatment with AEVU, at varying doses, resulted in a delayed onset of convulsions and a reduction in their duration, with a notable protective effect observed at 400 mg/kg body weight.

Histopathological examination revealed significant neuroprotective effects of AEVU at a dose of 400 mg/kg, with a moderate effect at 200 mg/kg. These findings suggest that AEVU exhibits antiepileptic properties comparable to those of the standard anticonvulsant, phenytoin sodium.

5. Conclusion

Epilepsy, a neurological disorder characterized by abnormal neuronal signaling leading to seizures, has emerged as a significant global health concern. In light of this, the present study was conducted to evaluate the antiepileptic potential of a total aqueous seed extract of *Vigna unguiculata* (L.) Walp. The extract was tested on Wistar albino rats using various experimental models at two different doses. The results demonstrate the extract's notable antiepileptic activity. However, further investigations are necessary to elucidate the precise mechanism of action, with particular emphasis on identifying the active phytochemical constituents responsible for this effect.

6. Source of Funding

None.

7. Conflict of Interest

None.

8. Ethics Approval and Consent to Participate

1. Institute Animal Ethics Committee approval was obtained for this study (Ref no- 2021-22/IAEC).
2. We confirm that the plant which was used for study, identified and authenticated from ICMR, Belgavi-590090 with accession number RMRC-1660 which is mentioned in the manuscript.
3. Consent to participate- ‘Not applicable’

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