IJP (2025), Vol. 12, Issue 2 **(Research Article)**

Received on 07 February 2025; received in revised form, 25 February 2025; accepted, 27 February 2025; published 28 February 2025

EVALUATION OF ANTI-EPILEPTIC EFFECTS OF BIOACTIVE FRACTIONS OF METHANOLIC EXTRACT OF *LAGENARIA SICERARIA*: A POTENT MEDICINAL VEGETABLE PLANT

Rakesh P. Prajapati [*1], Manisha V. Kalariya [2] and Sachin K. Parmar [3]

Department of Pharmacognosy [1], Vidhyadeep Institute of Pharmacy, Surat - 395017, Gujarat, India.
Department of Pharmacognosy [2], B. K. Mody Govt. Pharmacy College, Gujarat Technological University, Rajkot - 360003, Gujarat, India.
Department of Pharmaceutical Sciences [3], Saurashtra University, Rajkot - 360003, Gujarat, India.

Keywords:

Epilepsy, *Lagenaria siceraria*, Pentylenetetrazole induced convulsions, Maximal electroshock-induced seizures (MES), Preliminary phytochemical screening, Diazepam

Correspondence to Author:
Dr. Rakesh Prajapati

Associate Professor,
Department of Pharmacognosy,
Vidhyadeep Institute of Pharmacy,
Surat - 395017, Gujarat, India.

E-mail: rakeshpharma1510@gmail.com

ABSTRACT: Context: Epilepsy is a neurological disorder of brain in which the clusters of neurons, occasionally signal abnormally and cause strange emotions, sensations, and behavior, or sometimes muscle spasms, convulsions, and loss of consciousness. *Lagenaria siceraria* (Molina) Standley (LS), commonly known as "bottle gourd" (English), possesses several medicinal properties; little is known about its action as a nerve tonic. **Objective:** The purpose of this study was to characterize (or to study) the anti-epileptic potential of the bioactive fractions of methanolic extract of LS fruits through pharmacological screening. **Materials and Methods:** The experiment was conducted in specific animal models i.e., Pentylenetetrazole (PTZ)-induced convulsions and Maximal electroshock-induced seizures (MES) in Swiss albino mice to evaluate anti-epileptic effects. The effect of the fractions was also tested on motor coordination using the rota-rod apparatus. **Results and Conclusions:** Preliminary phytochemical screening of the methanolic extract of LS and its fractions showed a huge range of phytoactive compounds. Among all the fractions, chloroform and acetone fractions were found to have more number of such phytoactive compounds. Chloroform fraction of methanolic extract of LS (CFMLS) showed the presence of saponins, phytosterols, terpenoids, polyphenolic compounds and fats, while acetone fraction of methanolic extract of LS (AFMLS) showed the presence of saponins, phenolic compounds, flavonoids and tannins. Oral administration of 100, 200 and 400 mg/kg of CFMLS and AFMLS gave significant results during pharmacological evaluation. AFMLS more significantly increased the onset of myoclonic seizures in PTZ model as well as in MES model than CFMLS. The effect of both the fractions was comparable to that of the Diazepam (0.5 mg/kg, i.p.). Though diazepam and LS fractions do not produce any overt motor dysfunction, when they were evaluated by rota rod performance. The results of the study for the first time show that the plant possesses anti-epileptic activity, confirming the traditional claims. Future research should focus on the isolation, identification and the mechanism of action of the phytoactive constituents of the plant.

INTRODUCTION: In modern era of globalization people are very much vulnerable to various neurological and psychosomatic disorders such as anxiety, depression, epilepsy, stress, phobia etc [50].

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.IJP.12(2).146-53

Article can be accessed online on:
www.ijpjournal.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.IJP.12(2).146-53

Among them, epilepsy is the third most common neurological disorder after stroke and Alzheimer's disease [47, 50].

It is a neurological disorder characterized by recurrent seizures, which are sudden, unprovoked, and transitory episodes of abnormal hyper synchronous neuronal discharge. An epileptic seizure is an episode of neurologic dysfunction due to abnormal neuronal firing obviously occurring clinically via changes in sensory perception, motor

control, behavior, or autonomic function [40]. It is estimated that more than 50 million people worldwide are epileptic (1–2% of the world's population), out of whom 40 million are believed to be living in the developing countries [1, 27]. Current available anticonvulsant drugs are able to efficiently control epileptic seizures in about 50% of the patients; 25% of the cases may show improvement, whereas the rest of the patients do not benefit significantly [39].

Furthermore, undesirable side effects of the drugs used clinically often render treatment difficult; so that a demand for new types of anticonvulsants exists. Additionally, the high cost of newer and more effective antiepileptic drugs have led to a greater proportion of patients in Asia and possibly other third world countries, resorting to the use of traditional medicine. There is therefore a universal and local need for continued research into the development of newer and cost effective agents for the management of this disorder [5, 24, 28]. One of the approaches to search for new antiepileptic drugs is the investigation of naturally-occurring compounds, which may belong to new structural classes.

Traditional herbs are very useful and vital in the struggle for convulsion management and future new antiepileptic drugs development. Therefore alternative therapy including herbal drugs and complementary medicine is becoming increasing popular. *Lagenaria siceraria* (Molina) Standley (LS) syn. *L. leucantha* Rusby; (Family: Cucurbitaceae) is an outstanding natural vegetable plant, as it contains most of the essential and necessary constituents, which are required for good quality health [36]. LS is commonly known as 'Bottle gourd' (Image 1) in English and '*Lauki*' in Indian vernacular language. LS vegetable fruits were traditionally used for its cardioprotective, diuretic, general tonic, aphrodisiac and acts as alternate purgative [41]. It also relieves pain, ulcers, fever, and used for pectoral cough, asthma and other bronchial disorders [41]. The fruits are edible and considered as good source of vitamin C, β-carotene, vitamin B-complex, pectin and also contain highest choline level-a lipotropic factor [7, 36]. Modern phytochemical screening methods showed the presence of triterpenoid, fucosterol, campesterol and flavone C-glycosides [3, 10, 42]. There is little scientific evidence to till the date to support the traditional use of LS in the treatment of nervous disorders and the possible mechanisms involved. With this background the present study was intended to evaluate anti-epileptic/ anti-convulsant effect of LS by using suitable animal experimental models.

MATERIALS AND METHODS:

Collection and Authentication of Plant Materials: Fresh vegetable fruits of LS were purchased from local market of Surat, Gujarat. The plant was identified and authenticated by Prof. P. J. Parmar, Botanical Survey of India, Jodhpur. A specimen voucher (SU/DPS/Herb/05) (Image 2) of the plant has been deposited at Department of Pharmaceutical Sciences, Saurashtra University, Rajkot for future reference.

Extraction of the Plant Material: LS vegetable fruits were properly cleaned and cut into thin round slices and dried. The dried plant material was then made into a coarse powder. The coarsely powdered dried fruits of LS (20 gm) were extracted with methanol by hot extraction process (Soxhlet extraction) for 4 hours. At the end of extraction, the solvent was removed by distillation and concentrated *in vaccuo*.

Fractionation of the Crude Extract: The crude methanolic extract of LS was suspended in 250 ml of distilled water and subsequently extracted with petroleum ether, chloroform, acetone and n-butanol (250 ml each). The all fractions were collected separately, dried by rotary evaporator at 40 °C and stored at 4 °C throughout experiments.

Preliminary Phytochemical Screening: The crude methanolic extract and all the fractions were screened through qualitative phytochemical tests for the detection of various phytoconstituents [18].

Experimental Animals: Adult Swiss albino mice (25–30 g) were group housed (*n* 6) under a standard 12 hour light/dark cycle and controlled conditions of temperature and humidity (25 ± 2°C, 55–65%). Mice received standard rodent chow food (Pranav Agro Sales., Ahmedabad, India) and water *ad libitum*. Mice were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried out in a noise-free room between 08:00 and 15:00

hours. Separate groups (n = 6) of mice were used for each set of experiments. The animal studies were approved (protocol approval no. 1521/ac/07/CPCSEA) by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi.

Drugs and Chemicals: Pentylenetetrazole (PTZ), Diazepam and phenytoin sodium were purchased from Sigma (USA). The solvents used in study were of analytical grade.

Administration of Drugs: The bioactive fractions of methanolic extract of LS i.e., CFMLS and AFMLS were suspended in 1% w/v sodium carboxy methyl cellulose (SCMC) in distilled water and administered *via* p.o. route. Bioactive fractions were administered orally (p.o.) at dose levels of 100, 200 and 400 mg/kg of body weight, whereas standard drugs were administered intraperitoneally (i.p.). Control group animals received only vehicle (1% w/v SCMC, i.p.) All the test drugs were freshly prepared and administered 30 minutes prior to test.

Acute Toxicity Study: As per the OECD guidelines-420, the chloroform and acetone fractions were administered orally at doses of 5, 50, 300 and 2000 mg/kg and the animals were examined for toxicity symptoms. There was no death or any toxicity symptom, observed. So as per annexure 4, the fractions were classified in Category 5 in GHS. Moreover, the study was also performed at doses 3000 and 4000 mg/kg, which were exceeding than 2000 mg/kg. Thus the anticipated maximum safe dose was determined as 4000 mg/kg and so 10%, 20% and 40% of the safe dose were selected to perform pharmacological study (Anonymous, 2000).

Pentylenetetrazole (PTZ)-induced Convulsions in Mice [11]: For the evaluation of anti-convulsant effect, the method described by Fisher, R.S was adapted**.** In brief, clonic seizures were induced in drug/vehicle pretreated albino mice (25-50 g) by an intraperitonial injection of 100 mg/kg PTZ. The animals were pretreated with CFMLS & AFMLS (100, 200 & 400 mg/kg, p.o.) 30 minutes before the injection of PTZ. The control animals received 0.1% SCMC solution. After the PTZ injection, the animals were placed in separate transparent Plexiglas cages (25 cm×15 cm×10 cm). The latencies to myoclonic seizures were observed over a 30 min period. The ability of a drug/extract to prevent the seizures was considered as indications of anticonvulsant activity.

Maximal Electroshock-induced Seizures on Mice [38]: Electro-convulsive shock, inducing hind limb tonic extension (HLTE) in 99% of the animals was determined by a current intensity-percent effect curve. The electrical stimulus (50 mA, 50 Hz, 1 s duration) was applied through ear-clip electrodes using a stimulator apparatus (Indosati Scientific Lab Equipments, Ambala Cantt., India). Five groups of 6 mice (25-50 gm), each were pretreated with different CFMLS & AFMLS (100, 200 & 400 mg/kg, p.o.); phenytoin (25 mg/kg, *i.p*, as positive control/ Reference standard drug), 0.5% SCMC (*i.p*.) (10 ml/kg, as control). After 30 min the animals received transauricular electroshock. The criterion for the anticonvulsant effect was onset of THLE (absence of THLE within 10 s) after delivery of the electroshock [38].

Rotarod Performance on Mice: The effect of the fractions on motor coordination activity was measured using Rotamex-4/8 (Columbus Instrument, USA). During the test, albino mice were selected and screened primarily at 12 rpm for four consecutive times (an hour interval) for a day. On day 2, the speed was increased to 24 rpm and mice that could stay on the rotating rod for 2 or more min were selected and grouped into five: three dose levels of the fractions (100, 200 & 400 mg/kg, p.o.), Diazepam (0.5 mg/kg, i.p.), and one as 0.5% SCMC (vehicle) treated. The mice, in their various groups, were trained for two consecutive days with four training sessions (at 1 h interval) per day. On the day of the experiment, each mouse was given a drug-free rotation and 30 minutes later treated with the fractions, diazepam, or 0.5% SCMC and tested at every 30 minutes for 2 h. The latency to fall was recorded as the time spent on the rotating rod [18].

Statistical Analysis: All data were expressed as mean ± SEM (n=6) and analyzed by one-way analysis of variance (ANOVA), followed by Student Newman-Keuls test.

The groups treated with bioactive fractions and fluoxetine were compared with the respective vehicle group. P values <0.001 were considered statistically significant.

RESULTS:

Preliminary Phytochemical Screening: Preliminary phytochemical screening of the test samples indicated the presence of a huge number of various phytoactive constituents as per **Table 1.** The results showed that the fractions were in rich in the presence of phytoactive constituents. CFMLS showed the presence of saponins, phytosterols, terpenoids, polyphenolic compounds and fats, while AFMLS showed the presence of saponins, phenolic compounds, flavonoids, and tannins.

TABLE 1: RESULTS OF PHYTOCHEMICAL SCREENING OF METHANOLIC EXTRACT OF *L. SICERARIA* FRUITS AND THEIR FRACTIONS

Sr. no.	Test	Pet. Ether	Chloroform	Acetone	n-Butanol
1	Alkaloids	-	-	-	-
2	Carbohydrates	-	-	+	+
3	Phytosterols	+	+	-	-
4	Fixed oils and fats	+	+	+	-
5	Saponins	-	+	+	-
6	Terpenoids	-	+	-	-
7	Phenolic comp. & tannins	-	-	+	+
8	Proteins & amino acids	-	-	-	+
9	Gums and mucilage	-	-	-	-
10	Volatile oil	-	-	-	-

+: Present; ND: Absent.

Acute Toxicity Study: The results of acute toxicity studies showed that the LD_{50} of the MLSF in mice was 1000 mg/kg by i.p. route. So accordingly four dose levels 50, 100, 200 and 400 mg/kg, p.o. body weight were selected to perform tests, corresponding to 5, 10, 20 and 40% of LD_{50} value (1000 mg/kg, i.p.), respectively.

Pentylenetetrazole (PTZ)-induced Convulsions in Mice [11]: CFMLS and AFMLS (100, 200 and 400 mg/kg, p.o.) dose dependently reduced the onset of myoclonic seizures in mice **Table 2** and the reduction was quite significant (P<0.001) as compared to control group. AFMLS **Fig. 2** more significantly reduced the onset of seizures than CFMLS **Fig. 3.** Diazepam, at a dose of 4 mg/kg, i.p., also showed significant (P<0.001) reduction in the occurrence of seizures **Table 2, Fig. 2, 3.**

TABLE 2: EFFECTS OF CHLOROFORM FRACTION OF METHANOLIC EXTRACT OF *LAGENAIA SICERARIA* (CFMLS) & ACETONE FRACTION OF METHANOLIC EXTRACT OF *LAGENARIA SICERARIA* FRUITS (AFMLS) AND DIAZEPAM ON ONSET OF MYOCLONIC SEIZURES INDUCED BY PENTYLENETETRAZOLE IN MICE[A]

Group	Dose (mg/kg)	Onset of myoclonic seizures (sec)
Control	---	6.84±1.17
CFMLS	100	10.1±0.853*
CFMLS	200	13.1± 1.38***
CFMLS	400	17.9±1.33***
AFMLS	100	13.3±0.99***
AFMLS	200	14.8±1.16***
AFMLS	400	18.1±0.750***
Diazepam (*i.p)*	4 mg/kg	39.0±3.74***

[a]Values are expressed as mean ± SEM (n = 5). **P<0.01, ***P<0.001; compared with control (one way ANOVA followed by Student Newman Keuls test).

Maximal Electroshock-Induced Seizures on Mice: At dose of 100 mg/kg, CFMLS **Fig. 4** did not exhibit any protection in mice against seizures but at doses of 200 and 400 mg/kg (p.o.), CFMLS dose dependently and significantly (P< 0.001) reduced the onset of HLTE (Hind limb tonic extension) as compared to control group. While AFMLS **Fig. 5** indicated more significant results than CFMLS at all the selected doses.

Phenytoin sodium, at a dose of 25 mg/kg (i.p.), also showed significant (P<0.001) reduction in the onset of HLTE and occurrence of seizures and provided 100% protection **Table 3.**

TABLE 3: EFFECTS OF CHLOROFORM FRACTION OF METHANOLIC EXTRACT OF *LAGENAIA SICERARIA* (CFMLS) & ACETONE FRACTION OF METHANOLIC EXTRACT OF *LAGENARIA SICERARIA* FRUITS (AFMLS) AND PHENYTOIN SODIUM ON THE ONSET OF HLTE AND PROTECTION IN MICE[A]

Group	Dose (mg/kg)	Onset of HLTE (sec)	% Protection
Control	---	13.8±1.64	0
CFMLS	100	12.4±1.14^{ns}	33.33
CFMLS	200	10.8±0.84**	33.33
CFMLS	400	9.0±1.0***	66.64
AFMLS	100	10.4±1.14***	33.33
AFMLS	200	8.50±0.50***	49.98
AFMLS	400	7.30±0.67***	83.3
Phenytoin *(i.p)*	25 mg/kg	7.0±0.791***	100

[a]Values are expressed as mean ± SEM (n = 5). ** P<0.01, *** P<0.001; compared with control (one way ANOVA followed by Student Newman Keuls test).

Rota Rod Performance on Mice: Results of the study indicated that CFMLS and AFMLS at the dose of 100 mg/kg did not show any change in motor coordination. Though at doses of 200 and 400 mg/kg, both of them significantly (P<0.001) reduced the time spent on the rota-rod at 12 rpm over the 2-h period, as compared to CFMLS. Diazepam (4 mg/kg, i.p.), a reference standard muscle relaxant, produced significant effect on the skeletal muscle (P <0.001) **Table 4.**

TABLE 4: EFFECT OF CHLOROFORM FRACTION OF METHANOLIC EXTRACT (CFME) & ACETONE FRACTION OF METHANOLIC EXTRACT (AFME) OF *LAGENARIA SICERARIA* FRUITS AND DIAZEPAM ON ROTA-ROD PERFORMANCE/ MOTOR CO-ORDINATION IN MICE[A]

Treatment Group	Dose (mg/kg)	Total time spent on rod (sec)
Control	--	313.6 ± 36.83
CFMLS	100	303.6 ± 25.58^{ns}
CFMLS	200	197.2 ± 26.25***
CFMLS	400	173.4 ± 18.09***
AFMLS	100	299.2 ± 39.25^{ns}
AFMLS	200	180.2 ± 25.41***
AFMLS	400	136.4 ± 6.804***
Diazepam (*i.p.*)	0.5	104.4 ± 17.52***

[a]Values are expressed as mean ± SEM (n = 5); [b] intraperitoneal route $^{***}P$<0.001, compared with control (one-way ANOVA followed by Student-Newman-Keuls test).

DISCUSSION: Epilepsy is the second leading neurological disorder after stroke, involving at least 50 million worldwide [12]. Cognitive impairment, dose-related neurotoxicity, and a spectrum of systemic side effects are the main side effects due to antiepileptic drugs [35]. PTZ and MES are the most commonly used preliminary tests for screening of potential anticonvulsant drugs [23]. PTZ test represents a valid model for human generalized myoclonic and also absence seizures. It exerts action mainly through the t-butyl-bicyclo phosphorothionate/ picrotoxin site of the $GABA_A$ receptor. PTZ is a blocker of choice for the $GABA_A$ receptor chloride ionophore complex [45]. It has convulsant effects after repeated or single administration and affects several neurotransmitter systems, such as adenosinergic, GABAergic, and glutamatergic systems [9]. After PTZ-induced seizures, significant decreases in GSH, cysteine, glutathione disulfide, and protein thiols as well as increases in the protein disulfides and protein carbonyl levels were observed in the mouse cerebral cortex [34]. The MES test is considered to be a predictor of likely therapeutic efficacy against generalized tonic-clonic seizures. In the test, tonic hind limb seizures are induced by bilateral corneal or transauricular electrical stimulation, is believed to predict effectiveness of anticonvulsant drug against generalized tonic-clonic seizures [4]. Our results of phytochemical screening indicated that CFMLS showed the presence of saponins, phytosterols, terpenoids, polyphenolic compounds and fats, while AFMLS showed the presence of saponins, phenolic compounds, flavonoids and

tannins. During literature review, we could come to know that the constituents like terpenoids [14, 33, 6] and flavonoids [29] demonstrated the anti-convulsant effects of many of the plants. It directs that the one or more phytoconstituents of the fractions may be accountable for the anti epileptic effect of the fractions.

Drugs that enhance gamma amino butyric acid-type A ($GABA_A$) receptor-mediated inhibitory neurotransmission, such as benzodiazepines can also prevent PTZ-induced seizures [25]. Furthermore, activation of N-methyl-D-aspartate receptor appears to be involved in the initiation and generalization of the PTZ induced seizures [46]. Accordingly, drugs that block glutamatergic excitation mediated by NMDA receptor such as felbamate have anticonvulsant activity against PTZ-induced seizures [25]. Saponins have also NMDA receptor-blocking (Longhi-Balbinot DT, 2009) [22] and GABAA receptor positive-modulation properties [31]. Finally, saponins have been reported to protect NMDA-induced neuronal death *via* a competitive interaction with the glycine-binding site of NMDA receptors in cultured hippocampal neurons (Kim S, 2004). Saponins also block GABA specific transporters selectively, which results in inhibition of GABA uptake [13] and propounds saponin compounds as anticonvulsant agents [6]. These reports proved that CFMLS exhibited its anti epileptic potential because of its saponin content.

Moreover flavonoids are reported to potentiate GABA-induced currents in native $GABA_A$ receptors expressed in cortical neurons (Ren L, 2010) [37] and also to selectively modulate $GABA_A$ receptor subtypes (Wang F, 2010 [37], Nilsson J, 2011) [31]. Flavonoids can block NMDA receptors in a concentration-dependent manner (Zhang X, 2008; Huang R, 2010) [15]. These findings indicate that the anti-epileptic potential of AFMLS may be due to its flavonoid content. More than 5000 different flavonoids have been isolated so far and the pharmacological properties of many of them have been described [49]. The flavonoids from the medicinal plants such as valerian (*Valeriana officinalis*), chamomile (*Matricaria recutita*), and kava-kava (*Piper methysticum*) have sedative-hypnotic effects based on positive allosteric modulation of $GABA_A$ receptors [44]. The flavonoids belonging to these different chemical classes inhibit, at varying degrees, enzymes that phosphorylate (kinases) and dephosphorylate (phosphatases) critical proteins that signal transduction pathways, which regulate oxidative stress, inflammation, and cell survival [19]. These metabolites have been reported to have anticonvulsant activity. It has been previously shown in several studies that rutin, quercetin, and isoquercitrin have anticonvulsant effects on experimental epilepsy models [32]. Experimental evidences clearly demonstrated that flavonoids exert antiepileptic activity by modulating the $GABA_A$-Cl-channel complex, as they are structurally similar to benzodiazepines [8].

The flavonoids and isoflavonoids are probably electron donors. They have B-ring conjugated chemical structures rich in hydroxyl groups, which have potential antioxidant actions by reacting with and inactivating superoxide anions, oxygen lipid peroxide radicals, and/or stabilizing free radicals involved in the oxidative process by hydrogenation or complexing with oxidant species [26]. Therefore, OH· removal by apigenin displayed a considerable antioxidant activity and may be capable of inhibiting cell damage caused by that radical and significantly decreasing the production of nitrite [26], acting as CNS active molecules, in other words, as partial agonists of the GABAA receptor [49]. Apigenin also may block glutamatergic transmission through kainic acid receptors to prevent the generation and propagation of seizure-related neuronal discharges, potentially through inhibitory systems in the central nervous system. This flavonoid also has considerable anti-excitotoxicity effects [16].

Flavonoids have been shown to influence peripheral blood flow in humans. For example, in a brain imaging study, the consumption of flavanol-rich cocoa enhanced cortical blood flow. This result is important when considering mechanisms that increase cerebro-vascular function, especially in the hippocampus, a brain region that is important for memory and that may facilitate adult neurogenesis [29]. The flavonoids play a significant role in this regard by its antioxidant capacity. Many studies show that flavonoids act on GABA receptor potentiating its effect. So, it is a promising metabolite that may act in CNS disorders, including epilepsy.

Natural products and their derivatives comprise over 50% of all the drugs used in clinical settings worldwide. Medical plants can be applied because of their structural diversity and wide spectrum of pharmacological effects in contrast to common synthetic antiepileptic drugs [15]. The finding concluded that experiments on phytoactive compounds in the plant based extracts and their bioactive fractions may be fundamental to identify novel, effective and safe chemical compounds for development of antiepileptic drugs in the future.

ACKNOWLEDGMENTS: We are grateful to the Head, Department of Pharmaceutical Sciences, Saurashtra University, Rajkot, Gujarat, India, for providing the facilities during the course of this study. Special thanks to Prof. P. J. Parmar, Botanical Survey of India, for identification and authentication of the plant.

CONFLICT OF INTEREST: I declare that I have no conflict of interest.

REFERENCES:

1. Abourabl ME: Antiepileptic drugs: progress and development. Egypt Pharmaceut J 2018; 17: 129-140.
2. Anonymous. OECD- Guidance Document on Acute Oral Toxicity. Environmental Health and Safety Monograph Series on Testing and Assessment 2000; 24.
3. Baranowska MK and Cisowski W: High Performance Liquid Chromatographic determination of Flavone C-glycosides in some species of the Curcubiraceae family. J Chromato A 1994; 675: 240-243.
4. Barton ME, Peters SC and Shannon HE: Comparison of the effect of glutamate receptor modulators in the 6 Hz and maximal electroshock seizure models. Epilepsy Res 2003; 56(1): 17-26.
5. Brodie MJ and Kwan P: The star systems: overview and use in determining antiepileptic drug choice. CNS Drugs 2001; 15: 1-12.
6. Chindo BA, Anuka JA, McNeil L, Yaro AH, Adamu SS and Amos S: Anticonvulsant properties of saponins from *Ficus platyphylla* stem bark. BRB 2009; 78: 276-282.
7. Chopra RN, Chopra IC and Verma BS: Supplement of Glossary of Indian Medicinal plants, Council of Scientific and Industrial Research, New Delhi, India 1992; 51.
8. Choudhary N, Bijjem KRV and Kalia AN: Antiepileptic potential of flavonoids fraction from the leaves of *Anisomeles malabarica*. Journal of Ethnopharmacology 2011; 135(2): 238–242.
9. Diehl RG, Smialowski A and Gotwo T: Development and persistence of kindled seizures after repeated injections of pentylenetetrazol in rats and guinea pigs. Epilepsia 1984; 25(4): 506-510.
10. Duke JA: Handbook of Phytochemical and Constituents of Grass herbs and other economic plants, CrC press, Boco, Raton 1999; 98-119.
11. Fisher RS: Animal models of the epilepsies. Brain Res Rev 1989; 14(3): 245-278 [doi: 10.1016/0165-0173(89) 90003-9].
12. Forsgren L, Beghi E, Oun A and Sillanpaa M: The epidemiology of epilepsy in Europe–a systematic review. Eur J Neurol 2005; 12(4): 245-253.
13. Fulep GH, Hoesl CE, Höfner G and Wanner KT: New highly potent GABA uptake inhibitors selective for GAT-1 and GAT-3 derived from (R)-and(S)-proline and homologous pyrrolidine-2-alkanoic acids. Eur J Med Chem 2006; 41: 809-824.
14. Gareri P, Condorelli D, Belluardo N, Gratteri S, Ferreri G and Donato Di Paola E: Influence of carbenoxolone on the anticonvulsant efficacy of conventional antiepileptic drugs against audiogenic seizures in DBA/2 mice. Eur J Pharmacol 2004; 484: 49-56.
15. Gurib-Fakim A: Medicinal plants: traditions of yesterday and drugs of tomorrow. Mol Aspects Med 2006; 27(1): 1-93.
16. Han JY, Ahn SY and Kim CS: Protection of apigenin against kainate-induced excitotoxicity by anti-oxidative effects. Biological and Pharmaceutical Bulletin 2012; 35(9): 1440-1446.
17. Huang R, Singh M and Dillon GH: Genistein directly inhibits native and recombinant NMDA receptors. Neuropharmacology 2010; 58: 1246-1251.
18. Ibarrola MC, Ibarrola DA, Montalbetti Y, Kennedy, ML, Heinichen O, Campuzano M, Tortoriello J, Wasowski C, Marder M, De Lima TC and Mora S: The anxiolytic-like effects of *Aloysia polystachya* (Griseb.) Moldenke (Verbenaceae) in mice. J Ethnopharmacol 2006; 105: 400-408.
19. Keddy PGW, Dunlop K and Warford KJ: Neuroprotective and anti-inflammatory effects of the flavonoid-enriched fraction AF4 in a mouse model of hypoxic-ischemic brain injury, PLoS ONE 2012; 7(12): Article IDe 51324.
20. Kim S, Kim T, Ahn K, Park WK, Nah SY and Rhim H: Ginsenoside Rg3 antagonizes NMDA receptors through a glycine modulatory site in rat cultured hippocampal neurons. Biochem Biophys Res Commun 2004; 323: 416-424.
21. Kirtikar KR: Indian medicinal Plants, Oriental Enterprises, Dehradun, India 2012; 722-723.
22. Longhi-Balbinot DT, Pietrovski EF, Gadotti VM, Martins DF, Facundo VA and Santos AR: Spinal antinociception evoked by the triterpene 3beta, 6beta, 16beta-trihydroxylup-20(29)-ene in mice: evidence for the involvement of the glutamatergic system *via* NMDA and metabotropic glutamate receptors. Eur J Pharmacol 2009; 623: 30-36.
23. Loscher W and Schmidt D: Which animal models should be used in the search for new antiepileptic drugs? A proposal based on experimental and clinical considerations. Epilepsy Res 1988; 2: 145-181.
24. Loscher W: Current status and future directions in the pharmacotherapy of epilepsy. Trends Pharmacol Sci 2002; 23: 113–118.
25. Macdonald RL and Kelly KM: Antiepileptic drugs mechanisms of action. Epilepsia 1995; 36: 2-12.
26. Marques THC, de Melo CHS and de Carvalho RBF: Phytochemical profile and qualification of biological activity of an isolated fraction of Bellis perennis. Biological Research 2013; 46(3): 231-238.
27. McNamara JO, Bonhaus DW, Shin CY and Cambridge UK: Cambridge University Press. The kindling model of epilepsy. Epilepsy: Models, Mechanisms and Concepts 1993; 27-47.
28. McNamara JO: Emerging insights into the genesis of epilepsy. Nature 1999; 399(6738): 15-22.

29. Nassiri-Asl M, Mortazavi SR and Samiee-Rad F: The effects of rutin on the development of pentylenetetrazole kindling and memory retrieval in rats. Epilepsy and Behavior 2010; 18(1-2): 50-53.
30. Nassiri-Asl M, Shariati-rad S and Zamansoltani F: Anticonvulsant effects of intracerebro ventricular administration of rutin in rats. Prog Neuropsychopharma Biol Psychiatry 2008; 32: 989-993.
31. Nilsson J and Sterner O: Modulation of GABA (A) receptors by natural products and the development of novel synthetic ligands for the benzodiazepine binding site. Curr Drug Targets 2011; 12: 1674-1688.
32. Orhan N, Orhan DD, Aslan M, Ukurolu M and Orhan JE: UPLC-TOF-MS analysis of *Galium spurium* towards its neuroprotective and anticonvulsant activities. Journal of Ethnopharmacology 2012; 141(1): 220-227.
33. Pal D, Sannigrahi S and Mazumder UK: Analgesic and anticonvulsant effects of saponin isolated from the leaves of *Clerodendrum infortunatum* Linn. in mice. Indian J Exp Biol 2009; 47: 743-747.
34. Patsoukis N, Zervoudakis G, Panagopoulos NT, Georgiou CD, Angelatou F and Matsokis NA: Thiol redox state (TRS) and oxidative stress in the mouse hippocampus after pentylenetetrazol- induced epileptic seizure. Neurosci Lett 2004; 357(2): 83-86.
35. Perucca E, Gram L, Avanzini G and Dulac O: Antiepileptic drugs as a cause of worsening seizures. Epilepsia 1998; 39(1): 5-17.
36. Rahman ASH: Bottle Gourd (*Lagenaria siceraria*)-a vegetable for good health. Nat Prod Rad 2003; 2(5): 249-250.
37. Ren L, Wang F, Xu Z, Chan WM, Zhao C and Xue H: GABA (A) receptor subtype selectivity underlying anxiolytic effect of 6-hydroxyflavone. Biochem Pharmacol 2010; 79: 1337-1344.
38. Sayyah M, Moaied S and Kamalinejad M: Anticonvulsant activity of *Heracleum persicum* seed. J Ethnopharmacol 2005; 98: 209-211.
39. Schmidt D and Loscher W: Drug resistance in epilepsy: putative neurobiologic and clinical mechanisms. Epilepsia 2005; 46: 858-877.
40. Scott BW, Wojtowicz JM and Burnham WM: Neurogenesis in the dentate gyrus of the rat following electroconvulsive shock seizures. Exp Neurol 2000; 165(2): 231-236.
41. Shinrajan VV and Balachandra I: Ayurvedic Drugs and their plant source, oxford and IBH Publishers, New Delhi, India 1996; 176-177.
42. Shirwaikar A and Sreenivasan KK: Chemical investigation and anti-hepatotoxic activity of the fruits of *Lagenaria siceraria*. Ind J Pharm Sci 1996, 58(5): 197-202.
43. Sonja S and Hermann S: Analysis of *Curcubita cins* in medicinal Plants by HPLC-MS. Phytochem Analysis 2000; 11: 121.
44. Shrestha S, Park JH and Lee DY: *Rhus parviflora* and its biflavonoid constituent, rhusflavone, induce sleep through the positive allosteric modulation of *GABAA* benzodiazepine receptors. Journal of Ethnopharmacology 2012; 142(1): 213-220.
45. Velisek L, Kubova H, PohlM, Stankova L, Mare SP and Schickerova R: Pentylenetetrazol-induced seizures in rats: an ontogenetic study. Naunyn Schmiedebergs Arch Pharmacol 1992; 346(5): 588-591.
46. Velisek L, Kusa R, Kulovana M and Mares P: Excitatory amino acid antagonists and pentylenetetrazole-induced seizures during ontogenesis. I. The effects of 2-amino-7 phosphonoheptanoate. Life Sci 1990; 46: 1349-1357.
47. Vezzani M, French J, Bartfai T and Baram TZ: The role of inflammation in epilepsy. Nat Rev Neurol 2011; 7: 31–40.
48. Wang F, Xu Z, Ren L, Tsang SY and Xue H: GABA-A receptor subtype selectivity underlying selective anxiolytic effect of baicalin. Neuropharmacol 2008; 55: 1231-1237.
49. Du XM, Sun NY, Takizawa N, Guo YT and Shoyama Y: Sedative and anticonvulsant activities of goodyerin, a flavonol glycoside from *Goodyera schlechtenda liana*. Phytotherapy Research 2002; 16(3): 261-263.
50. Yuliya S, Prokopenko YS, Lina O, Perekhoda LO, Victoriya A and Georgiyants VA: Docking studies of biologically active substances from plant extracts with anticonvulsant activity. J Appl Pharm Sci 2019; 9(1): 66-72.
51. Zhang XN, Li JM, Yang Q, Feng B, Liu SB and Xu ZH: Anti-apoptotic effects of hyperoside *via* inhibition of NR2B-containing NMDA receptors. Pharmacol Rep 2010; 62: 949-955.

How to cite this article:
Prajapati RP, Kalariya MV and Parmar SK: Evaluation of anti-epileptic effects of bioactive fractions of methanolic extract of *Lagenaria siceraria*: a potent medicinal vegetable plant. Int J Pharmacognosy 2025; 12(2): 146-53. doi link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.12(2).146-53.