Chiroma *et al.*
Bulletin of the National Research Centre (2022) 46:205
https://doi.org/10.1186/s42269-022-00898-7

Bulletin of the National Research Centre

RESEARCH Open Access

Anti-seizure properties of *Ipomoea asarifolia* (Desr.) (Convolvulaceae) ethanolic leaf extract in laboratory animals

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Abstract

Background: Preparation of *Ipomoea asarifolia* (Desr.) (Convolvulaceae) is widely used in traditional African medicine for the treatment of different kinds of ailments such as syphilis, malaria, convulsions and rheumatism.

Aim: The present study examined the median lethal dose (LD_{50}) and possible anti-seizure potentials of *Ipomoea asarifolia* ethanolic leaf extract using acute seizure models.

Results: The intraperitoneal LD_{50} of *Ipomoea asarifolia* ethanolic leaf extract in mice and chicks was found to be 2,150 mg/kg. The *Ipomoea asarifolia* ethanolic leaf extract has shown significantly ($p < 0.05$) delayed time for the onset of seizure against pentylenetetrazole- and strychnine-induced seizures in a non-dose dependent manner both at 300 mg/kg. The extract has also shown significant ($p < 0.01$, $p < 0.001$ and $p < 0.001$) delayed time for onset of seizures against 4-aminopyridine-induced seizure model in a dose-dependent manner at doses of 150, 300 and 600 mg/kg respectively. The extract has not shown appreciable activity against picrotoxin and maximum electroshock-induced seizure models.

Conclusions: The present study revealed that *Ipomoea asarifolia* ethanolic leaf extract possesses anti-seizure properties which supports its folkloric use for the management of convulsions.

Keywords: Seizures, *Ipomoea asarifolia*, Epilepsy, Pentylenetetrazole, Strychnine, 4-aminopyridine

Background

Epilepsy is a neurological disorder usually characterized by continuous predilection to generate epileptic seizures, and it is associated with comorbidities such as neurobiologic, psychological, cognitive and social consequences (Fisher et al. 2014; Devinsky et al. 2018). With a lifetime prevalence of 7.6 per 1000 persons, epilepsy undeniably imposes a major burden on patients and the society in general (Fiest et al. 2017). About 80% of epilepsy patients live in resource-poor countries, in which most of them do not have regular access to antiepileptic drugs (AED) treatment (Espinosa-Jovel et al. 2018). Additionally, even though there are major advances in the field of research on epilepsy, approximately 30% epilepsy patients on AED are resistant to the pharmacologic therapy in spite of the adequate treatment (Fattorusso et al. 2021). Hence, investigations on medicinal plants with potential antiepileptic properties can be a promising field for this purpose.

Ipomoea asarifolia (Desr.) Roem. & Schult. belongs to the family Convolvulaceae. It grows well in sandy soil and found with crops along the margins of ponds. It is a perennial weed found throughout tropical Asia, America and West Africa (Burkill 1985). The English name of the plant is Morning glory, while in Nigeria it is commonly known by the local dialects as *Duman rafi* (Hausa), *gbọọrọ ayaba* (Yoruba) and *ewe-gboro* (Igbo). *Ipomoea*

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asarifolia has many ethno medicinal uses as preparations from its leaves, flowers or whole part are used for the management of different ailments in African traditional medicine (Akindele et al. 2015). Some of these health conditions include syphilis, guinea-worm sores, rheumatic pains, feverish chills (Burkill 1985), liver diseases (Farida et al. 2012), gastrointestinal disorders and diabetes (Atawodi and Onaolapo 2010), inflammation (Furtado et al. 2016) and dysmenorrhea (Jegede et al. 2009). In middle belt region of northern Nigeria, the leaves are used to relieve dysmenorrhea, while leaf poultice is applied to injury; the flowers are boiled with beans and used as remedy for syphilis (Jegede et al. 2009). It is used in Burkina Faso folk medicine to manage malaria, convulsions and rheumatism (Meda et al. 2017), while in Benin Republic it is used for treatment of fever and convulsion (Tsala 2013). Phytochemical analysis of the leaf extract of the *Ipomoea asarifolia* has shown the presence of flavonoids, saponins, alkaloids, tannins, steroids, triterpenes and terpenoids (Aliyu et al. 2011). In terms of scientific investigation of the traditional claims and usages, the radical scavenging (Atawodi and Onaolapo 2010), acetylcholinesterase inhibition (Feitosa et al. 2011), antibacterial (Aliyu et al. 2011), hepatoprotective (Farid et al. 2012) and anti-inflammatory (Furtado et al. 2016) activities of *Ipomoea asarifolia* extract have been confirmed and documented. Recently, the anticonvulsant activities of fractions of methanolic leaf extract of *Ipomoea asarifolia* have also been reported (Chiroma et al. 2022). The present study therefore was aimed at investigating the anticonvulsant activity of crude methanolic leaf extract of *Ipomoea asarifolia* against five different established animal models of seizures.

Methods

Drugs/chemical and equipment

Drugs/chemical and equipment used are: strychnine, 4–aminopyridine, pentylenetetrazole, picrotoxin (Sigma-Aldrich, St. Louis, USA), phenytoin (Pharma aid, Hamburg Germany), sodium valproate (Sanofi, France), Ugo Basile current electroshock machine (Model 7801), and diazepam (Roche, Germany).

Plant collection and authentication

Fresh leaves of *Ipomoea asarifolia* were collected in March 2020 at Dan Lasan Village, Kano State, Nigeria. The plant was identified and authenticated by Dr. Yusuf Nuhu at the Herbarium unit of the Department of Botany, Bayero University Kano. It was issued a voucher specimen number (BUKHAN 153) by comparing with a previously deposited voucher specimen.

Preparation and extraction of plant material

The leaves were air-dried under shade until constant weight was obtained and then pulverized with the aid of a pestle and mortar. The powder material was extracted with 70% ethanol using cold maceration technique with occasional shaking for 7 days. The mixture was filtered first with muslin cloth and then using Whatman filter paper No.1, and thereafter, the filtrate was concentrated using a rotary evaporator at 50 °C. The percentage yield of the extract was calculated using the formula shown below, and the extract (labeled as *Ipomoea asarifolia* ethanolic leaf extract, IALE) was stored in a desiccator until required for further studies.

$$\% \text{ Yield} = \frac{\text{Weight of extract}}{\text{Weight of powdered plant}} \times 100$$

Animals

Day old chicks (cockerel) weighing 30–40 g and Swiss mice weighing between 18 and 25 g were used in this study. The animals were kept in a well-ventilated room and maintained under normal light/dark cycle. The animals were given free access to feed and water, while their handling was performed in agreement with the Animal Research: Reporting of In Vivo Experiments (ARRIVE), which is also in line with the National Institute of Health Guidelines for the Care and use of Laboratory animals (Publication Nos. 85-23, Revised 1985).

Preliminary qualitative and quantitative phytochemical screening

The preliminary screening for phytochemical constituents was carried out as reported earlier (Sasidharan et al. 2011).

Acute toxicity study

Acute toxicity study in mice and chicks was conducted using the intraperitoneal (*i.p.*) route of administration (Lorke 1983). The study was carried out in two phases: In the initial phase, three groups of three animals each (mice or chicks) received *Ipomoea asarifolia* ethanolic leaf extract at doses of 10, 100 and 1000 mg/kg body weight and then observed for signs of toxicity and death within 24 h. In the second phase, three animals (mice or chicks) were treated with more specific doses (1600, 2900 and 5000 mg/kg) and also observed for signs of toxicity and death within 24 h. Thereafter, the intraperitoneal LD_{50} was calculated.

Screening for anti-seizures properties

Pentylenetetrazole (PTZ)-induced seizures in mice

The method used in the present study for the induction of PTZ seizure in mice was earlier described (Smith et al. 2007; Nazifi et al. 2020). A total of 30 mice were subdivided into 5 groups of 6 mice each. The mice in group 1

were administered normal saline 10 mL/kg *i.p*, groups 2, 3 and 4 mice were administered with 150, 300 and 600 mg/kg *i.p* of *Ipomoea asarifolia* ethanol leaf extract, respectively, and finally, group 5 mice were injected with sodium valproate 200 mg/kg bw *i.p*. After 30 min, PTZ 85 mg/kg subcutaneously (*s.c.*) was administered to the mice in all groups and was then observed for another 30 min for onset of seizures.

Maximal electroshock (MES)-induced seizures in chicks

The procedure followed and the apparatus used in the present study were earlier documented by Swinyard and Kupferberg 1985 and modified by Chiroma et al. (2022). Briefly, 50 chicks were randomly divided into 5 groups ($n=10$). Group 1 received normal saline 10 mL/kg *i.p*, while groups 2, 3 and 4 received 150, 300 and 600 mg/kg of the extract *i.p.*, respectively, and group 5 was injected with 20 mg/kg of phenytoin *i.p*. After 30 min of drug administration, maximal electric shock was induced using Ugo Basile electroshock machine. Seizures were manifested as tonic hind limb extension (THLE). The ability of the extract to prevent this feature or prolong the latency and/or onset of the THLE was considered as an indication of anticonvulsant activity (Baradaran Rahimi et al. 2019). The recovery time from seizures was recorded.

Strychnine-induced seizures in mice

The procedure adopted in the present study was earlier described (Porter et al. 1984). Briefly, 30 mice were randomly grouped into 5 ($n=6$). Group1 received normal saline (10 mL/kg *i.p*), while groups 2, 3 and 4 received 150, 300 and 600 mg/kg doses of *Ipomoea asarifolia* ethanolic leaf extract *i.p.*, respectively, and group 5 mice received diazepam 2 mg/kg *i.p*. After 30 min, all mice received 1 mg/kg of strychnine *s.c.* and were further monitored for another 30 min for manifestation of seizures.

4-aminopyridine (4-AP)-induced seizures in mice

The protocol earlier documented by Yamaguchi and Rogawski (1992) was followed. Briefly, 30 mice were divided into 5 groups ($n=6$) randomly. Group 1 received saline 10 mL/kg *i.p*, while groups 2, 3 and 4 received 150, 300 and 600 mg/kg doses of *Ipomoea asarifolia* ethanolic leaf extract *i.p*. respectively. Then, group 5 mice were pretreated with 10 mg/kg phenobarbitone *i.p*. Thirty minutes post-treatment, 4-AP (14 mg/kg *s.c.*) was given to each mouse and then monitored for seizures or death for another 30 min.

Picrotoxin-induced seizures in mice

This study followed the method earlier described by Vogel (2008). Briefly, 30 mice were randomly grouped in to 5 ($n=6$). Group 1 received normal saline 10 mL/kg *i.p.*, while groups 2, 3 and 4 received 150, 300 and 600 mg/kg doses of *Ipomoea asarifolia* ethanolic leaf extract *i.p.*, respectively. Group 5 mice received 10 mg/kg phenobarbitone *i.p*. Thirty minutes later, all groups of mice received picrotoxin (4 mg/kg, *s.c*) and then were monitored for another 30 min for seizures and death.

Statistical analysis

Statistical package for Social Sciences (SPSS) software (Version 20) was used for data analysis. Differences between means were analyzed using one-way analysis of variance (ANOVA) after which Dunnett's post hoc test was conducted. Values of $p<0.05$ (95% confidence interval) were considered statistically significant. The data obtained were presented as mean ± standard error of the mean (S.E.M).

Results

Extractive value of *Ipomoea asarifolia* ethanolic leaf extract

The extractive value of *Ipomoea asarifolia* ethanolic leaf extract was calculated to be 11.4% w/w.

Phytochemical constituents of *Ipomoea asarifolia* ethanolic leaf extract

Qualitative analysis revealed the presence of glycosides, flavonoids, saponins, alkaloids, tannins phenols and steroids in *Ipomoea asarifolia* ethanolic leaf extract (Table 1). These constituents were also shown quantitatively with flavonoid having the highest proportion of 46.2% (Table 2).

Table 1 Phytochemical constituents of *Ipomoea asarifolia* ethanolic leaf extract

Constituents	Inference
Glycosides	+
Flavonoids	+
Saponins	+
Alkaloids	+
Anthraquinones	–
Phlobatannins	–
Volatile oils	–
Tannins	+
Steroids	+
Phenols	+

+ (Present), – (Absent)

Table 2 Quantitative phytochemical constituents of *Ipomoea asarifolia* ethanolic leaf extract

S/No	Phytochemical	Weight (g)	Percentage (%)
1	Alkaloids	0.032	3.20
2	Flavonoids	0.462	46.20
3	Saponins	0.240	24.00
4	Tannins	0.022	2.20
5	Phenols	0.0204	2.04
6	Steroids	0.0351	3.51
7	Cardiac glycosides	0.0075	0.75

Table 3 Effect of *Ipomoea asarifolia* ethanolic leaf extract on PTZ-induced seizures in mice

Treatment (mg/kg)	Onset of seizures (Min.)	Quantal protection	Percentage protection
D/W 10 mL/kg	3.17 ± 0.48	0/6	0.00
IALE 150	4.33 ± 0.67	0/6	0.00
IALE 300	6.33 ± 0.95*	0/6	0.00
IALE 600	5.60 ± 0.40	1/6	16.67
V/A 200	8.33 ± 1.45**	3/6	50.00

Data are presented as Mean ± S.E.M., * = $p < 0.05$, ** = $p < 0.01$ as compared to D/W group—One-way ANOVA followed by Dunnett's post hoc test, $n = 6$, D/W = Distilled water, IALE = *Ipomoea asarifolia* leaf extract, V/A = Valproic acid

Table 4 Effect of *Ipomoea asarifolia* ethanolic leaf extract on MES-induced seizures in chicks

Treatment (mg/kg)	Recovery period (Min.)	Quantal protection	Percentage protection
D/W 10 mL/kg	8.50 ± 0.85	0/10	0
IALE 100	6.60 ± 0.52	0/10	0
IALE 200	6.66 ± 0.65	1/10	10
IALE 300	8.00 ± 1.10	4/10	40
PTY 20	–	10/10	100

Data are presented as mean ± S.E.M., No significant difference among the groups of chicks—One-way ANOVA followed by Dunnett's post hoc test, $n = 10$, D/W = Distilled water, IALE = *Ipomoea asarifolia* leaf extract, PTY = Phenytoin

Table 5 Effect of *Ipomoea asarifolia* ethanolic leaf extract on strychnine-induced seizures in mice

Treatment (mg/kg)	Onset of seizures (Min.)	Quantal protection	Percentage protection
D/W 10 mL/kg	4.17 ± 0.70	0/6	0.00
IALE 150	6.50 ± 0.22	0/6	0.00
IALE 300	7.33 ± 0.84*	0/6	0.00
IALE 600	5.33 ± 0.67	0/6	0.00
DZP 2	5.50 ± 0.99	0/6	0.00

Data are presented as Mean ± S.E.M., * = $p < 0.05$ as compared to D/W group—One-way ANOVA followed by Dunnett's post hoc test, $n = 6$, D/W = Distilled water, IALE = *Ipomoea asarifolia* leaf extract, DZP = Diazepam

LD_{50} of *Ipomoea asarifolia* ethanolic leaf extract

The intraperitoneal LD_{50} of *Ipomoea asarifolia* ethanolic leaf extract in mice and chicks was calculated as 2,150 mg/kg body weight.

Effects of *Ipomoea asarifolia* ethanolic leaf extract on PTZ-induced seizures in mice

In PTZ test, *Ipomoea asarifolia* extract delayed the onset of seizure in mice independent of the dose given. At dose of 300 mg/kg, the extract has significantly ($p < 0.05$) delayed the time onset of seizure in mice with mean onset time of 6.33 ± 0.94 when compared to negative control group (3.17 ± 0.48). However, at dose of 600 mg/kg, the extract has no statistically significant effect against seizure in the mice, although it appreciably increased the mean onset time for the seizures and offered 16.67% protection. The standard anti-seizures drug sodium valproate significantly ($p < 0.01$) protected the mice against seizures with the mean onset of seizure 8.33 ± 1.45 when compared to the negative control. It also offered 50% protection (Table 3).

Effects of *Ipomoea asarifolia* ethanolic leaf extract on MES-induced seizures in chicks

In MES-induced seizures in chicks, none of the doses of *Ipomoea asarifolia* used protected the chicks against seizures. However, the standard control drug (phenytoin, 20 mg/kg) prevented all the animals from electroshock-induced seizures. Notwithstanding, *Ipomoea asarifolia* extract (200 and 300 mg/kg) conferred 10 and 40% protection, respectively, against seizures in relation to negative control which gave 100% (Table 4).

Effects of Ipomoea asarifolia ethanolic leaf extract on strychnine-induced seizures in mice

The administration of *Ipomoea asarifolia* ethanolic leaf extract (300 mg/kg) significantly ($p < 0.05$) delayed the onset of strychnine-induced seizures with mean onset of 7.33 ± 0.84 min when compared to the negative control (4.17 ± 0.70 min). However, there was no protection against seizures (Table 5).

Effects of *Ipomoea asarifolia* ethanolic leaf extract on picrotoxin-induced seizures in mice

The administration of *Ipomoea asarifolia* (150, 300, 600 mg/kg) used did not offer a significant ($p > 0.05$) protection against picrotoxin-induced seizures. However, at the 150 mg/kg, the extract offered 16.67% protection against picrotoxin-induced seizures. The standard drug (phenobarbitone, 10 mg/kg) protected all the mice from seizures and conferred 100% protection in relation to negative control group (Table 6).

Table 6 Effect of *Ipomoea asarifolia* ethanolic leaf extract on picrotoxin-induced seizures in mice

Treatment (mg/kg)	Onset of seizures (Min.)	Quantal protection	Percentage protection
D/W 10 mL/kg	12.83 ± 1.28	0/6	0.00
IALE 150	14.40 ± 1.17	1/6	16.67
IALE 300	13.50 ± 2.26	0/6	0.00
IALE 600	13.33 ± 0.67	0/6	0.00
PHB 10	–	6/6	100.00

Data are presented as Mean ± S.E.M., No statistically significant differences among mice groups—One-way ANOVA followed by Dunnett's post hoc test, $n = 6$, D/W = Distilled water, IALE = *Ipomoea asarifolia* leaf extract, PHB = Phenobarbitone

Table 7 Effect of *Ipomoea asarifolia* ethanolic leaf extract on 4-aminopyridine-induced seizures in mice

Treatment (mg/kg)	Onset of seizures (Min.)	Quantal protection	Percentage protection
D/W 10 mL/kg	8.33 ± 0.56	0/6	0.00
IALE 150	14.00 ± 0.91*	0/6	0.00
IALE 300	16.50 ± 1.15**	0/6	0.00
IALE 600	18.33 ± 1.17**	0/6	0.00
PHB 10	–	6/6	100.00

Data are presented as Mean ± S.E.M., * = $p < 0.01$, ** = $p < 0.001$ as compared to D/W group—One-way ANOVA followed by Dunnett's post hoc test, $n = 6$, compared to D/W group, D/W = Distilled water, IALE = *Ipomoea asarifolia* leaf extract, PHB = Phenobarbitone

Effects of *Ipomoea asarifolia* ethanolic leaf extract on 4-AP-induced seizures in mice

The administration of *Ipomoea asarifolia* extract (150, 300 and 600 mg/kg) significantly ($p < 0.05$) delayed the onset of seizures induced by 4-aminopyridine, with the mean onset of seizure of 14.00 ± 0.91, 16.50 ± 1.15 and 18.33 ± 1.17 min, respectively, when compared to the negative control (8.33 ± 0.56). Phenobarbitone (10 mg/kg) which was the standard drug, fully secured the mice from seizures and conferred 100% protection (Table 7).

Discussion

Natural plant products are still the best sources for discovery of new therapeutic agents (Dzobo 2022). In the present study, phytochemical screening of leaves of *Ipomoea asarifolia* has shown the presence of flavonoids, saponins, alkaloids, tannins, steroids and terpenoids which was also corroborated by Aliyu et al. (2011). There are two animal experimental models of seizures (MES and PTZ tests) that serve as gold standard in the screening of plants with anticonvulsant properties, and both models were used in this study. The MES model of seizure corresponds to the "grand mal" which is also referred to the generalized tonic clonic seizures in human, while PTZ-induced seizure model corresponds to human generalized seizures of petit mal and myoclonic type (Löscher and Schmidt 1988; Wang et al. 2022). Other models used in this study include picrotoxin, strychnine and 4-aminopyridine-induced seizures.

Pentylenetetrazole induces seizures by impeding the chloride ion channel connected with gamma-aminobutyric acid type A ($GABA_A$) receptors which interferes with neurotransmission at the GABA receptor site. Drugs such as benzodiazepines that enhance the inhibitory effects of GABA can abolish the seizures induced by PTZ (Nicholson 2018). In this study, *Ipomoea asarifolia* ethanolic leaf extract has meaningfully increased the threshold of seizure in PTZ-induced mice model dose independently. The degree of protection exerted by the leaf extract of *Ipomoea asarifolia* on PTZ-induced seizure may be attributed to the presence of saponins and flavonoids as reported by preceding studies (Du et al. 2002; Choudhari et al. 2011; Singh et al. 2012). Quantitative phytochemical analysis of *Ipomoea asarifolia* leaf extract also revealed the occurrence of flavonoids and saponins in high proportion which further buttress the assertion that the anticonvulsant properties of the extract are attributed to the presence of flavonoids and saponins. Some flavonoids at high concentration act as agonist at the gate receptor in the absence of GABA. The flavonoids usually interact with two or more active sites on $GABA_A$ receptors (Wasowski and Marder 2012). The correlation for the anticonvulsant activity of the leaf extract of *Ipomoea asarifolia* with the presence of flavonoids has also been supported by the fact that several flavonoids have been found to be ligands for $GABA_A$ receptors and can act like benzodiazepine-like compounds (Jäger and Saaby 2011; Wasowski and Marder 2012).

Maximal electroshock induces synchronous neural discharge in the brain through the input of artificial current and is used to induce acute epileptic behaviors in animals, usually generalized tonic clonic seizures (Xiang et al. 2019; Kamiński et al. 2020). In the present study, *Ipomoea asarifolia* leaf extract could not safeguard the chicks from seizures nor reduced the mean recovery time from the MES-induced seizures, although the standard drug phenytoin (20 mg/kg) secured the chicks completely from THLE. Notwithstanding, *Ipomoea asarifolia* leaf extract at 300 mg/kg has conferred 40% protection against THLE. The level of protection against THLE by the extract shows its ability to curtail seizure discharges in the brain which is the characteristic of grand mal epilepsy. Available drugs in the market such as lamotrigine, phenobarbitone and phenytoin which are used clinically for the

management of partial seizures and generalized tonic clonic suppress THLE in the electroshock test model (Sarhan et al. 2016).

Strychnine produces seizures by interfering with the postsynaptic inhibition facilitated by glycine—an inhibitory neurotransmitter to the spinal cord neurons (Du et al. 2015). Strychnine increases the level of amino acid and glutamic acid in the brain, which acts as a neurotransmitter for excitatory nerve impulses leading to myocontraction (Gupta et al. 2014). In this study, *Ipomoea asarifolia* ethanol leaf extract (300 mg/kg) exerted anticonvulsant activity against strychnine-induced seizures by increasing the seizure threshold. This suggests that the extract might also be acting via glycinergic pathway.

Picrotoxin induces seizures in rodents by blocking the chloride ion channels linked to pentameric $GABA_A$ receptors between the α and β sub-unit of the receptor preventing the entry of chloride ions into the brain and consequently inhibitory transmission in the brain (Velíšková et al. 2017), unlike PTZ that acts on benzodiazepine site between α and γ sub-unit of the pentameric $GABA_A$ receptor (Ghit et al 2021). In this study, *Ipomoea asarifolia* ethanol leaf extract did not provide significant changes on the mean onset or quantal protection against picrotoxin-induced seizures which suggests its lack of participation on the chloride channel.

4-Aminopyridine acts by blocking potassium channel leading to seizures by increasing the release of neurotransmitter glutamate and calcium while preventing GABAergic neurotransmission (Yamaguchi and Rogaski 1992; Löhle et al. 2008). In the current study, *Ipomoea asarifolia* ethanol leaf extract protected the mice against 4-aminopyridine-induced seizure dose dependently. The protective role of the extract could be by interfering with the ability of 4-aminopyridine to induce seizure via the potassium channel (Wickenden 2002; Thouta et al. 2021).

Conclusions

This study has shown that *Ipomoea asarifolia* ethanolic leaf extract possesses anti-seizure activities against murine models of seizures. The finding has justified the folkloric usage of the plant for the management of convulsion.

Abbreviations

AED: Antiepileptic drugs; ARRIVE: Animal research: reporting of in vivo experiments; IALE: *Ipomoea asarifolia* Ethanolic leaf extract, NMDA: *n*-methyl-D-aspartate; PTZ: Pentylenetetrazole; THLE: Tonic hind limb extension; GABA: Gamma-aminobutyric acid; $GABA_A$: Gamma-aminobutyric acid type A; MES: Maximal electroshock.

Acknowledgements

Authors acknowledged the technical support by Aliyu Ahmed of Pharmacology and Therapeutics Laboratory, Bayero University Kano, Nigeria.

Author contributions

SSC, ABN, SMC, YJ, AM, LAB contributed to conceptualization; SSS and ABN were involved in experiments; YJ, AM and LAB contributed to supervision; SSC, ABN and SMC were involved in data analysis and writing draft; and YJ, AM and LAB reviewed and revised the manuscript. All authors read and approved the final manuscript.

Funding

No funding was received for this work.

Availability of data and materials

Data will be given on request through the corresponding author.

Declarations

Ethics approval and consent to participate

The experimental procedures were carried out strictly in accordance with the "Guide to the care and use of laboratory animals in research and teaching" as detailed in NIH publications volume 25 No.28 revised in 1996 (Council 2011).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 2 June 2022 Accepted: 28 June 2022
Published online: 15 July 2022

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