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EVALUATION OF ANTICONVULSANT ACVTIVITY OF METHANOL LEAF EXTRACT OF *AMARANTHUS SPINOSUS* L. (AMARANTHACEAE) ON LABORATORY ANIMALS

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Abstract

Amaranthus spinosus is a widely used medicinal plant in African traditional medicine. The ethno medicinal claim for the use of its leaf extracts in the management of convulsions is well acclaimed among communities of northern Nigeria. The objective of the study is to evaluate the anticonvulsant potentials of methanol leaf extract of *Amaranthus spinosus* in laboratory animals. Acute toxicity tests and phytochemical screening were performed. The anticonvulsant properties of the extract were assessed in chicks against electrically generated seizures and in mice against seizures induced by strychnine, pentylenetetrazole, and picrotoxin at dosages of 150, 300, and 75 mg/kg. In mice, the estimated intraperitoneal LD_{50} was 2000 mg/kg, whereas in chicks, it was 1000 mg/kg. The extract's phytochemical screening identified the following compounds: Anthraquinones, alkaloids, flavonoids, cardiac glycosides, saponins, streroids, tannins, and triterpines. Methanol leaf extracts of *Amaranthus spinosus* (MLEAS) provided 30 % protection against maximal electroshock induced seizure at 300 and 75 mg/kg. Protection of 16.67 % was offered at 150 and 75 mg/kg against pentylenetetrazole induced seizure. The extract similarly conferred 33.33 % protection at 75 mg/kg against Strychnine induced seizure and 16.67 % protection at 150 mg/kg against Picrotoxin induced seizure. Our findings therefore suggest that methanol leaf extract of *Amaranthus spinosus* possesses anticonvulsant activity and thus provide the ethno medicinal rationale for its use in the management of convulsions.

Keywords: *Amaranthus spinosus,* Anticonvulsant, Plant extracts, In-vivo activity

Introduction

Amaranthus spinosus L. is an annual or perennial herb of the *Amaranthus* genus and belongs to the family of Amaranthaceae, which is the largest of the family. Nigerian thorn, spiny amaranth, prickly amaranth, and spiny pigweed are a few of the plant's common names. Locally, it is referred to as 'Namijin Zaki Banza' (Hausa), 'Efotete' or 'Teteegun' (Yoruba), 'Haakoondiyam' (Fulfulde), and 'Nnunouku' (Igbo). *A. spinosus* is used ethno medically as a laxative, diuretic, stomachic, antipyretic, to improve appetite, in blood diseases, to treat burning sensation, epilepsy, piles, bronchitis, rat bite, leprosy, and leucorrhea. The roots and leaves of the plant are given to children as an emollient, laxative, poultice for boils and abscesses (Paula *et al.,* 2020). The plant is also employed in the treatment of hepatic problems and as an anti-inflammatory, antimalarial, antibacterial, antiviral, antidiuretic, and antimicrobial agent (Oladele, 2017, Stintzing, 2018). Since ancient times, Amaranthus extracts have been used to cure a variety of illnesses. Studies conducted in vivo and in vitro have shown that *A. spinosus* possesses a number of beneficial qualities, most of which are due to its potent antioxidant activity (Karki *et al.,* 2018). A certain degree of anti-inflammatory actions against cancer are produced by *A. spinosus* (Thongphasuk *et al.,* 2003). Amaranthine, isoamaranthine, hydroxycinnamates, quercetin, and kaempferol glycosides were discovered to be components of *A. spinosus* (Rajasekaran *et al.,* 2014).

World Health Organisation (WHO) defined epilepsy as 'a chronic non communicable disease of the brain that affects around 50 million people worldwide, characterized by recurrent seizures, which are brief episodes of involuntary movement that may involve a part of the body (partial) or the entire body (generalized) and are sometimes accompanied by loss of consciousness and control of bowel or bladder function' (WHO, 2023). It is one of the most prevalent neurological conditions that have a substantial effect on a person's quality of life (Neera *et al.,* 2020).

Although there are numerous underlying diseases that can cause epilepsy, the exact cause of the condition is still unknown in about 50% of cases worldwide. However, structural, genetic, infectious, metabolic, immune, anoxia, toxic, space-occupying lesions, circulatory disturbances, cerebral oedema, congenital, due to degenerative diseases, or it may have an unidentified cause are some of the other causes of epilepsy (WHO, 2017). Antiepileptic drugs (AEDs) are the cornerstone for the management of epilepsy. Treatment is initiated with a single AED administered at a low dosage, unless an immediate therapeutic impact is required, such as for status epilepticus or frequent seizures. The dosage should be gradually increased to the lowest practical maintenance dose in order to minimize side effects (Perucca *et al.,* 2018). The therapeutic objective of AED therapy, especially for individuals with intractable epilepsy, is to reduce seizure frequency at levels that have minimal adverse effects (Prabhaswara *et al.,* 2019).

A particular diet (the ketogenic diet) or a surgery to implant a tiny electrical device within the body may be able to manage seizures. Only about 70% of people are anticipated to have adequate seizure control with the available AEDs. Even in individuals for whom the medication is helpful, almost 60% have some sort of negative side effects, and of these, roughly 33% are forced to switch medications as a result of unacceptable side effects (NHS 2019, Maguire 2021).

Despite contemporary antiepileptic medications, many epileptic patients struggle to manage their seizures, to this cause, some turn to alternative or complementary therapies. The usage of traditional medical herbs (TMH) is growing in popularity, herbal medicines have been utilized to treat seizures for generations in Nigerian traditional medicine (Sahranavard 2014, Achika 2023).

The majority of customers believe herbal medicine, one of the most well-liked Complementary and alternative medicines (CAMs), to be both secure and efficient. Nigerians rely deeply on traditional medicine, about 80 % of its population uses it almost exclusively while 95 % use it together with western medicine. This is due to the belief that it treats the patient as a whole rather than simply one component of the illness (Toyin 2018, Samuel 2019).

The objective of the study was to evaluate the anticonvulsant potentials of methanol leaf extract of *Amaranthus spinosus* in laboratory animals using various acute seizure models; Pentylenetetrazole, Maximal Electroshock Test, Strychnine and Picrotoxin induced seizure models.

Materials and methods

Drugs, chemicals and equipment:

Sodium valproate (Unnati pharmaceuticals, India), Phenytoin sodium (Parker-Davis and Co Ltd. Detroit), Phenobarbitone (Lab Renaudin, France), Methanol, picrotoxin, pentylenetetrazole, and strychinine (Sigma chemical company, St. Louis, USA), analytical balance (Mettler Instrument Corporation, U.S.A.), electroconvulsive apparatus (Orchid scientific model EC - 01).

Animals

Swiss albino mice, weighing between 18 and 25 g of either sex, were procured from the Kano animal facility of Bayero University's Department of Pharmacology and Therapeutics. 30 to 40 g day-old Ranger cockerels were obtained from Yammfy chicks in Illemona, Kwara state. The animals were kept in the pharmacology laboratory animal house of the Department of Pharmacology and Therapeutics, Bayero University Kano, Nigeria, where they were given time to acclimate. The animals were housed in a well-ventilated room at room temperature and provided standard animal feed with ad libitum access to water. The animals were treated carefully in accordance with Bayero University's protocols for the use and care of laboratory animals.

Collection and identification of plant material

Amaranthus spinosus leaves were collected in the

month of October 2021. The plants were identified in the herbarium section of the Department of Biological Sciences, Faculty of life sciences, Bayero University Kano, by a taxonomist Baha'uddeen Sa'id Adam. Identification number was obtained (BUKHAN 0018) and deposited for future reference (Nazifi *et al.,* 2017).

Plant preparation and extraction

The leaves were shade dried for two weeks at room temperature to achieve constant weight. The dried leaves were then ground with a pestle and mortar into a fine powder. Using the cold maceration extraction method, 9 litres of 70 % v/v methanol (70 % Methanol: 30 % Water) were used to extract the powdered leaf (2000 g) for 1 week. The resulting extract was then evaporated at 50 ºC in a thermostat oven. After weighing, the dried extract was kept in a desiccator until when it is needed (Malami *et al.,* 2017).

Phytochemical screening

In order to confirm the presence or absence of secondary metabolites such as alkaloids, streroids, cardiac glycosides, flavonoids, tannins, terpenoids, anthraquinones, and saponins, phytochemical screening was conducted on the methanol leaf extract of *A. spinosus* based on the procedure prescribed by Sofowara Trease and Evans Pharmacognosy (Evans, 2009).

Acute toxicity studies

The procedure outlined by Lorke (1983) was used to determine the mice's median lethal dosage (LD_{50}) of *A. spinosus* methanol leaf extract. There were two phases to the study. In the first phase, nine mice of each sex were randomly divided into three groups of three mice each, and each group was given 10, 100, or 1000 mg/kg of *A. spinosus* methanol leaf extract. The animals were observed for 24 hours following treatment to look for any adverse effects, including death. In the second phase, three mice received more precisely calculated intraperitoneal (i.p.) doses of the extract based on the findings of the first phase, after 24 hours, they were also observed for signs of toxicity and mortality. The geometric mean of the lowest dose that resulted in death and the highest dose that was non-lethal to the animal was used to determine the LD_{50}.

Anticonvulsant studies

Maximal electroshock (MEST) - induced convulsion test in chicks

Using a technique outlined by Swinyard and Kupferberg (1985), the maximal electroshock (MEST) induced convulsion test was performed. Five sets of ten chicks each were formed at random. The first group served as the negative control and received distilled water (10 ml/kg i.p). Graded doses of the extract (150, 300, and 600 mg/kg, respectively) were administered to groups 2 through 4, whereas phenytoin (20 mg/kg, i.p) was given to group 5 as a positive control. Thirty minutes later, maximal electroshock was applied to induce seizures in the chicks using an Orchid

international electroconvulsiometer (EC – 01) coupled to corneal electrodes fixed on the chicks' upper eyelids after being dipped in normal saline. For the duration of the study, the electroconvulsiometer's parameters, such as current, pulse width, frequency, and shock duration—were set and kept at 150 mA, 0.6 ms-1, 50 Hz, and 0.2 s, respectively. The manifestations of the seizures were hind limb tonic extension (HLTE). One measure of the extract's anticonvulsant effectiveness was its capacity to inhibit the hind limb from tonic extension. The recovery time for convulsing chicks was noted.

Pentylenetetrazole (PTZ) - induced convulsion test in mice

The method described by Swinyard *et al.* (1989) was employed. Thirty mice of either sex were labeled and divided into 5 groups, each group consisting of 6 mice labeled 1 to 5. The first group was pretreated intraperitoneally with distilled water (10 mg/kg) as negative control. The second, third and fourth groups were pretreated with graded doses of 300, 150, and 75 mg/kg of the extract i.p respectively. The fifth group was pretreated with sodium valproate (200 mg/kg i.p) as positive control. After 30 minutes all pretreated groups were administered PTZ 80 mg/kg subcutaneously and observed for clonic spasms over a duration of 30 minutes. Convulsions were seen as episodes of clonic spasm (loss of righting reflex). The absence of loss of righting reflex during the 30 minutes of observation was regarded as protection against PTZ induced convulsions.

Strychnine (STC) - induced convulsion test in mice

The procedure outlined by Lehmann *et al.,* (1988) was used. Thirty mice were grouped up into five groups of six mice each. As a negative control, distilled water (10 ml/kg i.p.) was used as a pretreatment for the first group. In the second, third, and fourth groups, the extract was administered at doses of 300, 150, and 75 mg/kg, respectively, and the fifth group was given 30 mg/kg of phenobarbitone intraperitoneally. Mice in each group received an injection of strychnine (1 mg/kg sc) thirty minutes later. Within thirty minutes of administering strychnine, the prevention of tonic extension jerks in the hind limbs was considered to be a sign of anticonvulsant activity.

Picrotoxin (PCT) - induced convulsion test in mice

The procedure proposed by Ogbonnia (2003) was implemented. Thirty mice in total were randomly assigned to five groups of six mice each. As the negative control, the first group was pretreated with 10 ml/kg i.p. of distilled water. A. spinosus extract was given as follows, 300, 150, and 75 mg/kg (i.p.) to the second, third, and fourth groups respectively. As a positive control, 30 mg/kg (i.p.) of phenobarbitone was given to the fifth group. Thirty minutes after pretreatments, mice in all groups received freshly prepared picrotoxin (1.2

mg/kg, s.c.). The mice were watched for 30 minutes to see if they convulsed or not.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS statistics) version 28 was used to run the statistical analysis. The results were presented as mean ± standard error of the mean, and also as percentages were applicable. The study employed analysis of variance (ANOVA) and Dunnett's post hoc test to determine the significant differences between the control and test groups.

Results

Percentage yield of methanol leaf extract of *A. spinosus* was 9.26 % w/w. Phytochemical analysis revealed the presence of alkaloids, anthraquinones, cardiac glycosides, flavanoids, saponins, steroids, tannins and terpenes. Median lethal dose (LD_{50}) of the extract was precisely calculated to be 2154.07 mg/kg on mice (~2000 mg/kg) and 1000 mg/kg on chicks.

Effect of Methanol Leaf Extracts of *A. spinosus* on Maximal Electroshock Test Induced Convulsion in Mice.

The extract provided 30 % protection at 300 and 75 mg/kg. There was no significant difference($p>0.05$) in the mean recovery period between the extract tested group and the distilled water group. Phenytoin standard group conferred 100 % protection (Table 1).

Table 1: Effect of Methanol Leaf Extracts of *A. spinosus* on Maximal Electroshock Test Induced Convulsion in Mice

Treatment in (mg/kg)	Mean Recovery Time (min)	Quantal Protection	% Seizure Protection
DW 10ml/kg	8.20±0.94	0/10	0
MLEAS 300	11.86±2.03	3/10	30
MLEAS 150	15.71±3.19	2/10	20
MLEAS 75	11.33±1.82	3/10	30
PBT 20	-	10/10	100.00

Key: Onset of seizures presented as Mean ± SEM, no significant difference compared to distilled water control group – One-way ANOVA followed by Dunnett's*post hoc* test, n=10, DW – Distilled water, MLEAS = Methanol leaf extract of *Amaranthus spinosus*, PBT = Phenobarbitone

Effect of Methanol Leaf Extracts of *A. spinosus* on Pentylenetetrazole Induced Convulsion in Mice.

The extract provided protection at 150 mg/kg and 75 mg/kg (16.67 %). No significant prolongation (p

>0.05) in mean onset of seizure was observed in any of the doses administered, highest motality was seen at 150 mg/kg (33.33 %) (Table 2).

Table 2: Effect of Methanol Leaf Extracts of *A. spinosus* on Pentylenetetrazole Induced Convulsion in Mice.

Treatment in (mg/kg)	Mean Onset of Seizure (min)	Quantal Protection	% Seizure Protection	% Mortality
DW 10ml/kg	**8.83±0.40**	**0/6**	**0.00**	**33.33**
MLEAS 300	8.00±1.58	0/6	0.00	16.67
MLEAS 150	8.50±0.64	1/6	16.67	33.33
MLEAS 75	8.00±0.77	1/6	16.67	16.67
SVP 200	-	6/6	100.00	0.00

Key: Onset of seizures presented as Mean ± SEM, no significant difference compared to distilled water control group – One-way ANOVA followed by Dunnett's *post hoc* test, n=6, DW – Distilled water, MLEAS = Methanol leaf extract of *Amaranthus spinosus*, SVP=sodium valproate

Effect of Methanol Leaf Extracts of *A. spinosus* on Strychnine Induced Convulsion in Mice.

Methanol leaf extract of *A. spinosus* provided 33.33 % protection against strychnine induced seizure at 75 mg/kg. Among the treatments groups mortality recorded was highest at 300 mg/kg and 150 mg/kg (66.67 %). No significant increase ($p > 0.05$) in mean onset of seizure was seen (Table 3).

Table 3: Effect of Methanol Leaf Extracts of *A. spinosus* on Strychnine Induced Convulsion in Mice.

Treatment in (mg/kg)	Mean Onset of Seizure (min)	Quantal Protection	% Seizure Protection	% Mortality
DW 10ml/kg	**6.17±0.60**	**0/6**	**0.00**	**100**
MLEAS 300	10.00±1.87	0/6	0.00	66.67
MLEAS 150	8.50±0.80	0/6	0.00	66.67
MLEAS 75	9.75±0.85	2/6	33.33	50.00
PBT 20	-	6/6	100.00	0.00

Key: Onset of seizures presented as Mean ± SEM, no significant difference compared to distilled water control group – One-way ANOVA followed by Dunnett's *post hoc* test, n=6, DW – Distilled water, MLEAS = Methanol leaf extract of *Amaranthus spinosus*, PBT = Phenobarbitone

Effect of Methanol Leaf Extracts of *A. spinosus* on Picrotoxin Induced Convulsion in Mice.

Methanol leaf extract of *A. spinosus*provided 16.67 % protection against picrotoxin induced seizure at 150

mg/kg. Among the treatments groups mortality recorded was highest at 300 mg/kg (83.33 %). No significant prolongation ($p > 0.05$) in mean onset of seizure was seen in the treatment group when compared to distilled water group (Table 4).

Table 4: Effect of Methanol Leaf Extracts of *A. spinosus* on Picrotoxin Induced Convulsion in Mice.

Treatment in (mg/kg)	Mean Onset of Seizure (min)	Quantal Protection	% Seizure Protection	% Mortality
DW 10ml/kg	**16.0±2.51**	**0/6**	**0.00**	**33.33**
MLEAS 300	13.50±0.89	0/6	0.00	83.33
MLEAS 150	16.20±2.77	1/6	16.67	16.67
MLEAS 75	11.83±2.32	0/6	0.00	100
PBT 20	-	6/6	100.00	0.00

Key: Onset of seizures presented as Mean ± SEM, no significant difference compared to distilled water control group – One-way ANOVA followed by Dunnett's *post hoc* test, n=6, DW – Distilled water, MLEAS = Methanol leaf extract of *Amaranthus spinosus,* PBT = Phenobarbitone

Discussion

Certain flavonoids, monoterpenes, and alkaloids can prevent seizures caused by pentylenetetrazol, picrotoxin, and N-methyl-D, L-Aspartic acid (NMDLA) (Librowski *et al.,* 2000). Several experimental seizure models, including maximal electroshock and pentylenetetrazole have found triterpenic steroids and triterpenoidalsaponins to have anticonvulsant effect (Kasture *et al.,* 2002). Many phytochemical components are found to alter the functions of the central nervous system, for instance, saponins and flavonoids have been claimed to have anticonvulsant properties (Kavvadias *et al.,* 2019). Additionally, terpenoids, tannins, and alkaloids have potential of conferring antiepileptic effects (Hedge *et al.,* 2009, Kaur *et al.,* 2020). Hence the extract containing some amount of alkaloids, flavonoids, terpenoids, steroids, saponins, and tannins demonstrate their possibility to possess anticonvulsant activity induced by several proconvulsive agents. Methanol extracts of plants such as root of *Combretum micranthum* (Danmalam *et al.,* 2011), stem bark of *Boswellia dalzielli* (Nazifi *et al.,* 2017) and leaf of *Laggera aurita* (Malami *et al.,* 2017)demonstrated anticonvulsant activity and all have been reported to contain alkaloids, flavonoids, saponins and terpenoids, methanol leaf extracts was also found to contain the aforementioned phytochemicals and was equally found to possess anticonvulsant effect, so considering these fact we can infer that these phytochemicals have potential anticonvulsant activities.

Acute toxicity tests on mice indicated that the extract was mildly toxic, in line with the classification by Rang *et al.,* (2019). Following a

24-hour study period, no signs of toxicity or mortality were observed up to a dose of 1600 mg/kg. This indicates that the extract was deemed safe at the dosage levels that were examined. Since every animal was able to survive at a level of 1600 mg/kg body weight but died at 2900 mg/kg.

A. spinosus was found to demonstrate anticonvulsant activity against Pentylenetetrazole induced seizure which could be due to its ability to prevent the effect of Pentylenetetrazole on GABA-A receptors. Pentylenetetrazole a model of absence seizure may cause convulsions by preventing GABA from acting on GABA-A receptors (Vasconcelos *et al.,* 2007). It has been suggested that one of the underlying causes of epilepsy is the inhibition of GABA's neurotransmission, a crucial inhibitory neurotransmitter in the brain. Seizures are reportedly prevented by enhancing GABAergic neurotransmission while seizures are increased by lowering its neurotransmission (Amabeokua 2007; Silambujanaki 2010). GABA is the primary inhibitory neurotransmitter in the brain, whereas glutamic acid is an excitatory neurotransmitter (Neera *et al.,* 2020). Common antiepileptic drugs like phenobarbitone and diazepam are believed to function by increasing GABA-mediated inhibition in the brain. Since phenobarbitone and diazepam have been shown by numerous authors to increase GABA-mediated inhibition in order to achieve their anticonvulsant effects, it is anticipated that they will protect mice from seizures caused by pentylenetetrazole (Mahomed 2006, Rang 2019). The ability of the methanol leaf extract of *A. spinosus* to offer protection against PTZ induced seizures was likely brought on by the activation of GABA neurotransmission. Since the extract inhibited seizures, it can be concluded that the extracts may possess an anticonvulsant activity and hence, may likely be used in the treatment of petit mal type of seizures.

The grandmal type of epilepsy is represented by maximal electroshock-induced convulsion in animals; medications that treat generalized tonic-clonic seizures specifically inhibit the tonic extensor phase (Silambujanaki *et al.,,* 2010). The most notable effect of phenytoin was the inhibition of the tonic extensor phase of maximal electroshock seizures. Many medications that raise brain levels of gamma amino butyric acid have demonstrated anticonvulsant activity against maximal electroshock-induced seizures (Perucca *et al.,* 2018). Drugs can elevate seizure threshold and/or stop the spread of seizures through a variety of molecular mechanisms and attempts to link specific mechanisms of action with antiepileptic drug, some of the drugs include voltage-dependent Na^+ channels blocker, such as phenytoin, carbamazepine, lamotrigine, felbamate, and valproate (Mahomed & Ojewole 2006). The extract provided quantal protection against maximal electroshock type of seizure and hence may likely be effective in the management of grandmal type of epilepsy.

Picrotoxin is known to cause seizures by blocking the chloride channels connected to the GABA A receptor at allosteric site, which counteracts the

effects of GABA (Rang *et al.,* 2019). Due to picrotoxin's antagonistic activity on GABA in many brain regions, it typically results in generalized tonic-clonic convulsions that have the potential to be fatal (AbdulGhani 2013). The plant extract may include a component or compounds that enhance GABA transmission, as evidenced by the fact that it prevented some mice from experiencing convulsions caused by picrotoxin.

Strychnine is a competitive receptor antagonist of glycine (Rajendra *et al.,* 1997). The mechanism underlying strychnine-induced seizures is thought to involve direct antagonistic action on strychnine-sensitive glycine receptors in the brainstem, spinal cord, and higher brain areas. This results in the abolishment of spinal reflexes, which in turn causes motor disturbance, hypertonality, hyperactivity of sensory, visual, and auditory perception, tonic convulsions, and death via cardiac arrest, respiratory paralysis, or visual or auditory hallucinations (Philippe *et al.,* 2004). The fact that the extract protected mice against strychnine-induced seizures suggests the possibility of it containing compound(s) that likely act by facilitating glycine mediated inhibitory neurotransmission.

Conclusion

The result obtained from this study has shown that the methanol leaf extract of *A. spinosus* has demostrated anticonvulsant activity against Pentylenetetrazole (16.67 % protection at both 150 mg/kg and 75 mg/kg), Maximal electroshock test (30 %, 20 %, and 30% protection at 300, 150 and 75 mg/kg respectively), Stychnine (Conferred 33 % protection at 75 mg/kg) and Picrotoxin (16.67 % protection at 150 mg/kg) induced seizures, thus providing scientific justification for the ethnomedicinal use of the plant in the treatment of epilepsy.

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Conflict of interest

The authors declare no conflict of interest

References

AbdulGhani, A. S. (2013). Changes in amino acid concentrations in rat brain after pretreatment with neuroleptic drugs and picrotoxin. *Biochemical Society Transactions*.8, 64–65

Achika J, L., Yusuf, A. J., and Ayo R, G. (2023). Flavonoids from Nigerian medicinal plants and their bioactivities, a review. *Journal ofPhytomedicine*.100: 05.001

Amabeokua, G. J., Green, I., and Kabatende, J. (2007). Anticonvulsant activity of *Cotyledon orbiculata* L. (Crassulaceae) leaf extract in mice. *Journal of Ethnopharmacology* 112: 101-107.

Danmalam, U. H., Idoko, V. E., Yaro, A. H., Magaji, M. G., Agunu, A., and Abdurahman D. (2011). Phytochemical and Anticonvulsant Screening of the Aqueous Ethanol Extract of *Combretum Micranthum* Root (Combretaceae), *Nigerian Journal of Pharmaceutical Sciences* Vol. 10.

Evans, W.C. (2009). Trease and Evans Pharmacognosy 16th ed. *Elsevier Health Sciences*.p. 135-144.

Hegde, K., Thakker, S. P., Joshi, A. B., and Shastry, C. S. (2009). Anticonvulsant Activity of *Carissa carandas* Linn. Root Extract in Experimental Mice. *Tropical Journal of Pharmaceutical Research*, 8(2), 117–125

Karki, T., Harsha V. R., and Sambhu, R. (2018). Assessment of Quality of Life in Children with Epilepsy. *International Journal of Science and Research (IJSR)* ISSN: 2319-7064

Kasture, V. S, Kasture, S. B., and Chopde, C. T. (2002). Anticonvulsive activity of Buteamonosperma flowers in laboratory animals. *Pharmacology and Biochemical Behaviour*; 72: 965-972.

Kaur, J., Famta, P., Famta, M., Mehta, M., Satija, S., Sharma, N., Vyas, M., and Khurana, N. (2020) Potential Anti-epileptic Phytoconstituents: An Updated Review. *Journal of Ethnopharmacology*, 268(2), 113565.

Kavvadias, D., Sand, P., Youdim, K. A., Qaiser, M. Z., Rice-Evans, C., Baur, R., and Schreier, P. (2019). The flavonehispidulin, a benzodiazepine receptor ligand with positive allosteric properties traverses the blood brain barrier and exhibit anticonvulsant effects. *British Journal of Pharmacology*. 142: 811- 820.

Lehmann, J., Hutchison, A., McPherson, S.E., Mondadori, C., Schmutz, M., Sinton, C.M., Tsai, C., Murphy, D.E., and Wood, P.L. (1988). A selective and competitive N-methyl-D- aspartate-type excitatory amino acid receptor antagonist. *Journal of Pharmacology and Experimental Therapeutics*; 246: 65-75.

Librowski, T., Czarnecki, R., Mendyk, A., and Jastrzebska, M. (2000). Influence of new monoterpenes homologues of GABA on the central nervous system activity in mice. *Polish Journal of Pharmacology*; 52: 317-321.

Lorke, D. (1983). A new approach to practical acute toxicity testing. *Archives of Toxicology*, 54:275-287.

Maguire, J., Trina, B., Jay, A., and Salpekar D. (2021). Hypothalamic-pituitary-adrenal axis targets for the treatment of epilepsy.*Neuroscience Letters,* Volume 746, 135618.

Mahomed, I. M., and Ojewole, J. A. (2006). Anticonvulsant activity of Harpagophytum procumbens DC. (Pedaliaceae) secondary root aqueous extract in mice. *Journal of Pharmacology and Experimental Therapeutics* 69: 57-62.

Malami, S. H., Kyari, N. M., Danjuma, J., and Hussaini G. (2017). Anticonvulsant properties of methanol leaf extract of *Laggera Aurita* Linn. F. (Asteraceae) in laboratory animals, *Journal of Ethnopharmacology*, Volume 191, Pages 301-306, ISSN 0378-8741

Nazifi, A., Danjuma, N., Olurishe, T., and Ya'u, J. (2017). Behavioural Effects of Methanol Stem Bark Extract of *Boswellia dalzielii* Hutch (Burseraceae) in Mice,*African Journal of Biomedical Research.* Vol. 20; 103- 108

Neera, C., Abhilekh, S., and Cankatika, C. (2020). Newer Anti-Epileptic Drugs. *International Journal of Science and Research (IJSR)* ISSN: 2319-7064

NHS (2019). NHS to fast-track access to cannabis-based medicine for children with severe epilepsy, *Medicine* 5(8); 62-69

Ogbonnia, S.O., Jager, A.K., Van Staden, J., and

Coker, H.A.B. (2003). Anticonvulsant Activity of *Schumanniophyton magnificum* Roots extract in mice. West *African Journal of Pharmacology.*19 (182): 33-36

Oladele, A. O., Ibrahim, A. O., Almas J., Aisha, F., Mohammed, A. M., and Muhammad, S. A. (2017) Immunomodulatory activities of isolated compounds from the root-bark of *Cussonia arborea*.*Pharmaceutical Biology*, 55:1, 2240-2247

Paula, T. F., Dee, A., Snape, B., Roy, G., Beran, C., and Ann, J. (2020). Epilepsy stigma: What do we know and where next.*Epilepsy & Behavior* 22 55–62

Perucca, P., Ingrid, E. S. and Michelle, K. (2018). The management of epilepsy in children and adults. *Medical Journal of Australia;* 208 (5)

Philippe, L., Angenot, M., and Friedrich M. (2004). About the toxicity of some Strychnos species and their alkaloids,*Journal ofPharmacology,* vol. 44, no. 4, pp. 405–416,

Prabhaswara, A., Suryani, G., and Uni, G. (2019). Etiology of Symptomatic Focal Epilepsy based on Neuroimaging Result in Neurology Outpatient Clinic of Dr. HassanSadikin General Hospital. *Journal of Biomedical Research* 2(3); 526 - 538

Rajasekaran, M., Dinesh, D., Chandarasekharam, K., Fida, H., and Ahmed, B. (2014). *Amaranthus spinosus* leaf extracts and its anti-inflamatory effects on cancer, *Journal ofPharmacology.*55:1, 2358-2366

Rajendra, S., Lynch, J. W., and Schofield, P. R. (1997). The glycine receptor. *Pharmacology and Therapeutics.* 73,121–146

Rang, H. P., Dale, M. M., Ritter, J. M., and Moore, P. K. (2019). Changes in amino acid concentrations in rat brain after pretreatment with neuroleptic drugs and picrotoxin *Pharmacology 5th Edition.* pp 456-473.

Sahranavard, S., Saeedeh, G., and Mahmoud, M. (2014). Medicinal plants used in Iranian traditional medicine to treat epilepsy.*Seizure Handbook.* V23(5), P 328-332

Samuel, W., Hader, J. W., Jose, T., Amy, M., Lisbeth, H., Churl-Su, K., and Nathalie, J. (2019). Complications of epilepsy surgery: A systematic review of focal surgical resections and invasive EEG monitoring, *Epilepsia Handbook,* 54(5):840–847

Silambujanaki, P., Chitra, V., Kumari, S., Sankari, M., Raju, D., and Chandra, C. H. (2010). Anti-convulsant activity of methanolic extract of Buteamonosperma leaves. *Research Journal of Pharmaceutical, Biological and Chemical Sciences* 1: 431-435.

Stintzing FC, Kammerer D, Schieber A, Hilou A, Nacoulma, O., and Carle R. (2018). Betacyanins and phenolic compounds from *Amaranthus spinosusand Boerhaavia erecta*. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 59, 1–8.

Swinyard, E.A., and Kupferberg, H.J. (1985). Antiepileptic drugs: detection, quantification and evaluation. *Federal Proceedings*, 44: 39-43.

Swinyard, E.A., Woodhead, J.H., White, H.S., and Franklin, M.R. (1989). General Principles:Experimental selection, quantification, and evaluation of anticonvulsants. *Levy RH, Mattson B, Melrum JK and Dreifuss FE 3rd edition*. p. 85-103.

Thongphasuk, P., Suttisri, R., Bavovada, R., and Verpoorte, R. (2003). Alkaloids and a pimarane diterpenoid from Strychnos vanprukii. *Phytochemistry,* 64(4):897–901.

Toyin A. (2018). Traditional and orthodox medicinal system in Nigeria; the imperative of synthesis. *American journal of health research,* Vol 2, No 4, pp, 118-124.

Vasconcelos, S. M., Lima, N. M., Sales, G. T., Cunha, G. M., Aguiar, L. M., and Silveira, E. R. (2007). Anticonvulsant activity of hydroalcoholic extracts from Erythrinavelutina and Erythrinamulungu. *Journal ofEthnopharmacology.* 110: 271-27

WHO and International Bureau for Epilepsy (2017). ILAE/IBE/WHO Global Campaign Against Epilepsy. *A manual for Medical and Clinical Officers in Africa -Epilepsy*, 8(5) p123.

World health organization (2023). WHO Global Campaign against Epilepsy. *An Epilepsy Manual* 8(9) p154.