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Exploring the Antiepileptic Potential of *Amaranthus spinosus*: An Experimental Study in Albino Mice

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Abstract: About 60% of the world population relies on herbal medicine, and 80% depend almost entirely on it for their primary healthcare. Many of these herbs are rich in phytochemicals, thus valuable as potential sources of drugs. Amaranthus spinosus is a vegetable and ornamental plant used in African folklore to treat several illnesses. This study aimed to investigate the antiepileptic potential of the methanol leaf extract of *Amaranthus spinosus* in albino mice. Preliminary phytochemical screening and acute toxicity studies were conducted using standard methods. Anticonvulsant studies were conducted using chemo-shock models (pentylenetetrazole (PTZ) - and strychnine (STR)-induced seizures) in mice. Phytochemical screening has revealed the presence of terpenoids, tannins, saponins, alkaloids, anthraquinones, carbohydrates, cardiac glycosides, and flavonoids. Additionally, the acute toxicity studies of the extract revealed that the extract is safe in mice at 2000 mg/kg. The extract at 400 and 800 mg/kg produced a significant ($p<0.05$) delay in the mean onset of seizures, decreased the duration of seizures induced by PTZ in a dose-dependent manner, and protected the mice. The extract showed insignificant protection against strychnine-induced seizures in mice. This could serve as a scientific basis for further evaluation of the plant's potential in managing epilepsy, which can lead to the discovery of an effective antiepileptic agent with fewer side effects.

Introduction

The plant kingdom, an ancient source of medicines, comprises numerous plant species with medicinal values yet to be explored. About 60% of the world's population relies on herbal medicine, and about 80% of the population in developing countries depends almost totally on it for their primary healthcare needs (1, 2). These plants have been considered rich sources of phytochemicals, making them valuable therapeutic medicines with advantageous effects (2). Also, medicinal plants play an essential role in developing new drugs, and according to World Health Organization (WHO), about 25% of modern medicines are derived from plants (3). Many of these herbs have been used to treat seizure disorders. They were given priority due to their alleged supernatural abilities, accessibility, and affordability in contrast to the high cost and unfavorable side effects of standard antiepileptic medications in poor countries (4).

A. spinosus Linn. (Family: Amaranthaceae) is a cosmopolitan genus of annual or short-lived perennial plants. Traditionally, boiled leaves and roots of *A. spinosus* are given to children as laxatives (5). The concoction is also used traditionally as a diuretic, antidiabetic, antipyretic, anti-snake venom, antileprotic, antidepressant, and anti-gonorrhoeal, and for the treatment of convulsions (6). Several pieces of literature have reported the medicinal properties of *A. spinosus*, which scientists have scientifically validated. The analgesic activity of the petroleum ether, ethyl acetate, and methanol extracts of the whole plant of *A. spinosus* using acetic acid-induced writhing and radiant heat tail-flick models in mice was reported by Jamaluddin et al. 2011 (7). The methanolic extract of leaves of A. spinosus showed significant ($p<0.01$)

antipyretic activity by yeast-induced pyrexia method at concentrations of 200 and 400 mg/kg using Paracetamol as a standard drug (8). Also, Kumar et al. (2010) demonstrated the antioxidant activity of *A. spinosus*, while its immune-modulatory effects were reported by Lin et al. (2005) (9, 10). The antidepressant activity of the methanolic extract of *A. spinosus* was reported using Forced Swimming Test (FST) and Tail Suspension Test (TST), where it showed a significant (p<0.01) antidepressant activity comparable to Escitalopram and Imipramine (11). The methanol leaf extract was reported to possess antidiabetic, antitumor, antimicrobial, and anti-inflammatory activities (12-15). Other activities reported include diuretic, hepatoprotective, haematological, anthelmintic, laxative, spasmolytic, bronchodilator, and antiulcer activity (16-22).

Epilepsy is a group of neurological disorders characterized by recurrent seizures, varying from brief and nearly undetectable periods to extended episodes of vigorous shaking due to abnormal electrical activity in the brain (23). Recurrent motor and sensory neurologic episodes caused by abnormal brain function are the hallmark of epilepsy (24). Epilepsy affects more than 60 million people globally, and it affects people of all ages. It is more common in underdeveloped nations, associated with witchcraft and divine punishment (25, 26).

Current treatment strategies in epilepsy were designed to halt the initiation and propagation of seizures rather than treat the root cause. It has also been noted that the antiepileptic medications currently on the market neither cure the condition nor prevent relapses and are frequently linked to disabling side effects (27). The present antiepileptic medications have many drawbacks, including toxicity, intolerance, and lack of efficacy; as a result, epilepsy research has prioritized the creation of novel pharmacological compounds that can get around these obstacles. Medication adverse effects are reported in about 60% of people with epilepsy on treatments, 33% have to change drugs, and more than a quarter of people stop treatment because of many of these adverse effects (28-30). These and other challenges led to the pressing need for the development of accessible cheap, and safe medications for treating epilepsy. The current study evaluated the antiepileptic potential of methanol leaf extract of *A. spinosus* in albino mice.

Materials and Methods

Drugs and Chemicals

Normal Saline (Fidson Health Care Nigeria), Methanol (Sigma Chemical Co. St Louis, USA), Pentylenetetrazole (PTZ; Sigma Chemical Co., USA), Strychnine, and Diazepam (Alpha Laboratories Limited, India).

Collection, Identification, and Extraction of Plant Material

Fresh leaves of *A. spinosus* were collected from the Itas Gadau Local Government Area of Bauchi State in June 2021. Dr. Umar Aminu Muhammad, an ecologist, identified and authenticated the plant at the Herbarium Unit of the Department of Biological Sciences, Faculty of Science, Bauchi State University, Gadau (voucher number 00024).

Preparation of Plant Material

Fresh leaves of *A. spinosus* (Amaranthaceae) were separated from the tree branch, cleaned, air-dried in a shaded environment, and crushed into a coarse powder using a pestle and motor. 550 g of the crude powder was cold macerated with 2.5 litres of 70% methanol (in water) with constant agitation and shaking for 72 hours. The resultant mixture was filtered using Whatman No. 1 filter paper, and the filtrate was concentrated in a water bath at a temperature of 45 to 50°C to obtain a dried extract. The resulting extract was stored in a tightly labelled container for subsequent experiments.

Experimental Animals

Albino mice of both sexes (20–25 g) were obtained from the animal house of the Department of Pharmacology, Faculty of Basic Medical Sciences, Bauchi State University, Gadau. They were housed in well-ventilated cages and fed a standard rodent diet and water ad libitum. The animals were maintained under standard laboratory conditions following protocols approved by the Faculty of Basic Medical Sciences Research and Ethics Committee (FBMSRC) (BASUG/FBMS/REC/VOL.3/0092).

Preliminary Phytochemical Analysis

Preliminary phytochemical screening of the methanol leaf extract of *A. spinosus* for the presence of alkaloids, saponins, cardiac glycosides, triterpenes, flavonoids, carbohydrates, anthraquinones, and tannins was performed according to the method described by Trease and Evans (2002) (31).

Acute Toxicity Studies

The acute toxicity study of the extract was carried out using the limit test dose of Organization for Economic Cooperation and Development (OECD) guidelines 423 (32). However, a slight modification was made (addition of one mouse per group) to confirm the absence of mortality or severe toxicity (33). Before dosing, the animals fasted overnight for 12 hours with full access to water. Following the fasting period, the body weight of each animal was determined. A total of eight mice were used (four mice per group) for the study.

In the first group, the mice were subjected to acute

toxicity with the extract at a dose of 2000 mg/kg orally. Food was withheld for two h after the dosing. The animals were observed individually after dosing at least once during the first 30 minutes and periodically during the first 24 hours. The second group received 10 mL/kg of normal saline and observed as the first group. The animals were observed for signs of toxicity, including sleep changes, coma, convulsions, tremors, diarrhoea, mobility, and mortality for a total of 14 days.

Anticonvulsant Studies

Pentylenetetrazole-induced Convulsions

The method described by Mehrzadi et al. (2016) was slightly modified and used (34). Twenty mice were divided into five groups of four each. The first group was injected with 10 ml/kg of normal saline intraperitoneally. The second, third, and fourth groups were administered orally 200, 400, and 800 mg/kg of the e. The fifth group was administered 5 mg/kg diazepam intraperitoneally. Thirty minutes after pretreatment in groups 1 and 5 and 45 minutes after pretreatment in groups 2, 3, and 4, a post-treatment was made with 80 mg/kg pentylenetetrazole (PTZ) via the intraperitoneal route to induce convulsions in all five groups. Subsequently, the time of onset, duration of convulsion/tonic-clonic limb extension, percentage mortality, and the number of animals (s) protected in each group were individually observed for 30 minutes and recorded.

Strychnine-induced Convulsions

The methods described by Silambujanaki et al. (2016) were employed with modifications in the route of administration and the dose of strychnine (35). Twenty mice were divided into five groups of four each. The first group was injected with 10 ml/kg of normal saline intraperitoneally. The second, third, and fourth groups were administered 200, 400, and 800 mg/kg of the extract orally. The fifth group was administered 5 mg/kg diazepam intraperitoneally. Thirty minutes after pretreatment in groups 1 and 5 and 45 minutes after pretreatment in groups 2, 3, and 4, a post-treatment was made with 2.5 mg/kg of strychnine intraperitoneally to induce convulsions in all five groups. The time of onset, duration of convulsion/tonic-clonic limb extension, percentage mortality, and number of animals protected in each group were recorded. Mice that did not convulse 30 minutes after strychnine administration were considered protected.

Statistical Analysis

The data collected are expressed as the mean ± standard error of the mean (SEM), and the results are presented using appropriate tables. Data were compared using one-way analysis of variance (ANOVA) followed by the Dunnett post hoc test using Statistical Package for the Social Sciences (SPSS) version 22 software, where a p-value ≤0.05 was considered statistically significant.

Result

Extraction and Phytochemical Screening

A green powdered extract of 39 g was obtained from 550 g of the powdered starting material of *A. spinosus* leaves and was found to have a yield of 7.1%. Preliminary phytochemical screening of the extract revealed the presence of alkaloids, saponins, cardiac glycosides, triterpenes, flavonoids, carbohydrates, anthraquinones, and tannins (Table 1).

Table 1. Phytochemical constituents of methanol leaf extract of *A. spinosus*.

Test	Inference
Alkaloids	+
Anthraquinones	+
Carbohydrates	+
Cardiac glycosides	+
Flavonoids	+
Saponins	+
Tannins	+
Triterpenes	+

Key: (+) = Present

Acute Toxicity

The acute toxicity test was performed per the OECD guidelines 423 (limit test at 2000 mg/kg). The extract produced no mortality and was safe at a 2000 mg/kg high dose. Signs of toxicity observed include decreased water and food intake and activeness. The test animals recovered from all signs of toxicity within two days of observation. Based on the safety profile of the extract and the pilot test conducted, three graded percentages (10, 20, and 40%) were selected for the subsequent studies.

Pentylenetetrazole-induced Convulsions

The methanol leaf extract of *A. spinosus* (MLEAS) fully protected (100%) the mice against pentylenetetrazole-induced convulsions at 800 mg/kg, similar to the protective effects observed in the standard drug (diazepam 5 mg/kg) group. At 200 and 400 mg/kg doses, 25 and 75% protection against mortality was observed, respectively. The extract also showed a significant delay in onset and decreased duration of pentylenetetrazole-induced convulsions at both 400 and 800 mg/kg (Table 2).

Strychnine-induced Convulsions

The plant extracts protected 75% of the mice against strychnine-induced convulsions at 800 mg/kg, unlike the complete protection observed by the standard drug (diazepam, 5 mg/kg). At 200 and 400 mg/kg, 25 and 50% protection against mortality, respectively, were

observed. The decrease in onset and duration of seizures observed in all the tested doses of the plant were insignificant in strychnine-induced convulsions (Table 3).

Table 2. Effects of LEAS on pentylenetetrazole-induced convulsions in mice.

Group	Treatment (mg/kg)	Onset (sec)	Duration (sec)	% Protection
Normal saline	10 ml/kg	160.25±20.63	38.73±1.59	0
MLEAS	200	349.50±59.04	41.66±3.82	25
MLEAS	400	679.50±16.39*	20.61±5.27*	75
MLEAS	800	971.25±104.26*	2.17±0.79*	100
Diazepam	5	-	-	100

Note: Values are presented as the mean ± SEM; the significant difference was (*p<0.05) compared to the normal saline group. One-way ANOVA was used, followed by Dunnett's post hoc test for multiple comparisons. MLEAS; Methanol leaves extract of *A. spinosus*.

Table 3. Effects of MLEAS on strychnine-induced convulsions in mice.

Group	Treatment (mg/kg)	Onset (sec)	Duration (sec)	% Protection
Normal saline	10 ml/kg	265.5±24.20	58.67±2.33	0
MLEAS	200	402.25±28.44	52.27±1.94	25
MLEAS	400	415.75±23.48	64.58±2.14	50
MLEAS	800	533.75±14.88	63.60±1.16	75
Diazepam	5	1005.00±339.44*	3.76±1.82*	100

Note: Values are presented as mean ± SEM; the significant difference was (*p<0.05) compared to the normal saline group. One-way ANOVA was used, followed by Dunnett's post hoc test for multiple comparisons. MLEAS; Methanol leaves extract of *A. spinosus*.

Discussion

Preliminary phytochemical screening on the methanol leaves extract of *A. spinosus* revealed the presence of alkaloids, saponins, cardiac glycosides, flavonoids, carbohydrates, anthraquinones, tannins, and triterpenes. Previous studies on *A. spinosus* have reported the presence of various phytochemicals such as alkaloids, amino acids, flavonoids, glycosides, lipids, phenolics, terpenoids, steroids, saponins, betalains, catechuic tannins and carotenoids (36). These phytochemical constituents have been reported to be associated with different pharmacological activities and are explicitly related to some medicinal properties of *A. spinosus*. Flavonoids, saponins, alkaloids, triterpenes, and steroids were reported to enhance GABA-mediated inhibitory neurotransmission (37, 38). Thus, these phytochemicals in the methanolic leaf extract of *A. spinosus* may be responsible for the anticonvulsant activities observed in this study.

Toxicity is essential to examine compounds for potential inclusion in drug development. The aim is to ensure the safety of chemical compounds before they can be used as drugs or in clinical trials. The acute toxicity study revealed that the plant extract was safe at 2000 mg/kg. This result agreed with previous reports of the acute toxicity of *A. spinosus* that the LD50 is above 2000 mg/kg (11, 39, 40). Behavioural changes observed in the animals treated with the extract include decreased food and water intake and locomotion. Tannins, part of the phytochemical constituents, were reported to reduce feed intake, growth rate, and protein digestibility in experimental animals (41).

Pentylenetetrazole triggers convulsive episodes by inhibiting gabaergic pathways (42). PTZ-induced seizures are similar to the symptoms observed in absence seizures, and drugs such as valproate, diazepam, and ethosuximide, which are helpful in the treatment of the absence seizures, can suppress PTZ-induced seizures by promoting GABA-facilitated inhibition in the brain (43). GABA has been reported to be the predominant inhibitory neurotransmitter in the central nervous system of mammals and has been implicated in convulsions, as it mediates the inhibition of neuronal responsiveness and activity by increasing the chloride-ion conductance through the opening of the chloride ion channel (44). The ability of the plant extract to delay the onset of convulsions and shorten the duration of disruptions is considered an indication of anticonvulsant activity. Based on the data obtained, the anticonvulsant effects of the plant extract similar to diazepam in the PTZ model may be due to its action on the GABA system.

The convulsant action of strychnine is due to its interference with postsynaptic inhibition mediated by glycine, an important inhibitory transmitter of motor neurons and interneurons in the spinal cord. Strychnine is a selective competitive antagonist of glycine receptors (45). Although the plant extract did not significantly affect the onset and duration of strychnine-induced convulsions at the tested doses in the animals, the mean onset of convulsions is less compared to the negative control group. Also, some protection was observed against mortality, which indicates mild anticonvulsant activity against strychnine-induced convulsions.

Conclusion

The methanol leaf extract of *A. spinosus* was found to possess marked anticonvulsant activity against pentylenetetrazole-induced convulsions, possibly via the enhancement of GABA-mediated inhibitory

neurotransmission, and a mild activity against strychnine-induced convulsions. The anticonvulsant activity in this study might be attributed to different biologically active components in the leaf extract. Results from this study may lead to the development of an effective anticonvulsant agent with fewer side effects.

Declarations

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Conflict of Interest

The authors declare no conflicting interest.

Data Availability

The unpublished data is available upon request to the corresponding author.

Ethics Statement

The study was approved by the Faculty of Basic Medical Sciences Research and Ethics Committee (FBMSRC) with approval letter number of BASUG/FBMS/REC/VOL.3/0092.

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