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Antiepileptic Effects of Ethanol Leaf Extract of *Azanza garckeana* (F.Hoffm.) Exell & Hillc. on Strychnine-Induced Seizures in Wistar Mice

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ABSTRACT

Introduction: *Azanza garckeana* (Goron Tula) is an edible Indigenous fruit found in the northeastern region of Nigeria, known for its medicinal properties in treating bacterial infections, diabetes, infertility, and menstrual pain, among others. Pharmacological studies have reported various effects of *A. garckeana*, including antibacterial, antifungal, antihyperglycemic, antimalarial, antioxidant, and improved iron absorption activities. This study aimed to investigate the phytoconstituents, assess acute toxicity (LD50), and evaluate the antiepileptic effects of the plant's leaf extract.

Methods: The dried leaves were extracted using ethanol through Soxhlet extraction method, followed by phytochemical screening. LD50 was assessed using the intraperitoneal (ip) method based on Lorke's protocol, and the antiepileptic effect was tested in strychnine-induced mice. The statistical analysis was conducted on the antiepileptic activity.

Results: Phytochemical analysis revealed the presence of flavonoids, cardiac glycosides, terpenoids, carbohydrates, tannins, cardenolides, and saponins. The intraperitoneal LD50 was determined to be 2154 mg/kg. The ethanol extract demonstrated antiepileptic activity, providing 40%, 60%, and 60% protection at extract doses of 100, 200, and 300 mg/kg body weight, respectively.

Conclusion: The leaves of *A. garckeana* can be considered relatively safe for medicinal use and contain phytoconstituents that exhibit antiepileptic effects. Further research employing various extraction techniques, pharmacological models, and the isolation and identification of bioactive compounds is recommended.

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Introduction

Herbal medicine is among the most widely used therapeutic approaches worldwide. It involves treating illnesses and enhancing general health and wellbeing by using plants medicinally. Chemicals derived from plants, animals, and microorganisms have been utilized in medical treatments since the dawn of medicine (Newman & Cragg, 2020). Plant-based products have dominated human pharmacopoeia for thousands of years and are essential to the development of pharmaceuticals (Atanasov et al., 2021).

The World Health Organization (WHO) reports that 70% to 95% of the global population relies on traditional medicine as their primary health care, a reliance often anchored on plant-based treatments (World Health Organization, 2022; Yuan et al., 2016). These treatments, which range from concentrated extracts to herbal teas, address a number of severe medical conditions, such as AIDS, diabetes, and high blood pressure (Ekor, 2014). Within the Nigerian context, mothers often turn to herbal and other complementary approaches to manage chronic childhood conditions like sickle cell disease, asthma, and epilepsy, emphasizing the critical role these traditional therapies play in pediatric health (Oshikoya et al., 2008).

Traditional medicine has provided quantifiable health benefits since the beginning of recorded practice because it is more accessible to patients, has comparatively mild side effects, and is less expensive than synthetic pharmaceuticals. According to Tiwari and Rana (2015), secondary metabolites such as saponins, flavonoids, phenolics, alkaloids, and tannins are the primary source of the detectable bioactivity of plants for therapeutic purposes. However, in the last ten years, the increase in demand for aggressive herbal remedies has reduced the supply of genuine raw materials. As a result, the degree of deliberate contamination and frequent substitution has increased. Therefore, systematic harmonization is imperative, especially in light of the persistent rise in the retail price of herbal preparations and the concurrent emergence of multidrug resistance in illnesses ranging from protozoal fever to systemic bacterial infections, and the parallel emergence of multidrug resistance in conditions ranging from systemic bacterial infections to protozoal febrile syndromes and the syndromes associated with the sexually-transmitted viruses.

Azanza garckeana L. (Malvaceae), known as Goron Tula in northeastern Nigeria, is a natural fruit that is edible and popular in East, West, and Southern Africa. The species is found in semi-arid forests, disturbed regions, and termite mound settings, including open woodlands in northeastern Nigeria, between sea level and 1,700 meters above sea level (Maroyi, 2017).

Pharmacological studies reveals that *A. garckeana* shows antioxidant (Lawal et al., 2022), antimicrobial (Dikko et al., 2016), anti-inflammatory (Bukar et al., 2022), antidiabetic (Ibrahim et al., 2023; Yusuf et al., 2023), uterotonic (Chanda et al., 2020), antimalarial (Jada et al., 2024), and reproductive protective effects (Itodo et al., 2022) in preclinical studies. Its flavonoids and betulinic acid drive therapeutic potential, but clinical trials and standardized protocols are lacking. Further research is needed to validate efficacy, safety, and mechanisms for human use.

The growing complexity of epilepsy as a disease, coupled with the limited potency, high cost, and poor accessibility of modern antiepileptic drugs, has made its management increasingly challenging. In response to the rising demand for a total cure, there is a renewed interest in alternative pharmacotherapeutic approaches. One such promising candidate is the leaf of *A. garckeana* (F. Hoffm.) Exell et Hillc, traditionally used by medicine practitioners in the southeastern region of Nigeria to treat epilepsy. Given its folkloric relevance, it is crucial to scientifically evaluate and validate its antiepileptic properties. Establishing the efficacy and potency of crude extracts from *A. garckeana* could pave the way for developing a standardized dosage form, thereby promoting its safe and effective use in epilepsy management on a broader scale.

The aim and objectives of this study are to identify the phytochemical compounds present in the leaf of *A. garckeana* (F.Hoffm.) Exell et Hillc, determine the acute toxicity (LD50) of the leaf and evaluate the anti-epileptic effect of the ethanol extract of the leaf of *A. garckeana* (F. Hoffm.) Exell et Hillc. in strychnine-induced epilepsy in mice.

Materials and Methods

Source of Plant Material, Collection and Identification

The *A. garckeana* leaf with a Voucher Number (UMM/FPH/MAV/006) was collected from cultivated sources from Kaltungo, Gombe State, Nigeria and was identified and authenticated by Prof. S. S. Sanusi of Biological Sciences Department, Faculty of Life Sciences, University of Maiduguri, Borno State.

Preparation and Extraction of the Leaf of *A. garckeana*

The method of extraction employed in this study was the use Soxhlet apparatus. The dirt and other extraneous materials were removed from the fresh leaf of the plant by hand pick, size reduced and allowed to dry naturally (under shade) for two (2) weeks. It was then further pulverized into fine

powder using a mortar and pestle. The sample was kept in a cool dried place until required for use. One hundred and fifty grammes (150 g) of the plant material was packed into a thimble attached to a five litre (5 L) round bottom flask, containing 1.5 L of 97 % ethanol and a condenser fitted with a rubber tubing above the thimble chamber, for water to circulate. The extraction process lasted for 6 hours. The solution obtained was filtered using Whatman filter papers (grade 42:2.5 µm) to remove the debris. The filtrate was poured into an evaporating dish to concentrate on a hot air oven at 40oC that lasted for 3 hours. After evaporation, the extract was stored in an air tight container until required for further analysis.

Phytochemical Analysis

The ethanol leaf extract of *A. garckeana* was screened for phytochemical constituents using standard methods (Brain and Turner, 1975; Vishnoi, 1979; Markham, 1982; Silva et al., Sofowara, 2008; Evans, 2009).

Pharmacological Studies

Experimental Animal and Acclimatization

Forty adult mice of both sexes, weighing between 11.9-30.3 g, were used for the acute toxicity experiments (LD50 determination) and the epilepsy studies. To allow them to acclimate to laboratory conditions, these mice were bought and kept in standard wire-meshed plastic cages in the animal section of the Physiology Laboratory of Veterinary Medicine Faculty, University of Maiduguri, Maiduguri, Borno State, for two weeks. They were kept in standard conditions of temperature, light, and humidity. Standard livestock feed (Grand Cereals and Oils Mills Ltd.) and unlimited access to drinking water were provided to these animals at Bukuru, Jos, Plateau State, Nigeria. The protocol described by CIOMS and ICLAS (2012) was used to handle the animals, and was certified by the Animal Ethics Committee of the Faculty of Pharmacy, University of Maiduguri, with approval number FP/022023/FS05.

Determination of Acute Toxicity (LD50)

The ethanolic leaf extract of *A. garckeana* was tested for acute toxicity using the standard, conventional method outlined by Lorke (1983). The intraperitoneal route was the administration method employed in this investigation. There are two stages to this, which are as follows:

Phase I: This phase involved splitting the mice into three groups of three mice each, administering intraperitoneal (i.p.) doses of *A. garckeana* extract (10 mg/kg, 100 mg/kg, and 1000 mg/kg), and keeping an eye out for signs of acute toxicity and the animals were observed for mortality for a period of 14 days.

Phase II: Three groups of one mouse each were used for the intraperitoneal route 24 hours later, based on the findings of phase I. Three mice received doses of 1600 mg/kg, 2900 mg/kg, and 5000 mg/kg of *A. garckeana* extract, respectively. When required, the LD50 (acute toxicity) was calculated after a 24-hour observation period for signs of toxicity and mortality. The animals were also observed for mortality during the 14-day period.

$$LD50=\sqrt{a \times b}$$

Where: a= least dose that kills the animal

b= highest dose that those not kill the animal

Induction of Epilepsy using Strychnine

Strychnine, manufactured by HiMedia Laboratories (India), was used to induce seizures in the animals. Albino mice, both male and female, weighing 11.9–30.3 g, were used. The mice's feed was supplied by Grand Cereals and Oils Mills Ltd. The animals were fed and watered as they pleased and maintained at a consistent temperature of 25 to 28 degrees Celsius. The investigations were conducted at the Physiology Laboratory of Veterinary Medicine Faculty, University of Maiduguri, Maiduguri, Borno State, Nigeria. Strychnine was used to induce epilepsy by intraperitoneal injection at a dose of 2 mg/kg body weight.

Effect of Ethanol Leaf Extract of A. garckeana on Strychnine Induced Epilepsy in Mice

Twenty-five mice of both genders, with body weights ranging from 11.9 to 30.3 grams, were employed in the current study. The animals were given ad libitum amounts of food and water. The animals were divided into five groups (A, B, C, D, and E), each of which had five mice. Group A, as the negative control, received an intraperitoneal injection of 2 ml distilled water. Groups B, C, and D were administered the extract intraperitoneally at doses of 100 mg/kg, 200 mg/kg, and 300 mg/kg, respectively. Group E was treated intraperitoneally with diazepam 5 mg/kg, a standard known antiepileptic drug. The frequency of spasms and average onset time of convulsions were measured after termination of the experiment (Medugu et al., 2020). Percentage protection (%) was calculated using the formula:

$$\% \text{ protection} = \frac{\text{Mean convulsion in control group} - \text{Mean convulsion in treated group}}{\text{Mean convulsion in control group}} \times 100$$

Data Analysis

Graph Pad Prism Version 9.0 for Windows software was used to analyze the data and provide the results as Mean $\pm$ Standard Error of the Mean (SEM). To test comparing means at a 95% confidence level, one-way ANOVA was employed, followed by Turkey-Kramer's multiple comparison. A p-value of less than 0.05 was deemed significant.

Results

Percentage Yield and Physical Appearance of the Extract

Table 1 shows the weight, color, texture, and yield of the *A. garckeana* ethanolic leaf extract. The extract weighed 25 g, had a black color, and had a solid mass texture. Its yield was 16.67% w/w.

Phytoconstituents of the *A. garckeana* Leaf Extract

The phytochemical composition of the ethanol extract from *A. garckeana* leaves is shown in Table 2. The existence of flavonoids, cardiac glycosides, terpenoids, carbohydrates, tannins, cardenolides, and saponins was demonstrated by the chemical composition.

Acute Toxicity Studies of Ethanolic leaf extract of *A. garckeana*

The result of the LD50 study is as shown in Table 3. The intraperitoneal LD50 is 2154 mg/kg.

Table 1: Extraction profile of *Azanza garckeana* leaf

Parameters	Profile
Weight	25g
Colour	Brown
Texture	Solid mass
% yield (w/w)	16.67 %

Table 2: Phytoconstituents of *Azanza garckeana* leaf extract

Phytochemical	Inference
Alkaloid	-
Flavonoid	+
Saponin	+
Carbohydrate	+
Cardiac glycosides	+
Terpenoid	+
Tannins	+
Anthraquinone	-
Cardenolide	+

+ = present; - = absent.

Table 3: Intraperitoneal acute toxicity LD50 test of the crude ethanolic leaf extract of *Azanza garckeana* on mice (lorke's method)

Phase	No of mice	Dose (mg/kg)	Mortality	Quantal Death
1	3	10	zero	0/3
1	3	100	Zero	0/3
1	3	1000	Zero	0/3
2	1	1600	Zero	0/1
2	1	2900	One	1/1
2	1	5000	One	1/1

$LD50=\sqrt{a \times b}$

Where: a= least dose that killed the animal =2900 mg/kg

b= highest dose that did not kill the animal=1600 mg/kg

$LD50=\sqrt{2900 \times 1600}$ =2154 mg/kg

Anti-Epileptic Effect of Ethanol Leaf Extract of *A. garckeana* on Strychnine Induced Epileptic mice

The result (Table 4) obtained after 30 minutes of intraperitoneal administration of *A. garckeana* leaf extract showed that the control Group A, (negative control) which was pretreated with distilled water yielded an onset of convulsion with a mean onset of convulsion ± S.D. of 7.60 ± 0.25 and percentage protection of 0.00 %, Group B, 100 mg/kg of the *A. garckeana* leaf extract had mean onset of convulsion of 8.60 ± 0.25 and percentage protection of 40 %, Group C, 200 mg/kg of the *A. garckeana* leaf extract had mean onset of convulsion ± S.D. of 10.40 ± 0.51 and percentage protection of 60 %, Group D, 300 mg/kg of the *A. garckeana* leaf extract yielded mean onset of convulsion ± S.D. of 15.40 ± 0.68 and percentage protection of 60 %, and finally, Group E, diazepam (standard) [positive control] yielded mean onset of convulsion ± S.D. of 0 ± 0 with the highest percentage protection of 100 % than the other treatment groups (B, C and D). The extract reduced the number of spasm and prolong the onset of convulsion. There was a significant difference within the group and significance across the groups. ($p<0.05$) when compared with the positive control (diazepam standard).

Table 4: Anti-epileptic effect of ethanol leaf extract of *Azanza garckeana* on strychnine induced epileptic mice

Groups	Treatment (mg/kg)	Onset of Myoclonic jerks (min)	Onset of convulsion (min)	Protection (%)
A	Distilled water	4.40±0.25 [a]	7.60±0.25 [a]	0
B	100	5.40±0.25 [b]	8.60 ±0.25[b]	40
C	200	7.40±0.25 [c]	10.40±0.51[c]	60
D	300	9.00±0.32 [d]	15.40±0.68[d]	60
E	Diazepam*	-	-	100

*= Standard antiepileptic drug (5 mg/kg); n=5: Number of mice in each group within the columns; values with the same superscript are significantly different($p<0.05$); SEM: Standard error of the mean.

Discussion

From our phytochemical analysis, we found various compounds in the ethanol leaf extract of *A. garckeana*, including flavonoids, tannins, cardiac glycosides, carbohydrates, saponin glycosides, anthraquinones, and terpenoids. This aligns with findings by Momodu et al. (2021). Many plant-derived compounds have been shown to be effective as anticonvulsants in both in vitro and in vivo tests. Notably, the anticonvulsant properties of these plant extracts are often due to their presence. Flavonoids are polyphenolic compounds, have been shown to exhibit anxiolytic, anticonvulsant, and sedative effects. About five

thousand different flavonoids have been isolated, and their pharmacological properties are well-understood and coumarins have been found to interact with the benzodiazepine site of the Gamma-Aminobutyric acid sub-type A (GABA-A) receptor, along with various voltage-gated ion channels, which are also targets for synthetic AEDs. This modulation of ligand-gated and voltage-gated ion channels explains how these plant secondary metabolites can produce anticonvulsant effects. Numerous complex extracts and individual compounds from plants have demonstrated anti-inflammatory, neuroprotective, and cognition-enhancing activities, potentially aiding in epilepsy treatment (Sucher & Carles, 2015). A review of the literature reveals a lack of scientific studies on the antiepileptic effects of *A. garckeana*, with Abelmoschus angulosus being the only proven plant in the Malvaceae family with documented antiepileptic properties (Bhakuni et al., 1998). Previous research has also reported that chrysin, a simple flavone (5,7-dihydroxyflavone), acts as a competitive ligand at the benzodiazepine receptors (Medina et al., 1990). This presence of chrysin could help explain the antiepileptic effects of *A. garckeana* ethanolic leaf extract.

The toxicity study on the crude ethanol extract from *A. garckeana* leaves showed that the intraperitoneal (i.p) LD50 was 2154 mg/kg. As reported by Yakubu et al., substances with oral LD50 values of ≥1000 mg/kg and i.p LD50 values of ≥500 mg/kg are considered low toxicity, indicating they are generally safe (Yakubu et al. 2023). So, with an LD50 of 2154 mg/kg for the *A. garckeana* leaf extract, we can conclude it demonstrates low toxicity via the i.p route. This high LD50 suggests that the crude extract is quite safe, as higher LD50 values typically point to greater safety levels, and the broad LD50 range reinforces this safety profile.

Our findings indicate that the ethanol leaf extract from *A. garckeana* displays significant antiepileptic properties in mice experiencing strychnine-induced seizures. The extract showed a dose-dependent effect, greatly delaying the onset of myoclonic jerks and convulsions. At a dosage of 300 mg/kg, it pushed back the average onset of myoclonic jerks to 9.00 ± 0.32 minutes and convulsions to 15.40 ± 0.68 minutes, compared to the control group's 4.40 ± 0.25 and 7.60 ± 0.25 minutes, resulting in a 60% seizure protection (Table 4). These outcomes support the traditional use of *A. garckeana* in African medicine for treating neurological issues (Abdulrahman et al., 2019).

The observed delays in seizure onset imply that the plant likely contains bioactive compounds that can influence neuronal excitability, possibly through the central nervous system. Strychnine causes seizures in mice by functioning as a high-affinity competitive antagonist of glycine receptors, which are ligand-gated chloride channels, primarily in the brainstem and spinal cord. This eliminates inhibitory glycinergic control, leading to hyperexcitability of motor neurons, tonic-clonic convulsions, and possibly respiratory failure (Mahmood et al., 2022; Wu et al., 2024). Additionally, it has been demonstrated that glycine increases the severity of strychnine-induced convulsions by activating NMDA receptors in the spinal cord, suggesting that excitatory glycinergic mechanisms may exacerbate seizure severity (Larson & Beitz, 1988; Wu et al., 2024). The ethanol extract of *A. garckeana* likely protects against strychnine-induced convulsions in mice by enhancing Glycinergic inhibition, reducing oxidative stress and neuroinflammation, and possibly modulating ion channels or providing neuroprotection via flavonoids, betulinic acid, and alkaloids. This is similar to the effect of diazepam, a known anticonvulsant drug which offered full protection in the positive control group. Earlier phytochemical analyses have noted the presence of flavonoids, alkaloids, and saponins in *A. garckeana* leaves—compounds known for their anticonvulsant properties (Sodipo et al., 2020). For instance, flavonoids like quercetin can modulate GABA-A receptors, thus reducing seizure susceptibility (Marder & Paladini, 2002).

When we compare to other studies, the antiepileptic effect of *A. garckeana* at doses of 200 and 300 mg/kg (60% protection) is promising, even if it's not as strong as synthetic agents like diazepam. Bum et al. (2010) reported a 50–75% protection rate using Ficus sycomorus leaf extract under similar test conditions, suggesting comparable effectiveness among natural anticonvulsants. However, this research is the first to specifically showcase the effectiveness of *A. garckeana* against strychnine-induced seizures, as earlier studies have primarily focused on its antibacterial, antioxidant, and antidiabetic attributes (Abdulrahman et al., 2019). These findings expand the pharmacological potential of this plant and indicate it might be a candidate for developing antiepileptic drugs.

The uniqueness of this study lies in its focused examination of *A. garckeana* in a strychnine seizure model—an application that hasn't been deeply explored before. While it is traditionally used in northern Nigeria for treating convulsions (Abdulrahman et al., 2019), scientific backing has been sparse. The dose-dependent protection and significant delay in seizure onset give solid evidence for its use in traditional medicine. Additionally, using strychnine, which specifically impacts glycinergic pathways, provides a distinct mechanistic insight when compared to more common models like PTZ or electroshock.

These findings could be significant for creating affordable, plant-based antiepileptic treatments, especially in low-resource areas where *A.*

garckeana is widely accessible and culturally recognized. Its incorporation into standardized herbal formulations might be feasible due to its availability and traditional applications (World Health Organization, 2019). Nonetheless, issues like variability in plant material and the need for consistent extraction methods must be tackled to guarantee safety and effectiveness (Abdulrahman et al., 2019).

Conclusion

This study marks the first scientific investigation into the anticonvulsant potential of *A. garckeana* ethanol leaf extract, establishing a foundational step in exploring its neuropharmacological properties. Using a strychnine-induced seizure model in mice, the extract demonstrated significant antiepileptic activity, with an intraperitoneal LD_{50} of 2154 mg/kg, indicating a favorable safety profile. The efficacy of the extract might have been driven by its rich phytochemical composition, which are known to modulate inhibitory neurotransmission, enhance Glycinergic tone, and counteract excitotoxicity. These mechanisms may underlie its ability to delay seizure onset, reduce severity, and improve survival outcomes in the strychnine model, which mimics glycine receptor antagonism. In conclusion, *A. garckeana* shows promising anticonvulsant properties and could serve as a valuable lead for developing plant-based antiepileptic therapies. As this is the first report of its kind, further research is essential to isolate active constituents, elucidate mechanisms of action, and evaluate its clinical relevance.

To establish *A. garckeana*'s therapeutic promise, upcoming studies must map its mode of action using biomolecular methodologies, notably receptor-binding assays and precise delineation of pertinent molecular targets. Complementary protocols should assess its seizure-modulating activity in parallel rodent paradigms, engaging pentylenetetrazole, maximal electroshock, and 4-aminopyridine exposure, thereby reinforcing experimental substance beyond preliminarily observed phenomena. Concurrently, systematic isolation and comprehensive profiling of its active principal metabolites are warranted, so that contributions of discrete entities to the overall pharmacodynamic spectrum can be specified. A parallel strand of inquiry is to conduct extended toxicity evaluation, ensuring that any extract-associated pharmacological injections are favorably evaluated from the standpoint of chronic safety.

Declarations

Conflict of interest

The authors declare no conflict of interest.

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Consent for publications

All authors have read and approved the manuscript for publication.

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None.

Authors' contributions

OAS and BS conceived the research idea and designed the overall framework. AAT and BW performed all experiments, with AAT drafting the initial manuscript and collaborating with OAS on the literature review. AAT and JY handled formal analysis, data curation, and visualization. AAT secured funding, managed the project, and provided resources, while OAS supervised the research. JY implemented the software. JY and OAS validated the results. OAS and JY reviewed and edited the manuscript, and OAS, AAT, and JY approved the final version for publication.

Ethical considerations

The authors have fully adhered to ethical standards, ensuring no issues related to plagiarism, misconduct, data fabrication, falsification, duplicate publication or submission, or redundancy.

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