Anti-Epileptic Studies of *Chamaecrista mimosoides* Ethanol Extract

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Introduction

A large proportion of the population of developing countries uses traditional medicine alone or in combination with western drugs to treat a wide variety of ailments. There has seldom been an effective collaboration between the traditional and Western medicine practitioners which is largely due to the perception that the use of traditional and herbal medicines has no scientific basis.¹ As a result of renewed interest from western countries in herbal medicines and the increasingly urgent need to develop new effective drugs, traditionally used medicinal plants have recently received the attention of the pharmaceutical and scientific communities.¹

Over the past decades, interests have been revived in the study and uses in the traditional systems of medicine in different cultural settings. As a result, countries have sought cooperation with the World Health Organization (WHO) in identifying and using the safe and positive elements of traditional medicine in national health systems.² Traditional medicine is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.¹

Medicinal plant is any plant which, one or more of its parts, contains substances that can be used for therapeutic purposes or which are precursors for the synthesis of useful drugs.² Traditional Medical Practitioners (TMPs) use plants to cure various diseases. A survey conducted by the WHO showed that 60-80% of world’s population (mainly from the developing countries) depend primarily on herbal medicines for their health needs.³ Traditional medicine thus, offers the surest prospect of achieving total health care coverage of the world’s population. Many plants were known for their anticonvulsant activity and their extracts may be important source of chemicals for the development of better and safer drugs for the treatment of epilepsy.¹ Several plants reported to possess antiepileptic properties in different folklore cultures have been found to exhibit anticonvulsant activity in different animal models.⁴ Many plants with antiepileptic properties have been identified in Africa. It is because of this that the WHO recommended in 1991; in order to ensure the appropriate use of medicinal herbs by patients as well as physicians, efficient and scientifically proven traditional remedies be included in the drug policies of member states.³ About 80% of the world’s population relies on herbal medicines and governments of the third world countries are unable to sustain a complete coverage with western-type of drugs and have encouraged the rational development of traditional treatments. At present, the World Health Organization is taking an official interest in such development to facilitate its aim of making health care available for all. United Nations Industrial Development Organization (UNIDO) also supports the industrial utilization of medicinal plants which are a source of export earnings for the producers.³ There has been a rapid boom in the herbal industry across the African continent. It was reported that in 1986 alone, Cameroun earned about 3 billion francs (CFA) from trade in medicinal plants to the Western World.⁵ Therefore, plants (if its efficacy and safety are scientifically proven) could serve as raw materials for our pharmaceutical industries and when exported could provide a means of foreign exchange to the country.⁵

Plant has man’s most formidable friend for survival, both as food and medicine since time immemorial. This research work aimed to establish a scientific basis for the use of *Chamaecrista mimosoides* in traditional medicine as anti-epileptic medication. The study was carried out in two (2) phases. Phase I (Chemical Analysis): The whole plant part of *Chamaecrista mimosoides* was extracted with ethanol and screened for phytochemicals. Phase II (Pharmacological studies): Acute toxicity study was carried out using Lorke’s method and the antiepileptic activity was evaluated using maximal electroshock-induced seizure test in day-old chicks, pentylentetrazole (PTZ)- and strychnine-induced seizure in mice. The phytochemical study revealed the presence of saponins, cardiac glycosides, tannins, flavonoids, terpenoids and cardenolides. The intraperitoneal median lethal dose value (LD₅₀) of *Chamaecrista mimosoides* ethanol extract encoded CME in mice was greater than 5000 mg/kg, indicating the extract is relatively safe. The extract at the experimental doses of 250 and 500 mg/kg body weight protected 100% each, of animals against PTZ-induced convulsion; protected 60% and 80% of mice against death induced by strychnine; but had 0% protection of chicks against Tonic Hindlimb Extension (THLE) phase of the Maximal Electroshock Test (MEST) at p < 0.05.

Keywords: *Chamaecrista mimosoides*, Phytochemical, Antiepileptic, Pentylentetrazole (PTZ), Maximal electroshock, strychnine.

Original Research Article

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Currently available antiepileptic drugs (AED) are synthetic molecules that have serious adverse effects such as weight gain, hepatotoxicity, teratogenicity and withdrawal symptoms. Pharmacotherapy of epilepsy with available AED is symptomatic as these drugs inhibit seizure and do not cure the underlying disease process in the brain. It is generally estimated that up to 30% of patients are refractory to conventional AED treatment. Refractory epilepsy is also associated with increased morbidity, low rate of marriage, unemployment, overall reduced quality of life and a heavy burden on the society. There is thus a need for the development of safer AED with improved clinical profile.

Medicinal plants have been shown to have anticonvulsant activity. Plant extract may be an important source for the development of better and safer drugs for the treatment of epilepsy. Several plants with antiepileptic properties in different folklore cultures have been found to exhibit anticonvulsant activities in different animal models. Chamaecrista mimosoides is an annual or short-lived perennial herb, sometimes prostrate but more commonly growing as an erect shrub up to 1.2 metres. This widespread plant was once placed in the genus Cassia. It is a small perennial shrub up to about 60 centimetres high but sometimes much taller, has leaves with 20-60 pairs of leaflets, each 3-7 millimetres long and up to 1 millimetre wide. Flowers occur singly or in groups of 2-3. Petals are yellow, pods are up to 5 centimetres long, 4 millimetres wide and are flat; seeds are 12-24 and are orange brown in colour.

The significance of medicinal plants today is also shown by the increasing number of established research centres for analysis of active ingredients of the plants and for discovering biologically active natural materials. Over 5000 different species of plant substance have been recognized to occur in these areas and many of them have been found to be useful in traditional medicine for prophylaxis and cure of diseases.

Materials and Methods

Plant Collection and Identification

The whole plant (Chamaecrista mimosoides) was collected from Maiduguri in Jere local government area, Borno State. The collection was done between the months of June and August, 2017. The plant was identified and authenticated by Professor S.S. Sanusi; a Taxonomist with the Department of Biological Sciences, University of Maiduguri, Borno State, Nigeria. A voucher specimen of #541C was assigned to the plant specimen and was deposited for future reference.

Preparation of the Plant Extract

The whole plant (Chamaecrista mimosoides) was air dried at room temperature for 2 weeks and was pulverized into coarse powder using pestle and mortar. The powdered plant material (2 kg) was defatted with petroleum ether (2.5 L) for 24 hours using a soxhlet extractor. The marc was air dried and macerated with 5 L of ethanol (99% v/v) for 4 days with occasional shaking. The filtrate was evaporated to dryness in vacuum at 40°C and stored in desiccators. The extract was subsequently referred to as Chamaecrista mimosoides extract (CME). A fresh aqueous suspension of the extract in 2% tween-80 was prepared for each study.

Preliminary Qualitative Phytochemical Screening

The screening was done in accordance with the standard protocol as describe by Evans. The extract was screened for the presence of alkaloids, tannins, flavonoids, saponins, anthraquinones, terpenoids, cardiac glycosides, and carbohydrate.

Animals

Male and female Swiss albino mice (19-21 g) maintained at the animal house of the Department of Pharmacology and Toxicology, University of Maiduguri were used for the study. They were housed in a well-ventilated room, fed with standard laboratory feed (Vital feed). All experiments were conducted by following the standard ethics described by International Council of Laboratory Animal Science (ICLAS) and Council for International Organizations of Medical Sciences(CIOMS) and the National Institute of Health Guidelines for the Care and use of Laboratory Animals (NIH Publications No.80-23) as revised in 1996.

Drugs and Drug Solutions

Pentylenetetrazole was purchased from Sigma Chemical Co. (St. Louis, USA). Sodium valproate (Fawdon Manufacturing Centre, Newcastle-upon-Tyne, UK) and Phenytoin (Manfes Pharmaceutical limited, Nigeria). The drug solutions were prepared fresh for each day’s experiment to maintain stability of the drugs used. The solutions were kept in air-tight, amber coloured containers and stored in the refrigerator ready for use.
Routes of Drug Administration
The extract, phenytoin and sodium valproate were administered intraperitoneally while pentylentetrazole was administered subcutaneously.

Pharmacological Studies
Acute Toxicity Studies
The LD₅₀ of the crude extracts was determined using Lorke’s method. The rats were deprived of food for 16-18 hours before administration of the extract. The study was carried out in two phases. Phase 1 consist of three groups of three animals per group. The rats were administered intraperitoneally, geometrical doses of 10 mg/kg, 100 mg/kg and 1000 mg/kg of CME, respectively. The treated animals were observed for four hours post administration for signs of toxicity. Phase 2 was initiated after no death was recorded. In phase 2, three groups of one animal each were given the extracts intraperitoneally at doses of 1600 mg/kg, 2900 mg/kg and 5000 mg/kg, respectively. The animals were observed for signs of toxicity for the first 4 hours and mortality for 24 hours. The arithmetic mean of the lowest dose that kills an animal and the highest dose that does not kill any animal will be taken as the median lethal dose (LD₅₀) of the extract. i.e: 

\[ \text{LD}_{50} = \sqrt{ab} \]

Where - a = lowest dose that kills an animal b = highest dose that did not kill an animal

Pentylentetrazole-induced Seizure in Mice
Twenty-five mice (18-21 g) were divided into five groups each containing five mice. The first three groups received 100, 250 and 500 mg/kg bw. doses of CME. The fourth group received Valproic acid (200 mg/kg) and the fifth group received 10 mL normal saline per kg body weight intraperitoneally. Thirty minutes later, mice in all the groups received 60 mg/kg of pentylentetrazole subcutaneously and observed for 30 minutes. Absence of a clonic spasm of at least 5 seconds' duration indicated the compounds ability to abolish the effect of pentylentetrazole on seizure threshold.

Maximum Electroshock Induced Seizure in Chicks
Fifty (50) chicks of both sexes were used for this study. They were grouped into ten chicks per group. Group I received vehicular treatment; group II-IV received 100, 250 and 500 mg/kg bw. of CME i.p. Group V received phenytoin (20 mg/kg i.p) as a reference standard. Thirty minutes after pretreatment, maximal electroshock was administered to induce seizure in the chicks using Ugobasile Electroconvulsive machine (Model 7801) connected to Claude Lyons stabilizer with corneal electrodes placed on the upper eyelids of the chicks. The current, shock duration, frequency and pulse width were set and maintained at 90 mA, 0.80 second, 200 pulse/second and 0.8 ms, respectively. The ability to prevent this feature or prolong the latency and/or onset of the tonic hindlimb extension was considered as an indication of an anticonvulsant activity.

Strychnine-induced Convulsion in Mice
The method used is as described by Lehmann et al. In brief, strychnine convulsions followed by death was induced in mice by the subcutaneous injection of 1 mg/kg of strychnine nitrate. Thirty minutes prior to administration of strychnine, three groups of 5 mice each were intraperitoneally pretreated with 100, 250 and 500 mg/kg bw. doses of CME. The fourth group was treated with phenobarbitone sodium (20 mg/kg i.p) which served as the positive control while the fifth group received normal saline (10 mL/kg) as the negative control. Mice were observed for tonic extensor jerks of the hind limbs followed by death in 30 minutes. Abolition of tonic extensor jerks of the hind limb was considered an indicator that CME could prevent strychnine-induced seizures.

Statistical Analysis
Data obtained from convulsive tests were analysed using Graphpad Prism version 8.0 for windows. The results were expressed as mean ± standard error of mean (Mean ± SEM) for time of onset of convulsion, as well as percentage of inhibition of convulsion (percentage protection) and or percentage mortality. The results were analyzed for statistical significance using one-way ANOVA followed by Dunnet’s test.

Results and Discussion
Plant Extraction
The extractive value of the whole plant ethanol extract was found to be 152 g representing a yield of 5.2%.

Phytochemical Constituents of Ethanolic Whole Plant Extract of Chamaecrista mimosoides
The preliminary phytochemical screening of the whole plant extract of Chamaecrista mimosoides using ethanol and the 3 soluble portions using chloroform, ethyl acetate and n-butanol as solvents revealed the presence of some phytochemicals such as flavonoids, terpenoids, cardiac glycosides, saponins and tannins. Ethanol extract had the highest number of phytochemicals while ethyl acetate portion had fewer phytochemicals, most notably is the absence of terpenoids in ethyl acetate portion. Alkaloid, carbohydrates and anthraquinones were all absent in the ethanol extract and the three portions. The result of the phytochemical screening is shown in Table 1.

Table 1: Phytochemical screening of Crude Ethanol Extract Plant of Chamaecrista mimosoides

| Test             | Inference |
|------------------|-----------|
| Carbohydrate     | +         |
| Soluble starch   | -         |
| Tannins          | +         |
| Anthraquinones   | -         |
| Cardiac glycosides| +         |
| Terpenoids       | +         |
| Saponins         | +         |
| Flavonoids       | +         |
| Alkaloids        | -         |

(+ = Present, - = Absent, CME = Chamaecrista mimosoides)

Inference

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Pharmacological Studies

Acute Toxicity Studies

Signs and symptoms observed in test animals injected with crude extracts and partitioned portions included decreased locomotor activity, breathing difficulty and immobility (Table 2).

The intraperitoneal acute toxicity studies in mice showed the butanol-soluble fraction and crude ethanol extract have LD_{50} value of >5000 mg/kg bwt. while the chloroform and ethyl acetate fraction have LD_{50} value of 3808 mg/kg bwt. Clarke and Clarke were of the opinion that compounds with LD_{50} value of 1500 mg/kg and above have low toxicity. The extract is therefore safe, and this could explain the safe use of the plant by the local people who have been using it in traditional management of depressive illneses in North-Eastern Nigeria.28

Effects of Crude Extract of CME on Maximal Electroshock Test (MEST) in Chicks

The crude ethanol extract of *Chamaecrista mimosoides* at doses of 100, 250, and 500 mg/kg body weight did not protect the chicks against tonic hind limb extension (THLE) in maximal electro-shock test. It however significantly (p < 0.05) decreased the mean recovery time (VPA) from 1.00 ± 0.73 min (normal saline treated) by 78%, 75% and 83% minutes at the doses of 100, 250 and 500 mg/kg body weight, respectively in a dose-dependent manner (Table 3).

The maximal electroshock test (MEST) is a non-mechanistic seizures model that has clearly defined end points such as inhibition of HLTE.29 There is no false negative in the MES test and the currently available AEDs that are clinically effective in the management of generalized tonic-clonic and partial seizures such as carbamazepine, phenytoin, primidone, phenobarbital, valproate, and lamotrigine all suppress HLTE in MES test.30,31 Protection against hind limb tonic extension (HLTE) in the maximal electroshock test (MEST) predicts anticonvulsant activity of antiepileptic drugs (AED) that prevent the spread of the epileptic seizure discharges from an epileptic focus during seizures. The ethanol extract of the whole plant of *Chamaecrista mimosoides* and the three portions in MEST did not protect the chicks against seizures induced by maximal electroshock suggesting non-activity against generalized tonic clonic and partial seizures. They in fact, reduced onset of seizures in the animals.

Effect of Crude Extract of CME on Pentylenetetrazole-induced Convulsion in Mice

The crude extract of *Chamaecrista mimosoides* at higher doses of 250 and 500 mg/kg body weight protected 100% of mice against clonic spasm induced by pentylenetetrazole. It also significantly (p < 0.05) increased the latency of convulsed animals from 3.6 ± 0.40 min in normal saline treated group by 94% at 100 mg/kg body weight and completely blocked pentylenetetrazole-induced convulsion at 250 and 500 mg/kg body weight. Valproic acid (200 mg/kg) protected all the mice (100%) against clonic spasm induced by pentylenetetrazole (Table 4).

Pentylenetetrazole (PTZ) is a known convulant and anticonvulsant activity in subcutaneous pentylenetetrazole test identifies compounds that can raise the seizure threshold in the brain.30 Antiepileptic drugs (AEDs) effective in the therapy of generalized seizures of absence or myoclonic petit mal type such as Ethosuximide (ETX), Valproic acid (VPA), Phenobarbital (PB), and calamine (CH) exhibit dose-dependent suppression of various seizure patterns induced by PTZ.33 At cellular level, one of the basic mechanisms of actions of AEDs such as ETX and VPA is the suppression of T-type calcium currents in thalamic neurons.34,35 Besides increasing GABA levels, VPA may also have antiepileptic activity by reducing the high-frequency firing of neurons by blocking voltage-gated sodium, potassium, and calcium channels.36 All the experimental animals in the negative control, pretreated with distilled water, were not protected from the PTZ-induced chemoconvulsion and did not survive it. The PTZ-induced convulsion is like symptoms observed in absence seizures. On the other hand, drugs used in the treatment of absence seizures suppress PTZ-induced convulsions.37 Consequently, pharmacologically active chemical substances that can suppress or prevent PTZ-induced convulsion are often specified to have activity against absence seizures. PTZ is an antagonist of Gamma amino butyric acid (GABA) at GABA_A receptor which has been widely implicated in epilepsy.38 In addition, drugs which protect animals against the generalized clonic seizure induced by PTZ are effective in protection and management of petit mal epilepsy.39 Drug that are effective against petit mal seizure reduce T-type calcium current and these types of seizure can also be prevented by drugs that enhance GABA. In the positive control, sodium valproate (200 mg/kg), a standard antiepileptic drug was used as control and it yielded 100% protection against the PTZ-induced seizures. The standard drug protected all the mice from death due to PTZ. Consequently, it can be inferred that sodium valproate not only suppresses seizures but also has the capability of lowering the chances of mortality. It is believed to act by altering the function of the neurotransmitter GABA (as GABA transaminase inhibitor) in the human brain. Its principal mechanism of action is believed to be the inhibition of the transamination of GABA (by inhibiting GABA transaminase, then GABA would increase in concentration). However, several other mechanisms of action in neuropsychiatric disorders have been proposed for valproate in recent years. Sodium valproate also blocks the voltage-gated sodium channels and T-type calcium channel. These mechanisms make it a broad-spectrum anticonvulsant drug. The crude extract and the three portions at the tested doses demonstrated dose-graded protection against PTZ-induced seizures. The crude extract of *Chamaecrista mimosoides* at higher doses of 250 and 500 mg/kg body weight protected 100% of mice against clonic spasm induced by pentylenetetrazole.

Protection at 100 mg/kg body weight against the generalized clonic seizures induced by PTZ is significantly (P < 0.05) decreased the mean recovery time (VPA) from 1.00 ± 1.00 min in normal saline treated group to 0.37 ± 1.20, 21.5 ± 0.50 and 23.2 ± 0.86 min at doses of 100, 250 and 500 mg/kg body weight, respectively. Similarly, in the time of death, the crude extract of *Chamaecrista mimosoides* significantly (P < 0.05) prolonged the time of death of convulsed mice from 11.80 ± 0.37 min. in normal saline treated group to 18.00±1.53, 24.00±1.00 and 27.00±0.00 min at doses of 100, 250 and 500 mg/kg body weight respectively (Table 5).

In the strychnine-induced seizure model, it is known that strychnine damages amygdaloid and entorhinal cortex areas, and spinal reflexes from glycine receptors.40 The crude extract of the whole plant of *Chamaecrista mimosoides* at the dose of 250 mg/kg and 500 mg/kg protected 60% and 80% of the mice against strychnine-induced death. The convulsing action of strychnine is due to the interference with postsynaptic inhibition mediated by glycine, an important inhibitory transmitter of the motor neurons and interneurons in the spinal cord. Strychnine sensitive postsynaptic inhibition in higher centers of the CNS is also mediated by glycine. Strychnine acts as a selective, competitive antagonist at all glycine receptors.41,42 The ability of the crude extract of the whole plant of *Chamaecrista mimosoides* to prevent the strychnine-induced seizures demonstrate additional anticonvulsant effects mediated via glycine receptors.43,44
### Table 2: LD<sub>50</sub> values of Ethanol Extract of *Chamaecrista mimosoides*

| Group | Mice | Weight (g) | Dose mg/kg (i.p.) | Death |
|-------|------|------------|-------------------|-------|
| **PHASE I** | | | | |
| 1 | M1 | 19 | 10 | 0/3 |
| | M2 | 21 | | |
| | M3 | 19 | | |
| 2 | M1 | 20 | 100 | 0/3 |
| | M2 | 19 | | |
| | M3 | 21 | | |
| 3 | M1 | 18 | 1000 | 3/3 |
| | M2 | 21 | | |
| | M3 | 19 | | |
| **PHASE II** | | | | |
| 1 | M1 | 19 | 1600 | 0/1 |
| 2 | M2 | 20 | 2900 | 0/1 |
| 3 | M3 | 19 | 5000 | 0/1 |

i.p. = intraperitoneal

### Table 3: Effects of Crude Extract of CME on Maximal Electroshock Test (MEST) in Chicks

| Treatment (mg/kg) | Mean Recovery Time (min) | Quantal Protection | % Protection |
|-------------------|--------------------------|-------------------|--------------|
| N/Saline (10 mL/Kg) | 11.70 ± 0.73 | 0/10 | 0 |
| 100 | 3.10 ± 0.42* | 0/10 | 0 |
| 250 | 2.60 ± 0.32* | 0/10 | 0 |
| 500 | 2.00 ± 0.30* | 0/10 | 0 |
| Phenytoin (20 mg/kg) | 00* | 10/10 | 100 |

Data presented as Mean ± SEM, n = 10, CME = *Chamaecrista mimosoides*, *represent p < 0.05 by student t-test.

### Table 4: Effects of Crude Extract of *Chamaecrista mimosoides* on Pentylentetrazole-induced Convulsion in Mice

| Treatment (mg/kg) | Mean Onset of Convulsion (min) | Quantal Protection | % Protection |
|-------------------|---------------------------------|-------------------|--------------|
| N/Saline (10 mL/Kg) | 3.60± 0.40 | 0/5 | 0 |
| 100 | 7.00 ± 0.71* | 0/5 | 0 |
| 200 | 00* | 5/5 | 100 |
| 500 | 00* | 5/5 | 100 |
| Sodium Valproate (200 mg/kg) | 00* | 5/5 | 100 |

Data presented as Mean ± SEM, n = 5, CME = *Chamaecrista mimosoides*, *represent p < 0.05 by student t-test.

### Table 5: Effects of Crude Extract of *Chamaecrista mimosoides* on Strychnine-induced Convulsion in Mice

| Treatment (mg/kg) | Mean Onset of Convulsion (min) | Mean Time of Death (min) | Quantal Protection | % Protection |
|-------------------|---------------------------------|--------------------------|-------------------|--------------|
| N/Saline (10 mL/Kg) | 10.20 ± 0.37 | 11.80 ± 0.37 | 0/5 | 0 |
| 100 | 16.30 ± 1.20* | 18.00 ± 1.53* | 0/5 | 0 |
| 250 | 21.50 ± 0.50* | 24.00 ± 1.00* | 3/5 | 60 |
| 500 | 23.20 ± 0.86* | 27.00 ± 0.0* | 4/5 | 80 |
| Phenobarbitone (20 mg/kg) | 24.00 ± 0.00* | 24.00 ± 0.00* | 4/5 | 80 |

Data presented as Mean ± SEM, n = 5, CME = *Chamaecrista mimosoides*, *represent p < 0.05 by student t-test.
Conclusion
The phytochemical study revealed the presence of saponins, cardiac glycosides, tannins, flavonoids, terpenoids and cardenolides. The whole plant ethanol extract had no observable toxic effect on mice within the duration of time evaluated. The extract had no activity against generalized tonic-clonic seizures when maximal electroshock was used. Based on these observations it is possible that the anticonvulsant effect of the whole plant ethanol extract in this study contains active ingredients, which are suggested to have benzodiazepine-like activity, that may inhibit binding of strychnine with glycine receptor or may enhance glycine or GABA binding. These components may act synergistically with phytochemicals such as flavonoids, glycosides and saponins which possesses a considerable anticonvulsant activity. These findings justify the traditional use of this plant in the control and/or treatment of convulsions and epilepsy.

Conflict of interest
The authors declare no conflict of interest.

Authors’ Declaration
The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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