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Original Research Article

Anticonvulsant Studies on Ethanol Leaf Extract of *Cadaba farinosa* Forssk. in Experimental Models

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ABSTRACT

Cadaba farinosa Forssk. is widely distributed in tropical and sub-tropical regions. It is used in the treatment of pains, dysentery, rheumatism, cough, fever, as antidote and neurological disorders. The study evaluated the anticonvulsant activity of the ethanol leaf extract (CEE) of the plant in Swiss mice using maximal electroshock test (MEST), pentylenetetrazole (PTZ), strychnine (STN) and 4-aminopyridine (4-AP) induced seizures tests. The intraperitoneal (*i.p.*) median lethal dose (LD_{50}) of CEE was found to be 2154.1 mg/kg body weight in mice. There was no significant protection against maximal electroshock induced seizures in all treated groups and no difference in their mean recovery time. Only the standard drug (phenytoin) showed 40% protection. The extract did not protect the mice against pentylenetetrazole induced seizures at all doses. However, there was significant increase in the mean onset of seizures at all doses. There was significant ($p \leq 0.05$) 16.7% protection exhibited by the extract at 150 and 300 mg/kg. The extract at 75 mg/kg exhibited the highest protection of 83.3% against STN induced seizures in mice. At 75 mg/kg the extract exhibited highest protection of 83.3% against strychnine induced seizures in mice. Phenobarbitone caused an increase in the mean onset with 50% protection. The extract (300 mg/kg) offered 100% protection against 4-aminopyridine induced seizures in mice higher than that produced by phenobarbitone. However, there was no significant difference in the onset of seizure in the unprotected animals. The results suggest that ethanol leaf extract of *Cadaba farinosa* possesses anticonvulsant properties.

Keywords: Electroshock, Pentylenetetrazole, *Cadaba farinosa*, Strychnine, 4-aminopyridine, Seizure.

Introduction

Epilepsy is a major neurological disorder and up to 5% of the world population develops epilepsy in their lifetime.[1] It is a disease of complex nature and of different etiology with huge patient load of varying age groups involving both sexes.[2] On an average, 0.25 million new cases of epilepsy are reported every year. There are mainly two kinds of epilepsy, i.e. *grand mal* and *petit mal* which are prevalent.[3] Available drugs are effective in only 60-80 % of epileptic patients. During the past decade, several new drugs have been approved to be used as antiepileptic drugs (Rufinamide, Retigabine, Pregabaline, Remacemide, e.t.c.).[4] Despite the optimal use of available antiepileptic drugs (AEDs), many patients fail to experience seizure control and others do so only at the expense of significant toxic effects. It is estimated that available medication controls seizures in only 50 % of patients.[5]

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The current therapy of epilepsy with modern antiepileptic drugs is associated with side effects, dose-related and chronic toxicity, as well as teratogenic effects and approximately 30 % of the patients continue to have seizures with current antiepileptic drugs therapy.[6-8] Traditional systems of medicine are popular in developing countries and up to 80 % of the population relies on traditional medicines or folk remedies for their primary health care need.[9] Medicinal plants are believed to be an important source of new chemical substances with potential therapeutic effects.[10] Several plants used for the treatment of epilepsy in different systems of traditional medicine have shown activity when tested in modern bioassays for the detection of anticonvulsant activity[11] and many such plants are yet to be scientifically investigated. The aim of this study was to evaluate the anticonvulsant potential of the ethanol leaf extract of *Cadaba farinosa* in experimental animal models.

Materials and Methods

Collection, identification and preparation of plant material

Fresh leaves of the plant were collected on 29th September, 2012 from Maiduguri Metropolitan Council Area of Borno State, Nigeria. The plant specimen was identified and authenticated as *Cadaba farinosa* at the Herbarium section of the Department of Biological Sciences, Ahmadu Bello University in Zaria, Nigeria which corresponded with that of voucher specimen number V/No: 2744. The leaves were air-dried under shade for several days and pulverised into fine powder for extraction.

Extraction of plant material
The air-dried ground powdered leaf material (1,500 g) wasextracted exhaustively with 70% ethanol using cold maceration method for several days with occasional shaking with 6.5 liters of solvents. The ethanol leaf extract was concentrated to dryness on water bath at 50^{o} C and coded CEE – crude ethanol leaf extract of *Cadaba farinosa*. The coded extract (CEE) served as the working sample for the chemical investigations, acute toxicity determination as well as anticonvulsant investigations of the plant.

Animals
Adult Swiss mice (16-30 g) of either sex were acquired from Animal House facility of the Department of Pharmacology and Therapeutics, Ahmadu Bello University Zaria, Nigeria. The animals were fed with laboratory diet vital feeds, Vital Feeds PLC, Bukuru, Jos-Plateau State, Nigeria and water *ad libitum* and maintained under standard conditions in propylene cages at room temperature. Day old chicks (Ranger cockerels of 26-37 g body weight) obtained from National Agricultural Production and Research Institute (NAPRI) Shika, Zaria-Kaduna State, Nigeria. The ethical committee of the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria approved the experimental protocols with number: DAC/W-OT/301-28.

Drugs, Chemicals and Equipments
Maximal electroshock test in chicks
The **Maximal electroshock** apparatus (Ugobasile electroconvulsive unit - biological research apparatus Comario-(Va)-Italy (ECT UNIT 7801 with corneal electrodes) connected to Claude Lyon voltage stabilizers) with a current of = 90 mA; Pulse width of = 0.6 m/s (meter/second); Frequency/pulses of = 100 Hz and Shock duration of = 0.8 s (seconds) was used. Phenytoin by Hovid Bod, Malaysia. Dose: 20 mg/kg, Stop watch, etc.

4-aminopyridine-induced seizure in mice
4-aminopyridine by Merck Sohchard, Germany. Dose: 15 mg/kg
Phenobarbitone by Lab. Renuudin, France.

Pentylenetetrazole (PTZ) -induced seizure in mice
PTZ by Sigma Aldrich, USA. Dose: 90 mg/kg
Valproic acid by Sanofi Synthelabo Ltd, UK. Dose: 200 mg/kg

Strychnine (STN) -induced seizure in mice
Strychnine by Sigma Aldrich, USA. Dose: 2.4 mg/kg but seizures were just 50 %. Hence, the dose was increased to 3 mg/kg.
Phenobarbitone by Lab. Renuudin, France. Dose: 20 mg/kg.

Phytochemical screening
A little quantity each of the CEE (crude ethanol leaf extract) was subjected to qualitative phytochemical screening to test for the presence of alkaloids, anthraquinones, carbohydrates, cardiac glycosides, flavonoids, glycosides, saponins and tannins as described by [12-16]

Acute toxicity studies
The median lethal dose (LD_{50}) was determined as previously described.[17]Briefly, in the first phase; three mice of both sexes each were divided into three groups. The crude ethanol leaf extract of *Cadaba farinosa* (CEE) was administered intraperitoneally (*i.p.*)at doses of 10 mg/kg 100 mg/kg and 1,000 mg/kg per body weight respectively. The animals were observed for signs of toxicity and death within 24 hours. In the second phase, a mouse each in the three groups was administered intraperitoneally (*i.p.*) with the doses of 1,600 mg/kg, 2,900 mg/kg and 5,000 mg/kgbody weight of the crude extract based on result of the first phase and observed for signs of toxicity and death within 24 hours. The median lethal dose (LD_{50}) was estimated as geometric mean of lowest dose that caused death and the highest dose of survival (i.e. square root of the product of lowest lethal dose and highest non-lethal dose for which the animal survived).

Maximal electroshock-induced seizure test in chicks
Method previously described[18] and modified[19] was used. Fifty day old chicks were randomly divided into five Groups of ten chicks each. The first group was given 10 ml/kg *i.p.* normal saline. Groups two, three, and four received the extract 75 mg/kg, 150 mg/kg and 300 mg/kg *i.p.* respectively. While, the last (Group Five) was administered with 20 mg/kg phenytoin *i.p.* thirty minutes after treatment. Maximal electroshock was applied to induce seizure in all chicks using Ugobasile electro-convulsive machine (Model ECT UNIT 7801) connected to corneal electrodes placed on upper eyelids of the chicks to induce a generalized form of seizure. The current, pulse width, frequency and shock duration were 90 mA, 0.6 metre/sec, 100 Hz and 0.8 sec respectively. Episodes of hind limb tonic extension as well as latency to time of recovery from seizures were observed and recorded.

Pentylenetetrazole-induced seizure in mice
The method adopted was as previously described.[20]Mice in groups one, two, three and four received respectively 10 ml/kg normal saline, 75 mg/kg, 150 mg/kg and 300 mg/kg CEE of the plant intraperitoneally (*i.p.*). The fifth group received 200 mg/kg body weight of sodium valproate *i.p.* Mice in all the groups received 90 mg/kg (CD_{97}) of pentylenetetrazole subcutaneously *(s.c.)* after thirty minutes. All mice were observed within a period of thirty minutes for presence or absence of threshold seizure (episode of clonic seizures of at least five seconds duration).

Strychnine-induced seizure in mice
The method previously described[21] was adopted in this study. Mice in groups one, two, three and four received respectively 10 ml/kg normal saline, 75 mg/kg, 150 mg/kg and 300 mg/kg CEE of the plant intraperitoneally (*i.p.*). Group five had 20 mg/kg phenobarbitone *i.p.* Mice in all groups received 3 mg/kg of strychnine subcutaneously (*s.c.*) thirty minutes after pre-treatment Episodes of tonic convulsion (tonic extension jerks) and latency of death were observed and recorded.

4-Aminopyridine-induced seizure in mice
The method previously described[22] was adopted. Mice in groups one, two, three and four received respectively 10 ml/kg normal saline, 75 mg/kg, 150 mg/kg and 300 mg/kg CEE of the plant intraperitoneally (*i.p.*). Group five received 20 mg/kg phenobarbitone intraperitoneally.Subsequently, mice in all Groups were administered with 15 mg/kg body weight 4-aminopyridine (4-AP) subcutaneously (*s.c.*)30 minutes after pre-treatment. Episodes of hind limb tonic extension as well as latency to death were observed and recorded.

Statistical analysis
Results were expressed as mean ± standard error of mean (mean ± SEM). The data were then subjected to one-way Analysis of Variance (ANOVA). Where a statistically significant difference was obtained, a post hoc Dunnett's t-test for multiple comparisons was employed. Differences were considered significant at $p < 0.05$.

Results and Discussion

Phytochemical screening
The extractive value for the ethanol extract of *Cadaba farinosa* from 1,500 g plant material was found to be 12.63 % w/w (189.37 g; dark gummy mass).

Acute toxicity studies
The intraperitoneal (*i.p.*) median lethal dose (LD_{50}) value of ethanol extract of *Cadaba farinosa* was found to be 2154.1 mg/kg body weight in mice. The preliminary phytochemical examinations of the crude and the solvents partitioned portions revealed the presence of alkaloids, anthraquinones, carbohydrates, cardiac glycosides, flavonoids, glycosides, saponins and tannins.
The extract of *Cadaba farinosa* contain substances with potential values in the treatment of general body pains, dysentery, rheumatism, cough, fever, poisoning, amenorrhea, dysmenorrhea, liver damage, cancer and uterine obstruction amongst others.

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Maximal electroshock-induced seizure test in chicks

There was statistically no significant protection against seizure in all treated groups and no difference in the mean recovery time. Only phenytoin showed 40 % protection (Table 1).

Protection against hind limb tonic extension in MEST predicts anticonvulsant activity similarly to that of antiepileptic drugs such as phenytoin, carbamazepines, oxcarbazepine and lamotrigine, which prevent the spread of seizure discharge from an epileptic focus during seizure activity.[19] Hence, the ability of the antiepileptic agent to protect against thus MEST is used to predict benefit of antiepileptic agent in the treatment of generalized tonic-clonic and partial seizures.[23] Antiepileptic drugs which act via this pathway are able to limit the repetitive firing of action potentials by slowing the rate of recovery of voltage activated Na^+ channels from inactivation and suppress hind limb tonic extension in maximal electroshock seizures.[24] The extract therefore may not have activity via these mechanisms as there was no protection at all the doses tested and therefore may not be beneficial in treatment of generalized seizures. Only phenytoin at 20 mg/kg exhibited 40 % protection and therefore may not be beneficial in the management of generalized seizures.

Pentylenetetrazole-induced seizure in mice

The extract did not protect the mice against PTZ induced seizure at all doses tested. However, there was a significant increase in the mean onset of seizures time at all the doses tested(Table 2).

The results indicated CEE of *Cadaba farinosa* contained active compounds that may have some antagonistic action against pentylenetetrazole (PTZ) induced seizures. Previous studies indicated PTZ-induced seizures were due to blockage of major inhibitory pathways mediated by predominant inhibitory neurotransmitter Gamma Amino Butryric Acid (GABA) at all levels of the central nervous system (CNS).[25] Antiepileptic drugs (e.g. phenobarbitone, valproic acid, benzodiazepines, ethosuximide, e.t.c) effective in the therapy of generalized seizures of absence or myoclonic *petit mal* type can suppress various seizure patterns induced by PTZ.[26] One of the mechanisms by which antiepileptic drugs such as ethosuximide and valproic acid act is the suppression of T-type Ca^{2+} currents in thalamic neurons.[24, 27] A possible mechanism by which the extract exhibited some anticonvulsant activities may be due to enhancement of GABA mediated neural inhibition. The mild or moderate anticonvulsant activity against PTZ exhibited by the extract suggests that it may be beneficial in *petit mal* epilepsy.

Strychnine-induced seizure in mice

There was statistically significant ($p \leq 0.05$) 16.7 % protection exhibited by 150 mg/kg and 300 mg/kg tested doses of crude extract. The crude extract at 75 mg/kg exhibited the highest protection of 83.3 %. There was then increase in the mean onset only in phenobarbitone at 20 mg/kg with 50 % protection when compared with normal saline at 10 ml/kg (Table 3).

Strychnine (STN) has been known to be a competitive antagonist of glycine which is an inhibitory amino acid as well as neurotransmitter.[28] The convulsant effect of strychnine is known to be by interfering with the inhibitory action on glycine receptors and other interneurons in the spinal cord as well as post synaptic inhibition in the higher centers of the CNS.[29] The protection observed at 75 mg/kg of the extract and 20 mg/kg of phenobarbitone could be due to enhancement of glycinegic neurotransmission of the receptors (glycine) by substances present in doses tested. The decrease of activity at higher doses tested, suggest that the extract may contain compounds with opposite effects, some of which may be antagonizing the inhibitory action of glycine.

4-Aminopyridine-induced seizure in mice

The extract at 300 mg/kg offered 100 % protection against 4-AP induced seizure. This was greater than that produced by Phenobarbitone. However, there was no statistically significant difference in the onset of seizure in the unprotected animals (Table 4).

4-aminopyridine (4-AP) induces clonic-tonic convulsions by blocking potassium channels.[23] The K^+ channels play a vital role in the control of neuronal excitability and seizure susceptibility and would be of importance for the suppression of seizure initiation and spread.[30] The ability of the extract to produce 100 % protection at the dose of 300 mg/kg suggests that it may be acting via modulation of potassium channels.

Table 1: Effect of the ethanol extract of *Cadaba farinosa* on maximum electroshock-induced seizure in chicks

Treatment	Dose (mg/kg)	% Protection	Mean recovery time (min)
N/Saline	10 (ml/kg)	0.00	5.2 ± 0.4
CEE	75	0.00	5.5 ± 0.5
CEE	150	0.00	4.9 ± 0.5
CEE	300	0.00	6.2 ± 0.6
Phenytoin	20	40.00	3.2 ± 1.0

N/Saline = normal saline; CEE = crude ethanol leaf extract and n = 10.

Table 2: Effect of the ethanol extract of *Cadaba farinosa* on pentylenetetrazole-induced seizure in mice

Treatment	Dose (mg/kg)	% Protection	Mean onset of seizure (min)
N/Saline	10 (ml/kg)	0.00	3.0 ± 0.4
CEE	75	0.00	11.0 ± 3.7[a]
CEE	150	0.00	11.8 ± 2.6[b]
CEE	300	0.00	10.8±2.5[b]
Sodium valproate	200	83.33	18.00 ± 0.00

N/Saline = normal saline; CEE = crude ethanol leaf extract; [a]$p \leq 0.05$ and [b]$p \leq 0.01$ (compared with control. Dunnett's test for multiple comparison); n = 6

Table 3: Effect of the ethanol extract of *Cadaba farinosa* on strychnine-induced seizure in mice

Treatment	Dose (mg/kg)	% Protection	Mean onset of seizure (min)
N/Saline	10 (ml/kg)	16.7	7.60 ± 0.68
CEE	75	83.3	23.0 ± 0.0
CEE	150	16.7	7.2 ± 1.7
CEE	300	16.7	9.60 ± 1.33
Phenobarbitone	20	50.0	10.7 ± 0.9[a]

N/Saline = normal saline; CEE = crude ethanol leaf extract; [a]$p \leq 0.05$ (compared with control. Dunnett's test for multiple comparison) and n = 6.

Table 4: Effect of the ethanol extract of *Cadaba farinosa* on 4-aminopyridine-induced seizure in mice

Treatment	Dose (mg/kg)	% Protection	Mean onset of seizure (min)
N/Saline	10 (ml/kg)	0.00	8.33 ± 0.62
CEE	75	16.7	8.8 ± 1.7
CEE	150	0.00	9.67 ± 1.05
CEE	300	100	0.0 ± 0.0[c]
Phenobarbitone	20	83.3	18.0 ± 0.0

N/Saline = normal saline; CEE = crude ethanol leaf extract; [c]$p \leq 0.001$ (compared with control. Dunnett's test for multiple comparison) and n = 6.

Conclusion

The plant was found to be safe when administered intraperitoneally. The plant's extract possesses significant anticonvulsant activity which may be beneficial in *petit mal* epilepsy and its action may be mediated via GABAregic, glycinegic and potassium channels.

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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