E- ISSN: 2384-6836

ASN- PH-020919
ISSN: 2315-537X

International Journal of Herbs and Pharmacological Research
IJHPR, 2015, 4(2): 25 - 32
www.arpjournals.com; www.antrescentpub.com

RESEARCH PAPER

ANTICONVULSANT POTENTIALS OF METHANOL LEAF EXTRACT OF *CISSUS CORNIFOLIA* PLANCH (VITACEAE) IN MICE AND CHICKS

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Received: 5th April, 2015 Accepted: 29th April, 2015 Published: 30th April, 2015

***Endorsed By**: Innovative Science Research Foundation (ISREF). **Indexed By**: African Journal Online (AJOL); Texila American University; Genamics; Scholarsteer; EIJASR; CAS-American Chemical Society*; and *IRMS Informatics India* (*J-Gate)*

ABSTRACT

Cissus cornifolia Baker-Planch is an annual herb used in traditional medicine for the treatment of epilepsy. The anticonvulsant effects of the methanol extract of *Cissus cornifolia* leaf was evaluated in chicks using maximal electroshock test, and in mice using 4-aminopyridine, pentylenetetrazole, strychnine and picrotoxin induced seizure models at doses of 75, 150, 300 and 600 mg/kg. The extract of *Cissus cornifolia* leaf significantly ($p<0.05$) prolonged the latency to convulsions in 4-aminopyridine, pentylenetetrazole and strychnine-induced seizure models. *Cissus cornifolia* extract at doses of 300 and 600 mg/kg provided 66.67% protection against picrotoxin induced convulsions. It also significantly ($p<0.05$) prolonged the latency to picrotoxin-induced convulsions at the same doses. On the other hand, the extract did not protect the chicks against hind limb tonic extension in maximal electro-shock test. The results obtained indicated potential anticonvulsant activity of the methanol leaf extract of *Cissus cornifolia*, thus giving credence to the traditional use of this plant in the treatment of epilepsy.

Keywords: *Cissus cornifolia*, Epilepsy, Chemoconvulsant, Anticonvulsant

INTRODUCTION

Epilepsy is the second most common neurological disorder affecting about 50 million people worldwide; of which nearly 80% of the people with epilepsy are found in developing regions (WHO, 2012). Epilepsy is managed mainly with drugs; however, antiepileptic drugs currently in use neither provides a cure nor prevent relapse and are associated with many side effects such as fatigue, allergies, sedation, blood dyscrasias and teratogenesis, changes in mood and memory problems (Loscher, 2002; LaRoche and Helmers, 2004). As a result of this, development of new, affordable and accessible pharmacological agents that can overcome these limitations has become a major goal in epilepsy research. In this regard, the plant kingdom has become a major target in the search for new drugs as many plants are known for their anticonvulsant activity and their extracts can be important source of chemicals for the development of better and safer drugs for the treatment of epilepsy (Lucindo *et al.*, 2008; Kumar *et al*., 2012).

Cissus cornifolia Baker-Planch (Family -Vitaceae) is an annual, sub-erect herb found mainly in the rocky environment and Savannah regions of Ghana and Northern Nigeria. The herb is locally called “Rigarbiri” or “Duwawun biri” among the Hausa speaking people of Northern Nigeria (Burkill, 2000). The plant parts are used in

African ethnomedicine for wide variety of illness such as a remedy for gonorrhoea, malaria, pharyngitis and as a sedative in cases of mental derangement (Burkill, 2000). The plant is used locally to manage convulsions, fever and stomach problems (Personal communication, Zaria).

Our previous studies revealed that the leaf and root methanolic extracts of *Cissus cornifolia* possess central nervous system depressants and sedative properties in mice (Musa *et al*., 2008; Yaro *et al*., 2009). Other studies revealed that the methanol leaf extract of *Cissus cornifolia* possess antidiarrhoeal activity (Tanko *et al*., 2011) and hypoglycemic effects (Jimoh *et al*., 2013). To our knowledge, the anticonvulsant potentials of any part of the plant have not been reported and therefore, this study aimed at investigating the pharmacological basis for the use of *Cissus cornifolia* in traditional medicine.

MATERIALS AND METHODS

Animals: Albino mice (18-25g) of either sex maintained in the Animal House of the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria, were used for the study. In addition, one-day old cockerels, obtained from the National Animal Production and Research Institute (NAPRI), Shika, Zaria, were used. The animals were housed in well ventilated rooms (at room temperature), fed on pelletized Vital Feed® (obtained from Bukuru, Jos) and water *ad libitum.* All experimental protocols were approved by the Ahmadu Bello University Animal Ethics Committee.

Plant material: The leaves of *Cissus cornifolia* was freshly collected from Basawa, Sabon-Gari Local Government area of Kaduna State, Nigeria in the month of October, 2008. It was identified and authenticated by a taxonomist in the herbarium section of the Department of Biological Sciences, Ahmadu Bello University, Zaria, by comparing with a voucher specimen (number 024) previously deposited as reference in the department.

Preparation of the plant extract: The leaves of *Cissus cornifolia* were air dried under shade until constant weight was obtained and then pulverized using pestle and mortar. The powdered leaves (500g) was macerated in 2 liters of 70% $^{v}/_{v}$ aqueous methanol (70% methanol: 30% water) solution, with occasional shaking for 14 days and then filtered. The filtrate was evaporated to dryness *in vacuo* at 40^{o}C and then stored in a dessicator until required for the main study.

Test drugs and chemicals: Pentylenetetrazole, Strychnine, 4-aminopyridine and Picrotoxin (obtained from Sigma-Aldrich Chemical Co., St. Louis, USA) were the chemoconvulsants used, while the standard drugs used are sodium valproate (Sanofi-aventis, UK), phenytoin sodium (Zydus neuroscience, Ahmadebad) diazepam (Roche, France) and phenobarbitone (Lab-Renaudin, France).

Acute Toxicity Studies: The acute toxicity of the crude methanol leaf extract was investigated in mice via intraperitoneal route of drug administration. The method used was as described by Lorke (1983).The study was carried out in two phases. In the initial phase, three groups of three mice each were used. The first group received the extract at a dose of 10mg/kg, while the second and third groups received extract at doses of 100 and 1000mg/kg body weight respectively. The animals were observed for signs of toxicity and death within 24 hours. In the second phase, three groups of one mouse each were used. Specific doses (1600, 2900 and 5000mg/kg body weight) were administered. The animals were monitored for signs of toxicity including death. The LD_{50} (dose that is responsible for the death of 50% of an animal population) value was calculated as the square root of the product of the lowest lethal dose and the highest non-lethal dose, that is the geometric mean of consecutive doses for which 0 and 100% survival rates were recorded.

ANTICONVULSANT STUDIES

Maximal electroshock test: The methods of Swinyard and Kupferberg (1985) and Browning (1992) were employed. The apparatus used was the Ugo Basile Electroconvulsive Machine (Model 7801) with corneal electrodes placed on the upper eyelid of the chicks after dipping them in normal saline. A day-old chick has an underdeveloped blood brain barrier thereby facilitating easy passage of drugs and current into the brain (Browning, 1992). A current which induces tonic convulsion in 80-90% of a control group (normal saline) of chicks was selected. The current shock duration, pulse width and frequency were set and maintained at 80 mA, 0.6 sec., 0.6 ms, and 100 pulses per second respectively. A second group of ten chicks was pretreated with phenytoin (20 mg/kg) *i.p.* 30 minutes later; they were subjected to electrical stimulation as in normal saline treated controls. Tests chicks were then intraperitoneally pretreated in groups of ten with 75, 150, 300, and 600 mg/kg of *Cissus cornifolia* leaf extract, before being electrically shocked 30 minutes later. Results were recorded as either positive or negative depending on

whether tonic hind limb extension (THLE) was produced or not. The time of recovery of convulsed chicks was also recorded and the percentage of convulsed animals calculated.

4-aminopyridine-induced convulsion in mice: The method adopted for this study was described by Rogawski and Porter (1990) and Yamaguchi and Rogawski (1992). Mice were randomly divided into six groups of 6 mice each and intraperitoneally treated as follows: groups one to four received the leaf extract (75, 150, 300 and 600 mg/kg); the fifth group received phenobarbitone sodium (20 mg/kg) while the last group was treated with normal saline 10 ml/kg. Thirty (30) minutes post treatment mice in all the groups were administered 4-aminopyridine 15 mg/kg subcutaneously. The mice were observed for 30 minutes for characteristic behavioural signs, such as hyperactivity, trembling, intermittent forelimb extension, tonic seizures and death. The ability of the extract to protect the mice from lethality within 30 minutes observation period was considered as an indication for anticonvulsant activity (Yamaguchi and Rogawski, 1992).

Pentylenetetrazole induced convulsion in mice: Mice were injected with a convulsive dose (CD_{97}), that is the dose that produces convulsions in 97% of animals (90 mg/kg pentylenetetrazole subcutaneously). They were then observed for the presence or absence of threshold seizures (an episode of clonic spasm of at least 5 seconds duration) according to the method of Swinyard *et al*. (1989). Four groups of 6 mice each were intraperitoneally pretreated with 75, 150, 300 and 600 mg/kg *Cissus cornifolia* leaf extract, a fifth group was pretreated with valproic acid 200 mg/kg body weight *i.p.* Another group was given normal saline 10 ml/kg *i.p.* and served as negative control. Thirty minutes later, all the mice were injected with 90 mg/kg pentylenetetrazole subcutaneously. They were then observed for the presence or absence of clonic spasm. The time of onset of convulsion, the number of animals protected (including percentage protection), and the number of animal(s) that died per group were recorded.

Strychnine-induced convulsion in mice: The method used is as described by Lehmann *et al*., 1988. Strychnine convulsions followed by death were induced in mice by the subcutaneous injection of 2.4 mg/kg of strychnine nitrate. Thirty minutes prior to administration of strychnine four groups of 6 mice each were intraperitoneally pretreated with the leaf extract (75, 150, 300, and 600 mg/kg). The fifth group was treated with phenobarbitone sodium (20 mg/kg *i.p.*) which served as the positive control while the sixth group received normal saline 10 ml/kg as the negative control. Mice were then observed for tonic extensor jerks of the hind limbs followed by death in 30 minutes. Abolition of tonic extensor jerks of the hind limbs was considered an indicator that the extract could prevent strychnine-induced seizures (Raza *et al*., 2001).

Picrotoxin-induced convulsion test in mice: The method described by Vogel, 2008 was adopted in this study. Thirty six mice were randomly divided into six groups containing six mice in each group. The first group served as negative control and was pretreated with normal saline 10 ml/kg. The second, third, fourth and fifth groups were pretreated with 75, 150, 300 and 600 mg/kg of the extract respectively, while the sixth group served as a positive control and was pretreated with 3 mg/kg diazepam all through the intraperitoneal route. Thirty minutes post treatment all mice were treated with 3.5 mg/kg picrotoxin by subcutaneous route. Immediately after picrotoxin injection mice were observed for the following symptoms during the next 30 min: clonic seizures, tonic seizures and death.

Statistical analysis: Data were expressed as mean ± standard error of mean (S.E.M.) and as percentages where appropriate. Differences between means were analyzed using students't-test and values of $p < 0.05$ were considered significant.

RESULTS

Percentage yield of methanol leaf extract of *Cissus cornifolia* was 9.60% $^{w}/_{w}$, while the intraperitoneal LD_{50} of the extract in mice was calculated to be 2154.1 mg/kg body weight. The crude leaf extract of *Cissus cornifolia* (at doses of 75, 150, 300, and 600 mg/kg) did not protect chicks against hind limb tonic extension (HLTE) in maximal electro-shock test except with 600 mg/kg which offered only 20% protection. Phenytoin (20 mg/kg body weight) used as positive control produced 100% protection of the chicks against HLTE (Table 1).

The results of 4-aminopyridine-induced convulsion test showed that the leaf extract of *Cissus cornifolia* significantly ($p < 0.05$) delayed the latency to convulsion and death at doses of 150, 300 and 600 mg/kg body weight when compared with normal saline treated group. The extract at doses of 300 and 600 mg/kg also protected 16.67 and 33.33% of mice against convulsion and death induced by 4-aminopyridine. The positive control, phenobarbitone (20 mg/kg) protected 66.67% of animals against 4-aminopyridine-induced convulsion. It also significantly ($p< 0.001$) delayed the latency of the convulsed mice (Table 2).

Cissus cornifolia leaf extract (CCLE) at higher doses of 300 and 600 mg/kg protected 33.33% of mice against clonic spasm induced by pentylenetetrazole. It also significantly ($p< 0.05$) increased the latency of convulsed animals from 8.40±1.00 minutes in normal saline treated group to 14.20±0.60 and 14.60±1.20 minutes at doses of 600 and 300 mg/kg respectively. Valproic acid produced 100% protection against clonic spasm induced by pentylenetetrazole (Table 3).

Cissus cornifolia leaf extract significantly ($p< 0.05$) prolonged the latency of convulsed mice from 6.80±0.06 minutes in normal saline treated group to 9.30±1.10, 10.10±1.70 and 9.80±1.00 minutes at doses of 600, 300 and 150 mg/kg respectively. The extract at doses of 150 and 300 mg/kg also protected 33.33% of mice against convulsion induced by strychnine. The positive control, phenobarbitone (20mg/kg) protected 83.33% of mice against convulsion induced by strychnine (Table 4).

CCLE at doses of 600 and 300 mg/kg protected 66.67% of mice against convulsion induced by picrotoxin and significantly ($p< 0.05$) prolonged the latency of convulsed animals at the same doses. At doses of 150 and 75 mg/kg, the leaf extract significantly ($p< 0.05$) increased the time of onset of convulsion when compared with normal saline treated group. The positive control, diazepam (3mg/kg) protected 83.33% of mice against picrotoxin-induced convulsion (Table 5).

Table 1: Effect of Methanol Leaf extract of *Cissus cornifolia* on maximal electroshock test in chicks

Treatment (mg/kg)	Mean recovery time (min.)	Quantal protection	% protection
N/Saline (10 ml/kg)	6.10 ± 0.45	0/10	0.00
CCLE (600)	5.30 ± 0.95	2/10	20.00
CCLE (300)	5.80 ± 0.52	0/10	0.00
CCLE (150)	6.90 ± 0.43	0/10	0.00
CCLE (75)	6.40 ± 0.38	0/10	0.00
Phenytoin (20)	0.00 ± 0.00	10/10	100.00

Recovery time presented as Mean ± S.E.M., n = 10, CCLE = *Cissus cornifolia* leaf extract

Table 2: Effect of Methanol leaf extract of *Cissus cornifolia* on 4-aminopyridine-induced convulsion in mice

Treatment (mg/kg)	Mean onset of convulsion (min.)	Quantal protection	% protection
N/Saline (10 ml/kg)	12.30 ± 1.00	0/6	0.00
CCLE (600)	17.50 ± 2.50[a]	2/6	33.33
CCLE (300)	21.00 ± 2.40[b]	1/6	16.67
CCLE (150)	15.40 ± 1.10[a]	0/6	0.00
CCLE (75)	13.50 ± 1.20	0/6	0.00
PBT (20)	23.40 ± 0.60[c]	4/6	66.67

Onset of convulsion presented as Mean ± S.E.M, n = 6, a, b, and c represent $p < 0.05$, 0.005 and 0.001 respectively – students' test, CCLE = *Cissus cornifolia* leaf extract, PBT = phenobarbitone

Table 3: Effect of Methanol leaf extract of *Cissus cornifolia* on pentylenetetrazole-induced convulsion in mice

Treatment (mg/kg)	Mean on set of Convulsion (min)	Quantal Protection	% protection
N/Saline (10 ml/kg)	8.40 ± 1.00	1/6	16.67
CCLE (600)	14.20 ± 0.60[c]	2/6	33.33
CCLE (300)	14.60 ± 1.20[b]	2/6	33.33
CCLE (150)	8.50 ± 1.30	0/6	0.00
CCLE (75)	9.20 ± 1.40	0/6	0.00
VPA (200)	0.00 ± 0.00	6/6	100.00

Onset of convulsion presented as Mean ± S.E.M, n = 6, b and c represent $p < 0.005$ and $p < 0.001$ respectively – students'-test, CCLE = *Cissus cornifolia* leaf extract, VPA = Valproic acid

Table 4: Effect of Methanol Leaf extract of *Cissus cornifolia* on Strychnine-induced convulsion in mice

Treatment (mg/kg)		Mean on set of Convulsion (min.)	Quantal Protection	% protection
N/Saline	(10 ml/kg)	6.80 ± 0.60	0/6	0.00
CCLE	(600)	9.30 ± 1.10[a]	0/6	0.00
CCLE	(300)	10.10 ± 1.70[a]	2/6	33.33
CCLE	(150)	9.80 ± 1.00[a]	2/6	33.33
CCLE	(75)	8.30 ± 0.80	1/6	16.67
PBT	(20)	17.20 ± 0.00	5/6	83.33

Onset of convulsion presented as Mean ± S.E.M, n = 6, a represent $p < 0.05$ – students't-test, CCLE = *Cissus cornifolia* leaf extract, PBT = Phenobarbitone

Table 5: Effect of Methanol Leaf Extract of *Cissus cornifolia* on Picrotoxin-induced convulsion in mice

Treatment (mg/kg)		Mean onset of convulsion (min.)	Quantal protection	% Protection	% Mortality
N/Saline	(10 ml/kg)	10.30 ± 0.30	0/6	0.00	83.33
CCLE	(600)	21.00 ± 5.00[a]	4/6	66.67	0.00
CCLE	(300)	14.50 ± 0.50[c]	4/6	66.67	16.66
CCLE	(150)	13.30 ± 0.80[b]	2/6	33.33	16.66
CCLE	(75)	13.80 ± 1.60[a]	0/6	0.00	50.0
Diazepam	(3)	27.00 ± 0.00	5/6	83.33	0.00

Onset of convulsion presented as Mean ± S.E.M, n = 6, a, b and c represent $p < 0.05$, $p < 0.005$ and $p < 0.001$ respectively – students't-test, CCLE = *Cissus cornifolia* leaf extract

DISCUSSION:

Intraperitoneal acute toxicity studies conducted in mice showed a moderate toxicity for the methanolic extract of *Cissus cornifolia* leaf according to Lu (1996) classification of LD_{50} values. 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. Compounds, such as phenytoin, carbamazepine, oxcarbazepine and lamotrigine suppress HLTE in MEST (Browning, 1992). The lack of protection against HLTE by *Cissus cornifolia* leaf extract in MEST suggests that the extract is not effective in the treatment of generalized tonic-clonic and partial seizures.

4-aminopyridine is a known potassium channel blocker and a powerful convulsant in animals and man (Yagamuchi and Rogawski, 1992). Potassium channels play a major role in the control of all aspect of neuronal excitability, including resting membrane potential, responsiveness to synaptic inputs, frequency adaptation and neurotransmitter release (Wickenden, 2002). Drugs like phenytoin which block seizure spread are effective antagonists of seizures induced by potassium channel blockade while those with specific actions on other cellular targets may be weak or inactive, presumably because they are unable to attenuate the spread of intense (non-NMDA receptor mediated) excitation evoked by 4-aminopyridine (Yagamuchi and Rogawski, 1992). The ability of *Cissus cornifolia* leaf extract to significantly prolong the latency to convulsion by 4-aminopyridine suggests it interacts with potassium channel to produce anticonvulsant activity.

Pentylenetetrazole (PTZ) is a known convulsant and anticonvulsant activity in subcutaneous PTZ test identifies compounds that can raise the seizure threshold in the brain (White *et al.*, 1998). AEDs effective in the therapy of generalized seizures of (absence or myoclonic) petitmal type such as ethosuximide (ETX), valproic acid (VPA), phenobarbitone, and benzodiazepine exhibit dose-dependent suppression of various seizure patterns induced by PTZ (Loscher *et al*., 1991). 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 (Rho and Sankar, 1999; Meldrum, 1996). The significant increase in latency of convulsions by *Cissus cornifolia* leaf extract suggests the presence of bioactive compounds effective in the therapy of absence or myoclonic seizures.

Strychnine is a competitive glycine receptor antagonist (Rajendra *et al*., 1997). The protection provided by *Cissus cornifolia* leaf extract as well as its ability to significantly increase the latency to first tonic extensor jerk and death suggests the leaf extract may act by enhancing inhibitory neurotransmission mediated by glycine.

Picrotoxin is used in determining mechanism of action of sedative-hypnotic and anticonvulsants (Vogel, 2008). Picrotoxin induces convulsions by blocking the inhibitory synaptic action of GABA on $GABA_A$ receptor chloride channels, although, not competitively (Rang *et al*., 2007). As an antagonist of GABA inhibitory action in different areas of the central nervous system, picrotoxin produces general clonic-tonic convulsions which lead to death in most cases (Abdul-Ghani *et al.,* 1980). *Cissus cornifolia* leaf extract protected animals against clonic-tonic convulsions induced by picrotoxin and also significantly prolonged the latency of convulsed animals at all doses tested. Therefore, the methanol leaf extract may act to enhance GABA-mediated inhibitory neurotransmission by interacting with $GABA_A$ – receptor activated chloride channel to produce the anticonvulsant action. This is further supported by the result of PTZ-induced convulsion test.

In conclusion, the findings of this study suggest that methanol leaf extract of *Cissus cornifolia* leaf possesses anticonvulsant activity and thus provides a rationale for its use in traditional treatment of epilepsy.

ACKNOWLEDGMENT

The authors would like to thank Malam Ibrahim Adamu and Malam Ya'u of Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria, for their technical assistance.

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AUTHOR'S CONTRIBUTIONS

Dr. Yaro A.H. and Dr. Magaji, M.G. were involved in the Pharmacological studies while Dr. Musa A.M. and Nazifi A.B. phytochemical screening and prepared the manuscript respectively.