ISSN (Print): 2476-8316
ISSN (Online): 2635-3490
Dutse Journal of Pure and Applied Sciences (DUJOPAS), *Vol. 6 No. 2 June 2020*

Anticonvulsant Activity of Aqueous Stem Bark Extract of *Securidaca longipedunculata* Fresen (Polygalaceae)

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Abstract

The present study was aimed to evaluate the phytochemical constituents and anticonvulsant property of the aqueous extract of Securidaca longipedunculata stem bark using three models of epilepsy. The preliminary phytochemical screening revealed the presence of cardiac glycosides, tannins, steroids, terpenoids, alkaloids, flavonoids, anthraquinones, phenolic compounds, saponins and carbohydrates. The anticonvulsant study shows that the extract afforded 80% protection to the laboratory animals against the chemically induced convulsion of pentylenetetrazole at 50 and 100 mg/kg body weight, it also prolonged the onset of convulsion which was statistically significant ($p<0.05$) when compared to the untreated group. The extract also gave 50% protection against the maximal electroshock induced convulsion at 50 mg/kg body weight, the duration of convulsion decreases at all the three doses which was statistically significant ($p<0.05$) when compared to the untreated group. On the other hand, the extract did not protect the animals against the chemically induced convulsion of 4-amino pyridine, however, it prolonged the onset of convulsion at 100 and 200 mg/kg body weight which was statistically significant ($p<0.05$) when compared to the untreated group. The present study shows that the stem bark of S.longipedunculata possesses anticonvulsant activity, and this may account for its use in Nigerian traditional medicine for the management of epilepsy. Studies are currently on-going to isolate, characterize and identify the bioactive compounds responsible for the anticonvulsant activity of the plant.

Keywords: Bioactive compounds, Convulsion, Epilepsy, Traditional medicine

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INTRODUCTION

Epilepsy is defined as a chronic and often progressive disorder characterized by the periodic and unpredictable occurrence of epileptic seizures which are caused by an abnormal discharge of cerebral neurons (Löscher, 1998). It is a second neurological disorder and has no age, racial, social, sexual or geographical boundaries. From many studies around the world, it has been estimated that the mean prevalence of active epilepsy is approximately 8 per 1,000 of the general population, while in developing countries including Nigeria the mean prevalence is more than 10 per 1,000. Thus, it is likely around 50 million people in the world have epilepsy (WHO, 2002).

The current therapy of epilepsy with modern antiepileptic drugs (AEDs) is associated with many side effects such asteratogenic effects, chronic toxicity, psychiatric effects, weight changes, dose-related, hypersensitivity and approximately 30 % of the patients continue to have seizures with the current antiepileptic drugs therapy. Therefore, there is need for new AEDs with greater efficacy and novel mechanisms of action to serve as alternate therapy for the treatment of resistant epilepsy (Blumer *et al*., 1995; Samren *et al*., 1999; Wickenden, 2002; Tomson and Battino, 2005; Ben-Menachem, 2007).

Several medicinal plants have been studied for their anticonvulsant activity and many studies have been conducted at molecular level and the phytochemicals responsible for the anticonvulsant activity have been isolated, identified and characterized (Mohammad, 2013).

Securidaca longipedunculata is locally called *Sanya* or *Uwarmagunguna* (Hausa), *Ezeogwu* (Igbo) and *Alali* (Fulani). The reported biological activities of *S.longipedunculata* include antibacterial and antifungal (Adebayo and Osman 2012; Karou*et al*., 2012; Musa *et al*., 2013; Ndamitso *et al*., 2013) anti trypanosomal(Freiburghaus *et al*., 1996), antioxidant (Muanda *et al*., 2010; Karou *et al*., 2012), antiplasmodial(Bah *et al*., 2007; Haruna *et al*., 2013), insecticidal, molluscicidal and pesticidal (Boeke *et al*., 2004; Olofintoye, 2010; Afful *et al*., 2012; Eziah *et al*.,2013).In Northern Nigeria, the stem bark of *S. longipedunculata* is used by traditional healers for the management of epilepsy without any scientific validation, thus, this study was aimed to evaluate the antiepileptic or anticonvulsant activity of this important medicinal plant.

MATERIALS AND METHODS

Animals

Swiss albino mice of both sexes, weighing 18-25 g were obtained from the Animal House of the Department of Pharmacology and Therapeutics, Bayero University, Kano, Nigeria. In addition, day old white ranger cockerels were obtained from the National Animal Production Research Institute (NAPRI) Shika, Zaria. The animals were housed under standard conditions of temperature (25 ± 2^{o}C), 12/12 hour light/dark cycle, fed with standard diet (Feeds Masters Plc. Ilorin, Nigeria), and given water *ad libitum*. All experiments performed in this work followed the principles of laboratory animal care outlined by the ethical committee of Bayero University, Kano, Nigeria.

Collection and Identification of Plant

The plant was collected from Gwaram Town, Jigawa State, Nigeria, it was identified in the field using taxonomic characters and then taken to the Herbarium of Ethno botany and Multidisciplinary Research Division of Bioresources Development Centre, Kano for authentication, a reference voucher number: BDCKN/EB/1898 was deposited in the Herbarium. The stembark was air dried and then ground into fine powder using mortar and pestle.

Extraction of the Powdered Plant Material

The powdered plant material(100g) was macerated with distilled water (500ml) for 24 hours, and was shaken occasionally. The filtrate obtained was evaporated to dryness at 40^{o}C using rotary evaporator and water bath.

Preliminary Phytochemical Screening

The Preliminary phytochemical screening of the aqueous stem bark extract of *S. longipedunculata* was conducted using the standard laboratory procedures as described by Evans (1996) and Harbone (1998).

Anticonvulsant Activity

The maximal electroshock test, pentylenetetrazole (PTZ) and 4-aminopyridine induced seizures were employed for testing the anticonvulsant activity of the extract which have been described as follows;

Pentylenetetrazole-Induced Seizure

The method of Swinyard *et al* (1989) was employed. Twenty five mice were divided into 5 groups of 5 mice per group. The first group received normal saline at 10 ml/kg body weight *(i.p).* Groups 2-4 received the extract at the doses of 50, 100 and 200 mg/kg body weight respectively, while animals in the fifth group were treated with 200 mg/kg *(i.p)* valproate. Thirty minutes later, mice in all groups received PTZ at 90 mg/kg (*sc*). The mice were observed for 30 minutes for the onset and incidence of seizures. Absence of an episode or clonic spasm of at least 5 seconds was considered as the ability of the extract to abolish the effect of PTZ on seizure threshold or ability to prolong mean onset of seizure was an indication of the extract ability to reverse the effect of PTZ (Raza *et al.,* 2001).

Maximal Electroshock-Induced Seizure

The methods of Swinyard and Kupferberg (1985) and Browning (1992) were employed. Fifty-one day old chicks were randomly divided into 5 groups of 10 chicks per group. The first group received normal saline at 10 ml/kg body weight (*i.p*), groups 2-4 received the extract at the doses of 50, 100 and 200 mg/kg body weight respectively, while the fifth group received phenytoin (*i.p*) at 20 mg/kg body weight, 30 minutes later, maximal electroshock was delivered to induce seizure in the chicks using Ugo basile electroconvulsive machine (model 1801) with corneal electrodes placed on the upper eyelid of the chick after dipping them in normal. The current, shock duration, frequency and pulse width were set and maintained at 90 mA, 1.0 second, 200 Hz and 1.0 m/s respectively. An episode of tonic extension of the hind limbs of the

chicks was considered as full convulsions. Lack of tonic extension of the hind limbs was considered as protection.

4-Amino Pyridine-Induced Seizure

The method described by Yagamuchi and Rogawski (1992) were adopted. Twenty-five albino mice were randomly divided into 5 groups of 5 mice per group. The first group received normalsaline at 10 ml/kg body weight *(i.p).* Groups 2-4 received the extract at the doses of 50, 100 and 200 mg/kg body weight respectively, while animals in the fifth group were treated with Phenobarbitone at a dose of 30 mg/kg body weight, 15 minutes post treatment; 4-amino pyridine was administered at a dose of 15 mg/kg body weight to each group (*s.c*). The mice were observed for 30 minutes for characteristic behavioral 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.

Statistical Analysis

The results were presented in the tables and expressed as Mean ± Standard Error of Mean (SEM). The level of significance was tested using one-way ANOVA followed by Duncan Multiple Range Test (DMRT), the results were regarded as significant when $p<0.05$.

RESULTS

The preliminary phytochemical screening of aqueous extract of *S. longipedunculata* stem bark revealed the presence of tannins, cardiac glycosides, steroids, terpenoids, alkaloids, flavonoids, anthraquinones, saponins, phenolic compounds and carbohydrates (Table 1);

Table 1: Phytochemical Constituents of Aqueous Extract of *S. longipedunculata*

Phytochemicals Tested	Inference
Tannins	Present
Anthraquinones	Present
Alkaloids	Present
Flavonoids	Present
Saponins	Present
Carbohydrates	Present
Phenolic compounds	Present
Glycosides	Present
Terpenoids	Present
Steriods	Present

Anticonvulsant Activity of Aqueous Extract of *S. longipedunculata* Stem Bark Pentylenetetrazole (PTZ) Induced-Seizure

The aqueous stem bark extract of *S. longipedunculata* afforded 80% protection at 50 and 100 mg/kg body weight to the animals against the chemically induced convulsion of PTZ. It also prolonged the onset of convulsion which was statistically significant ($p<0.05$) when compared to the untreated group (Table 2). Also, the standard antiepileptic drug, valproate afforded 80 % protection to the animals in the positive control group.

Table 2: Effects of Different Doses of Aqueous Stem Bark Extract of *S. longipedunculata* on the Convulsive Activities ofPentylenetetrazole

Treatment	Mean Onset of Convulsion ± SEM (minutes)	Quantal Protection	Percentage Protection	Percentage Mortality
Normal saline (10 ml/kg)	8.20 ± 0.20[b]	0/5	0	40
50 mg/kg	25.80 ± 0.20[a]	4/5	80	0
100 mg/kg	25.80 ± 4.20[a]	4/5	80	20
200 mg/kg	22.60 ± 4.53[a]	3/5	60	40
Valproate (90 mg/kg)	27.00 ± 0.40[a]	4/5	80	20

Values represent Mean ± SEM of N=5. Values in the same column with different superscript differs significantly (p<0.05)

Maximal Electroshock-Induced Seizure

The aqueous stem bark extract of *S. longipedunculata* afforded 50% protection at 50 mg/kg body weight (lowest dose used) to the laboratory animals against the maximal electroshock induced convulsion, which was not dose dependent. The duration of convulsion decreases at all the three doses which was statistically significant (p<0.05) when compared to the untreated group (Table 3). The standard anticonvulsant drug, phenytoin (at a dose of 20 mg/kg body weight) protected all the animals in the positive control group.

Table 3: Effects of Different Doses of Aqueous Stem Bark Extract of *S. longipedunculata* on the Convulsive Activities of Electroshock

Treatment	Mean Recovery Time ± SEM (minutes)	Quantal Protection	Percentage Protection	Percentage Mortality
Normal saline (10 ml/kg)	13.90 ± 0.23[c]	0/10	0	0
50 mg/kg	3.90 ± 1.30[a]	5/10	50	
100 mg/kg	9.50 ± 1.07[b]	1/10	10	0
200 mg/kg	6.10 ± 1.34[a]	3/10	30	0
Phenytoin 20 mg/kg	-	10/10	100	0

Values represent Mean ±SEM of N=10. Values in the same column with different superscript differs significantly (p<0.05)

4-Amino Pyridine Induced-Seizure

The aqueous stem bark extract of *S. longipedunculata* did not protect the animals against the chemically induced convulsion of 4-amino pyridine as shown in Table 4, however, the extract prolonged the onset of convulsion at 100 and 200 mg/kg body weight which was statistically significant (P<0.05) when compared to the untreated group.

Table 4: Effects of Different Doses of Aqueous Stem Bark Extract of *S. longipedunculata*on the Convulsive Activities of 4-Amino Pyridine

Treatment	Mean Onset of Convulsion ± SEM (minutes)	Quantal Protection	Percentage Protection	Percentage Mortality
Normal saline (10 ml/kg)	7.80 ± 0.37^{c}	0/5	0	100
50 mg/kg	8.20 ± 0.20^{c}	0/5	0	100
100 mg/kg	11.20 ± 0.20^{b}	0/5	0	100
200 mg/kg	13.80 ± 0.20^{a}	0/5	0	100
Phenobarbitone (30 mg/kg)	-	5/5	100	0

Values represent Mean ±SEM of N=5. Values in the same column with different superscript differs significantly (p<0.05)

DISCUSSION

The preliminary phytochemical screening showed that terpenoids, tannins, alkaloids, flavonoids, anthraquinones, saponins, phenolic compounds, carbohydrates, cardiac glycosides and steroids were all present in the stem bark of *S. longipedunculata*. Previous studies showed that alkaloids, flavonoids, terpenoids and saponins are commonlyimplicated in the anticonvulsant activity of many medicinal plants; thus, the anticonvulsant activity observed in this study could be attributed to one or more of these phytoconstituents (Mu *et al.,* 1986; Medina *et al.,* 1990; Zhou, 1991; Avallone *et al.,* 2000; Lian *et al.,* 2005; Park *et al.,* 2007; Bhutada *et al.,* 2010; Costa *et al.,* 2012; Da Cruz *et al.,* 2013).

The ability of the extract to protect the animals, delayed the onset of convulsion and/or shortened the duration of convulsion was considered as an indication of anticonvulsant activity (Priscilla*et al*., 2013). The aqueous stem bark extract of the violet tree exhibited a strong anticonvulsant activity against the chemically induced convulsion of PTZ; it conferred 80% protection at 50 and 100 mg/kg body weight. The extract also prolonged the onset of convulsion which was statistically significant when compared to the negative control group. Previous studies revealed that the aqueous root extract of *S. longipedunculata* afforded 100% protection against chemically induced convulsion of PTZ (Okomolo*et al*., 2011), it also produced a significant dose dependent increase in the onset of convulsion against strychnine induced seizure at the doses of 100 to 400 mg/kg body weight. These findings justified the use of *S. longepedunculata* root and stem bark in African traditional medicine for the management of epilepsy (Adeyemi *et al*., 2010).

The mechanism by which PTZ produces seizures has been shown to be due to inhibition and/or attenuation of GABAergic neurotransmission. Therefore, it is likely that the root and stem bark of *S. longipedunculata* produces their anticonvulsant effect directly or indirectly by enhancing GABAergic neurotransmission in the brain (Gale, 1992; Katzung, 2004). Pentylenetetrazole induced convulsion usually identify anticonvulsant drugs which could be effective against generalized myoclonic, clonic and non-convulsive seizures, thus, the stem bark of *S.*

*longipedunculata*may contain compounds that could be useful in the treatment of such type of seizures in humans (Löscher, 1998).

The study also indicates that aqueousextract of *S. longipedunculata* stem bark protected 50% and 30% of the animals against the maximal electroshock induced convulsion at 50 mg/kg and 200 mg/kg respectively,also, the duration of convulsion decreases at all the three doses which was statistically significant (p<0.05) when compared to the untreated group.Previous studies revealed that the aqueous root extract of *S. longipedunculata* at the doses of 500mg/kg and 1000 mg/kg body weight completely protected the laboratory animals against the maximal electroshock induced seizure (Okomolo*et al*., 2011).

The maximal electroshock induced seizure test is one of the most commonly used animal models in the search for new antiepileptic or anticonvulsant drugs. In this model, tonic hind limb seizure is induced by bilateral corneal or transauricular electrical stimulation, and isthought to be predictive of anticonvulsant drug which could be effective against generalized tonic-clonic seizures (Löscher, 1998). The ability of the aqueousextract to protect the animals against the maximal electroshock induced convulsion suggests that the stem bark of *S. longipedunculata* could prevent the spread of the epileptic seizure from an epileptic focus during seizure activity; it may also prevent seizure discharge within brainstem substrate. The plant may also contain bioactive compounds that could be useful in the treatment of generalized tonic-clonic and partial seizure (Browning, 1992; Macdonald and Kevin, 1995; Löscher, 1998).

On the other hand, the aqueous extractof *S. longipedunculata* stem bark did not protect the animals against the chemically induced convulsion of 4-amino pyridine, a well-known potassium channel blocker. However, the extract prolonged the mean onset of convulsionwhich was statistically significant (P<0.05) when compared to the untreated group, and this could be due to the activation of potassium channels or conductance (Yamaguchi and Rogawski, 1992).

CONCLUSION

The present study showed that the stem bark of *S.longipedunculata* possesses anticonvulsant activity, and this may account for its use in Nigerian traditional medicine for the management epilepsy. Studies are currently on-going to isolate, characterize and identify the bioactive compounds responsible for the anticonvulsant activity of the plant.

ACKNOWLEDGEMENT

The authors acknowledged the technical assistance of all the Technologists in the Department of Pharmacology and therapeutics, Bayero University, Kano, Nigeria. We are also grateful to Dr Sani Malami, Dean Faculty of Pharmaceutical Sciences, Bayero University, Kano, Nigeria.

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