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Evaluation of Anticonvulsant Activity of Methanol Leaf Extract of *Peristrophe bicalyculata* (Acanthaceae) in Experimental Animals

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Abstract

Peristrophe bicalyculata (Retz) Nees, a perennial herb found throughout tropical Africa, is used in Nigerian ethnomedicine for the management of pain and convulsions. The objective of this study is to screen for the anticonvulsant activity of methanol leaf extract of *P. bicalyculata* at doses of 200, 400 and 800 mg/kg in experimental animals. Preliminary phytochemical screening and acute toxicity studies were carried out. The extract was evaluated for anticonvulsant activity using maximal electroshock induced seizure test in day-old chicks, pentylenetetrazole- (PTZ), strychnine-, 4-aminopyridine- and picrotoxin-induced seizures models in mice. Phytochemical screening showed the presence of alkaloids, anthraquinones, glycosides, cardiac glycosides, saponins, steroids, triterpenes, tannins and flavonoids, while the intraperitoneal median lethal dose was estimated to be 3800 mg/kg in mice. *P. bicalyculata* extract at 200 mg/kg protected 30% of chicks against tonic hind limb extension. In the PTZ test, the extract at 800 mg/kg offered 66.67% protection against seizures. It also significantly ($p<0.01$) increased the mean onset of seizures at 200 mg/kg when compared to control. However, the extract offered no protection against strychnine, 4-aminopyridine and picrotoxin-induced seizures. The results revealed that, the methanol leaf extract of *Peristrophe bicalyculata* possess anticonvulsant activity and therefore lend some scientific support for its ethno-medical use in the management of convulsions.

Keywords: *Peristrophe bicalyculata,* Anticonvulsant, Epilepsy, Pentylenetetrazole

Introduction

Epilepsy is defined as a disorder of the brain characterized by at least two unprovoked seizures occurring in 24 hours apart, with probability of having similar attacks within 10 years accompanied by epilepsy syndrome (Fisher *et al.,* 2014). Epilepsy is one of the most common neurological disorders of the brain which affects approximately 50 million people worldwide. The estimated proportion of the general population with active epilepsy is between 7 and 14 per 1000 people and these people live in low-and middle income countries. Globally 2.4 million people are diagnosed with epilepsy each year (WHO, 2017). Even with the introduction of valuable antiepileptic drugs, there is no known cure for epilepsy and relapse is still high (Loscher, 2002). It is therefore important to broaden the search for newer drugs to include plants with ethnomedical relevance for the treatment of epilepsy.

The plant kingdom has become an important target in the search of new drugs and lead compounds in the treatment of many neurological disorders including epilepsy (Chindo *et al*., 2014). The World Health Organization (WHO) estimated that 80% of the world's population relies on traditional healing modalities including herbal medicine for primary health care and wellness (WHO, 2002;Karunamoorthi *et al*., 2013). *Peristrophe bicalyculata* (Retz) Nees (Family: Acanthaceae) is a perennial herb that is distributed throughout tropical Africa and toIndia, Burma and Thailand (Burkill, 1985). In Nigeria, it is locally known as "TubaninDawaki" (Flower of the horse) by the Hausa tribe. The leaf extract of the plant is used traditionally in the treatment of ear and eye infections as well as venomous stings and bites (Burkill, 1985).A review on *P. bicalyculata* revealed that the plant is used as a traditional remedy for tuberculosis, snake bites, hysteria and psychomotor disorders (Rashmi*et al*., 2010). Studies on *P. bicalyculata* extract have shown that it possesses antihypertensive (Abdulazeez *et al*., 2011), antibacterial (Janakiraman *et al*., 2012), anti-cancer (Tanavade *et al*., 2012), hepatoprotective (Essien *et al*., 2013), anti-trypanosomal (Abimbola *et al*., 2013) and anti-epileptogenic activities (Wapa *et al*., 2018). The effectiveness of the leaf extract in the management of convulsions is widely acclaimed among the convulsions among herbal medical practitioners especially in Zaria, Kaduna State, Nigeria (Rabi'uSalihu, Personal Communication, July 2016). The aim of this study is to establish the anticonvulsant activity of methanol leaf extract of *Peristrophe bicalyculata* in laboratory animals using acute seizure models.

Materials and methods

Drugs, chemicals and equipments

Methanol, strychinine, pentylenetetrazole and picrotoxin (Sigma chemical Co., St. Louis, USA) and 4-amino pyridine (Merch-schuchardt, Germany), sodium valproate (Sanofi-aventis, UK), phenobarbitone (Lab Renaudin, France), phenytoin (Parker-Davis and Co. Ltd), diazepam (Roche Ltd,France), Electroconvulsive machine (Ugo Basile, Model 7801, Italy), analytical balance (Mettler Instrument Corporation, U.S.A.) and soxhlet apparatus.

Animals

Swiss albino mice (18-25g) of either sex were obtained from Animal Facility, Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria. One day old Ranger cockerels (30-40 g) were obtained from National Animal Production and Research Institute (NAPRI), Shika, Zaria, Nigeria. The animals were kept in a well-ventilated condition at ambient temperature and fed with a standard animal feed with adequate access to water *ad libitum*. The experimental animals used were handled in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals (NIH Publications No.80-23) revised in 1996.

Collection and preparation of plant material

Fresh leaves of *P. bicalyculata* were collected from Lere

Local Government area, Kaduna state, Nigeria, in the month of August, 2016. It was identified and authenticated by Mallam Namadi Sanusi, a taxonomist with the Department of Botany, Faculty of Life Sciences, Ahmadu Bello University, Zaria, Nigeria by comparing with an already deposited voucher specimen number, (2863) as reference at the Herbarium Section of the department. The leaves of the plant were air dried at room temperature for three weeks until constant weight was attained. The dried leaves were then milled into fine powdered form using pestle and mortar. The powdered leaf (500g) was extracted with 2.5 liters of 90% $^{v}/_{v}$ methanol (90% Methanol: 10% water) for 72 hours exhaustively using the soxhlet extraction method. The extract obtained was then evaporated in a thermostat oven at 50 ºC. The dried extract was weighed and then stored in a desiccator until needed for the main experiments.

Phytochemical screening

Phytochemical screening was conducted on the methanol leaf extract of *P. bicalyculata* to validate the presence or otherwise of secondary metabolites such as alkaloids, cardiac glycosides, saponins, tannins, streroids and anthraquinones using standard methods as described by Evans, (2009).

Acute toxicity studies

Median lethal dose (LD_{50}) of methanol leaf extract of *P. bicalyculata* was determined via intraperitoneal route (*i.p*) in mice as described by Lorke (1983). The study was carried out in two phases. In the first phase, nine mice of either sex were randomly selected and divided into three groups of three mice per group, which were treated with 10, 100, 1000 mg/kg of the methanol leaf extract of *P. bicalyculata*. The treated animals were then observed for signs of toxicity including death over a period of 24 hours. In the second phase, three micewere treated with more specific doses of the extract *i.p* (based on the outcome of first phase study) and also observed for signs of toxicity and death in 24 hours. The LD_{50} was calculated as the geometric mean of the lowest dose that caused death and the highest dosage for which the animal survived.

Anticonvulsant studies

Maximal electroshock- (MEST)-induced convulsion test in chicks

The method described by Swinyard and Kupferberg (1985) and Browning (1992) were employed. Fifty day old cockerels were randomly divided into five groups each containing ten chicks. The 1st group received normal saline (10 ml/kg) *i.p* and served as a negative control. Groups 2-4 received the extract (200, 400 and 800 mg/kg *i.p* respectively) while the 5th group received phenytoin (20 mg/kg, *i.p*) and served as positive control. Thirty minutes later, maximum electroshock was administered to induce seizure in the chicks using Ugo basile electro convulsive machine connected to a stabilizer with corneal electrodes, placed on the upper eyelids of the chicks after dipping them in normal saline. The current, shock duration, frequency and pulse width were set and maintained at 80 mA, 0.8s, 100 Hz and 0.6 ms^{-1} respectively throughout the study. Convulsion was considered as a tonic hind limb extension. The ability of the extract to prevent this feature of the tonic hind limb extension was considered an indication of anticonvulsant activity.

Pentylenetetrazole-induced convulsion test in mice

The method described by Swinyard *et al*., (1989) was adopted. Thirty mice were randomly divided into five groups of six mice each. The 1st group received normal saline (10 ml/kg*i.p.*); the 2nd, 3rd and 4th groups were treated with 200, 400 and 800mg/kg (*i.p*) of *P. bicalyculata* extract respectively and the 5th group received 200 mg/kg of valproic acid. Thirty minutes post treatment,mice in all the groups were administered 90 mg/kg body weight of freshly prepared pentylenetetrazole (PTZ) subcutaneously (*s.c.*). Each mouse was observed for 30 minutes for onset of seizures. Episodes of clonic spasm (loss of righting reflex) for at least 5 seconds was considered as convulsions. The absence of loss of righting reflex during the 30 minutes of observation was regarded as protection against PTZ-induced convulsions.

Strychnine-induced convulsion test in mice

The study was conducted on 30 mice which were divided into five groups of six mice each. The 1st group received normal saline (10 ml/kg body weight *i.p.*); the 2nd, 3rd and 4th groups were treated with 200, 400 and 800 mg/kg (*i.p*) of *P. bicalyculata* extract respectively. The 5th group received 30 mg/kg of phenobarbitone*i.p.* Thirty minutes later, mice in all the groups were treated with 1.0 mg/kg (*s.c.*) of freshly prepared strychnine. Abolition of tonic extensor jerks of the hind limbs and/or latency of death was considered as protection against strychnine induced convulsion(Krall *et al*., 1978).

4-aminopyridine-induced convulsion test in mice

The study was performed as described by Yamaguchi and Rogawski (1992). Thirty (30) mice were divided into five groups each containing six mice each. The 1st group served as negative control and was pretreated with normal saline 10 ml/kg (*i.p.*) body weight. The 2nd, 3rd and 4th groups were treated with 200, 400 and 800 mg/kg (*i.p*) of *P. bicalyculata* extract respectively where as the 5th group were pretreated with 30 mg/kg body weight phenobarbitone(*i.p*). Thirty minutes after pretreatment; 4-aminopyridine was freshly prepared and administered at a dose of 14 mg/kg body weight (*s.c.*) to each mouse in all the groups. The mice were observed for 30 minutes for presence or absence of tonic extension as well as onset of seizures.

Picrotoxin-induced convulsion test in mice

The method described by Vogel (2008) was adopted. Thirty mice were randomly divided into five groups containing six mice in each group. The first group served as control and was pretreated with normal saline 10ml/kg body weight *i.p.* The 2nd, 3rd and 4th groups were pretreated were treated with 200, 400 and 800mg/kg (*i.p*) of *P. bicalyculata* extract respectively while the 5th group were pretreated with 10 mg/kg (*i.p.*) diazepam. Thirty minutes after pretreatments; mice in all groups were treated with freshly prepared picrotoxin(4mg/kg, *s.c*). The mice were then observed for presence or absence of convulsion for 30 minutes.

Data analysis

Data obtained were analyzed by one way analysis of variance (ANOVA) followed by Dunnett post hoc test using Statistical Package for Social Sciences (SPSS) software. Values of $p \leq 0.05$ were considered statistically significant. The data were then presented as mean ± the standard error of the mean (S.E.M.).

Results

Phytochemical screening

The methanol leaf extract of the plant showed the presence of cardiac glycosides, alkaloids, saponins, triterpenes,

tannins and flavanoids (Table 1).

Acute toxicity study

The intraperitoneal LD_{50} of the methanol leaf extract of *P. bicalyculata* in mice was found to be 3800 mg/kg body weight.

Effect of methanol leaf extract of P. bicalyculata on maximal electroshock test in chicks

The methanol leaf extract of *P. bicalyculata* at 200 mg/kg body weight provided 30% protection against tonic hind limb extension (THLE) in the maximal electroshock induced convulsion test. The standard drug phenytoin (20 mg/kg) provided 100% protection against THLE (Table 2).

Effect of methanol leaf extract of P. bicalyculata on pentylenetetrazole-induced seizures in mice

P. bicalyculata extract produced a significant (p<0.01) increase in the mean onset of seizures at 200 mg/kg (7.67±1.17) compared to the saline control group (3.20±0.49). The extract showed 66.67% protections and 83.33% protection against mortality at 800 mg/kg while the standard anticonvulsant, sodium valproate, showed 100% protection against PTZ-induced convulsion (Table 3).

Effect of methanol leaf extract P. bicalyculata on 4-aminopyridine-induced convulsion in mice

P. bicalyculata extractdid not produce significant(p>0.05) increase in the mean onset of seizures induced by 4-aminopyridine at all the tested doses when compared to normal saline control.

Also, there was no protection against seizures. However, phenobarbitone, the standard anticonvulsant used produced 100% protection against convulsion and mortality (Table 4).

Effect of methanol leaf extract of P. bicalyculata on strychnine-induced seizures in mice

P. bicalyculata extract exhibited 16.67 % protection against strychnine-induced seizures at 400 mg/kg while doses of 200 and 800 mg/kg offered no protection. The extract at the doses of 400 and 800 mg/kg both provided only 16.67% protection against mortality. The standard drug (phenobarbitone, 30 mg/kg) significantly (p<0.05) increased the latency of convulsion when compared to normal saline group. It also provided 33.33% protection against seizure and 83.33% protection against mortality (Table 5).

Effect of methanol leaf extract of P. bicalyculata on picrotoxin-induced seizures in mice

*P. bicalyculata*extract offered 16.67% protection against picrotoxin-induced seizures at 400 mg/kg. The standard drug (diazepam, 10 mg/kg) protected 100% of the mice against seizure and mortality (Table 6).

Table 1: Phytochemical constituents of methanol leaf extract of *Peristrophe bicalyculata*

Constituents	Inference
Alkaloids	+
Cardiac glycosides	+
Saponins	+
Flavonoids	+
Triterpenes	+
Tannins	+
Steroids	-
Anthraquinones	-

Key: Present = (+), Absent = (–)

Table 2: Effect of methanol leaf extract of *P. bicalyculata* on maximal electroshock test in chicks

Treatment (mg/kg)	Mean recovery period (min)	Quantal protection	Percentage protection(%)
N/S (10 ml/kg)	6.67±1.46	1/10	10.00
MLPB (200)	6.71±1.08	3/10	30.00
MLPB (400)	13.33±4.21	1/10	10.00
MLPB (800)	17.10±3.17	0/10	0.00
Phenytoin (20)	–	10/10	100.00

Values are expressed as Mean ± S.E.M., n = 10, N/S = Normal saline, MLPB = Methanol leaf extract of *Peristrophebicalyculata*

Table 3: Effect of methanol leaf extract of *P. bicalyculata* on pentylenetetrazole-induced seizures in mice

Treatment(mg/kg)	Mean onset of seizure (min)	Quantal Protection	% Protection	%Protection against mortality
N/S (10ml/kg)	3.2 ± 0.49	0/6	0	16.67
MLPB (200)	7.67 ± 1.17*	0/6	0	66.67
MLPB (400)	4.67 ± 0.71	0/6	0	33.33
MLPB (800)	7.50 ± 0.50	4/6	66.67	83.33
VA (200)	–	6/6	100	100

Values are expressed as Mean ± S.E.M. *=p<0.01 compared to N/S group -One way ANOVA followed Dunnett test, n=6, N/S = Normal saline, MLPB = Methanol leaf extract of *Peristrophe bicalyculata*,VA= Valproic acid,

Table 4: Effect of methanol leaf extract of *P. bicalyculata* on 4-aminopyridine-induced seizures in mice

Treatment(mg/kg)	Mean onset of seizure (min)	Quantal Protection	% Protection	% Protection against mortality
N/S (10 ml/kg)	10.17 ± 0.31	0/6	0	0
MLPB (200)	16.83 ± 2.74	0/6	0	0
MLPB (400)	15.00 ± 2.70	0/6	0	0
MLPB (800)	15.83± 1.48	0/6	0	0
PHB (30)	–	6/6	100	100

Values are expressed as Mean ± S.E.M., n=6, N/S = Normal saline, MLPB = Methanol leaf extract of *Peristrophe bicalyculata,* PHB = Phenobarbitone

Table 5: Effect of methanol leaf extract of *P. bicalyculata* on strychnine-induced seizures in mice

Treatment(mg/kg)	Mean onset of seizure (min)	Quantal Protection	% Protection	%Protection against Mortality
N/S (10ml/kg)	6.0 ± 0.73	0/6	0	0
MLPB (200)	7.50 ± 0.62	0/6	0	0
MLPB (400)	8.0 ± 1.00	1/6	16.67	16.67
MLPB (800)	9.0 ± 1.48	0/6	0	16.67
PHB (30)	10.75 ± 1.89*	2/6	33.33	83.33

Values are expressed as Mean ± S.E.M. *= p<0.05 compared to N/S group -One way ANOVA followed Dunnett test, n=6, N/S = Normal saline, MLPB = Methanol leaf extract of *Peristrophebicalyculata,* PHB = Phenobarbitone,

Table 6: Effect of methanol leaf extract of *P. bicalyculata* on picrotoxin-induced seizures in mice

Treatment (mg/kg)	Mean onset of seizure (min)	Quantal Protection	% Protection	%Protection against mortality
N/S (10 ml/kg)	16.67 ± 1.82	0/6	0	100
MLPB (200)	15.00 ± 1.00	0/6	0	100
MLPB (400)	12.80 ± 0.80	1/6	16.67	100
MLPB (800)	12.17 ± 0.91	0/6	0	83.33
DZP (10)	–	6/6	100	100

Values are expressed as Mean ± S.E.M, n= 6, N/S = Normal saline, MLPB = Methanol leaf extract of *Peristrophebicalyculata,*DZP = Diazepam,

Discussion

Phytochemical screening of methanol leaf extract of *P. bicalyculata* revealed the presence of some important secondary metabolites which might be responsible for the anticonvulsant activities observed. Several medicinal plants with established anticonvulsant activities such as *Randianilotica* (Danjuma *et al*., 2009), *Synedrellanodiflora* (Amoateng *et al*., 2011), *Ficusplatyphylla* (Chindo *et al*., 2014)and *Carissa edulis* (Ya'u *et al*., 2015) are largely attributed to the presence of some of these phytoconstituents. LD_{50} determination is intended to give an insight on how toxic or safe a compound is, in relation to its therapeutic doses (Van Boxtel and Buitenhuis, 2001). The estimated LD_{50} value of methanol leaf extract of *P. bicalyculata* suggests that it is slightly toxic in mice following intraperitoneal administration (Corbett *et al*.,1984).

MEST model predicts anticonvulsant activity of antiepileptic drugs that act by preventing the spread of the epileptic seizure discharges from an epileptic focus during seizures. It is a non-mechanistic seizure model with clearly defined endpoints (THLE)(Stables andKupferberg, 1997; Porter and Meldrum, 2018). Antiepileptic drugs (AEDs) such as carbamazepine, phenytoin, lamotrigine and oxcarbazepine inhibit THLEinduced by MEST (Porter and Meldrum, 2018). In this study, lack of significant protection against THLE by methanol leaf extract of *P. bicalyculata* in the MEST suggests ineffectiveness against generalized tonic-clonic and partial seizures.

PTZ is a well-known proconvulsant and it has been established that it diminishes the GABAergic tone by inhibiting the benzodiazepine site of the gamma amino butyric acid (GABA) receptor complex (De Deyn *et al.,* 1992). GABA is a major inhibitory neurotransmitter in the brain, inhibition of GABAergic neurotransmission has been thought to be an underlying cause of epilepsy. In the same way, enhancement of GABAergic neurotransmission is reported to antagonize seizures (Leonard, 2003). AEDs found to be effective in the therapy of generalized seizures (absence or myoclonic) petitmal type include valproate, phenobarbitone, benzodiazepines and ethosuximide (McNamara, 2006). The protection offered by *P. bicalyculata* leaf extract and its ability to significantly prolong the latency of convulsion induced by PTZ suggests the presence of bioactive compounds effective in the therapy of absence seizures (petit mal) or myoclonic seizures.

4-aminopyridine induces convulsions by antagonizing potassium channels (Yamaguchi and Rogawski, 1992). It interferes with all aspects of neuronal excitability, including resting membrane potential responsiveness to synaptic inputs and neurotransmitters release. Thus, the potassium channel plays an important role in prevention of seizures generation (Wickenden, 2002). Drugs such as phenobarbitone and phenytoin which block seizure spread are effective antagonist of seizures induced by potassium blockade, while other drugs with specific actions on other cellular targets may be weak or inactive, possibly because they are unable to attenuate the spread of intense excitation generated by 4-aminopyridine (Yamaguchi and Rogawski, 1992). The methanol leaf extract of *P. bicalyculata* at all the doses tested offered no protection against 4-aminopyridine induced convulsion. This suggests that, the extract may not be interacting with K^+ channels to produce its anticonvulsant activity.

Strychnine is a selective, competitive antagonist at all glycine receptors (Larson, 1969; Rajendra *et al.,* 1997). Strychnine induces convulsion by interfering with postsynaptic inhibition mediated by glycine, which is an important inhibitory transmitter of the motor neurons and inter-neutrons in the spinal cord. The inability of methanol leaf extract of *P. bicalyculata* to protect the mice against the seizure induced by strychnine suggests that it does not act by enhancing inhibitory neurotransmission mediated by glycine.

Picrotoxin is a non-competitive antagonist of $GABA_A$ receptor chloride channels (Leonard, 2003). AEDs such as phenobarbitone, sodium valproate, benzodiazepines and the newer antiepileptics such as tiagabine and gabapentin were effective in suppressing seizure induced by picrotoxin (Porter *et al.,* 1984; Taylor, 1995). The inability of *P. bicalyculata* extract to protect the mice against seizure induced by picrotoxin suggest that its anticonvulsant action may not interact with picrotoxin sites of in GABA-chloride channel complex.

In summary, the findings of this study suggest that the methanol leaf extract of *Peristrophe bicalyculata* contains bioactive constituents that may be beneficial in absence

seizures and further provides scientific justification for the use of its leaf extract in ethnomedicine against convulsions.

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