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ANTICONVULSANT ACTIVITY OF ETHANOL LEAF EXTRACT OF *Clerodendrum capitatum* (VERBENACEAE) IN MICE AND CHICKS

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ABSTRACT

Clerodendrum capitatum is used in traditional folk medicine to manage a plethora of diseases including tuberculosis, epilepsy, fever, obesity, diabetes mellitus, diarrhea, asthma, hypertension, and erectile dysfunction. The main objective of this study was to evaluate the anticonvulsant activity of the ethanol leaf extract of *Clerodendrum capitatum*. Preliminary phytochemical screening and acute toxicity studies were conducted. Anticonvulsant activity was evaluated in mice and chicks using pentylenetetrazole, strychnine and maximal electroshock-induced convulsion models at doses of 100, 200 and 400 mg/kg. The oral median lethal dose of the plant was estimated to be greater than 5,000 mg/kg. The ethanol leaf extract of *Clerodendrum capitatum* at all tested doses significantly ($p<0.05$) delayed the onset of pentylenetetrazole-induced seizures in mice providing percentage protection of 33.33% at the 100 and 200 mg/kg doses respectively. In the strychnine-induced seizure model, the extract significantly ($p<0.05$) increased the mean onset of seizures at 200 and 400 mg/kg doses, however only the 400 mg/kg dose produced 16.67% protection against seizures. The extract at all doses did not protect the chicks from maximal electroshock-induced convulsions. Phytochemical screening of the ethanol leaf extract of *Clerodendrum capitatum* revealed the presence of phytochemical constituents including alkaloids, flavonoids, tannins, carbohydrates, cardiac glycosides, anthraquinones and steroids. The results obtained from this study suggests that the plant possesses anticonvulsant activity validating its traditional use in the management of epilepsy.

Keywords: Acute toxicity, Anticonvulsant, *Clerodendrum capitatum*, Epilepsy

INTRODUCTION

Epilepsy is the one of the most prevalent neurological diseases affecting around 50 million people globally (WHO, 2019). It is characterized by unprovoked and repeated seizures resulting from excessive irregular synchronous electrical discharges from the cerebral neurons in the brain (Manchishi, 2018). Epilepsy affects people of all age groups with a higher prevalence in the developing world (Reddy *et al*., 2018). Generally, many causes of epilepsy are idiopathic in nature, but other cases may result from brain injury, stroke, brain tumor, severe malaria, drug abuse and genetic mutation (Beghi, 2019). Symptoms of epilepsy range from brief episodes of absence to generalized convulsive seizures which

may last up to several minutes depending on the function of the brain region that is affected (Schallenberger *et al*., 2017). Epilepsy not only reduces the quality of life of the patient, it also increases the risk of injury and may even lead to death if not promptly and properly treated (Muche *et al*., 2020).

Currently available anti-epileptic drugs have achieved seizure control in only about 70% of patients, however seizure control has not been achieved in the remaining 30% of epileptic patients (Shetty and Upadhya, 2016; Beghi, 2019). These drugs have been associated with numerous problems including cost, side effects, dose-related neurotoxicity as well as teratogenic effects (Abdullahi *et al*., 2019). This situation has fueled the widespread and growing use of medicinal plants as alternative therapy in several traditional societies in the management of epilepsy.

The use of medicinal plants, which are popular in developing countries, offers and important alternative source of phytochemicals with potential therapeutic benefits in the management of various illnesses. Reports show that more than 80% of Asian and African countries still rely on these medicinal plants for their primary health care needs (WHO, 2013). Some of these medicinal plants have shown potential to serve as sources of as new, effective and safe treatment options for many diseases' epilepsy inclusive (Montevalian *et al*., 2017). One of such plants is *Clerodendrum capitatum* which has been used traditionally for the management of epilepsy.

The plant *Clerodendrum capitatum* (Willd) Schumach et. Thonn. (Verbenaceae), commonly known as glorybower, bagflower, and bleeding-heart is an indigenous erect tropical well branched African plant that grows up to 0.5–2 m (Adeneye *et al*., 2008). Traditionally various parts of the plant have been used to treat many diseases including venereal diseases, diabetes mellitus, paralysis, epilepsy, convulsions, oedema, gout, spasm, obesity and hypertension (Burkill, 2000; Abdelwahab *et al*., 2008). The plant has been reported to possess numerous biological activities including: antidiabetic and antilipdemic activity (Adeneye *et al*., 2007, Adeneye *et al*., 2008), erectogenic activity (Abdelwahab *et al*., 2012), antimicrobial activity (Usman *et al*., 2017) and insecticidal activity **(**Adesina *et al*., 2015, Adesina *et al*., 2019**).** The present study was thus conducted to validate the folkloric claim of the plant in the management of epilepsy.

MATERIALS AND METHODS

Collection and Identification of the Plant – *Clerodendrum capitatum*

Fresh leaves, fruits, stem and roots of the plant were collected from Kudingi forest located in Sabon Gari Local Government Area of Kaduna State, Nigeria. The plant was identified and authenticated by Mr Namadi Sanusi in the Herbarium Unit, Department of Botany, Ahmadu Bello University, Zaria by comparing with existing voucher specimen (No 902).

Preparation of Leaf Extract of *Clerodendrum capitatum*

The leaves of the plant were collected and thoroughly washed with distilled water and shade dried till a constant weight was obtained. The dried leaves were size reduced using mortar and pestle. Two hundred grams (200 g) of the size reduced sample was then extracted with 1 Litre of 90 %v/v ethanol using cold maceration extraction method for one week. The ethanol extract was concentrated on a water bath at 50ºC to constant weight. The extract was then stored in a tightly closed jar placed in a desiccator. Fresh solution of extract was prepared for each study.

Phytochemical Screening

Phytochemical screening of the ethanol leaf extract of *Clerodendrum capitatum* was carried out to test for the presence of various phytochemicals using standard methods as described by Trease and Evans, (2004).

Experimental Animals

Swiss albino mice of either sex weighing between 18-22 g were obtained from Animal House, Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria. The animals were maintained in a well-ventilated room in a laboratory animal house under normal laboratory conditions of temperature and light. They were fed with standard laboratory animal feed and water *ad libitum*. Day old Rangers cockerels (35±5g) were also obtained from the National Animal Production Research Institute (NAPRI), Shika, Kaduna state, Nigeria. All experimental protocols were in accordance with Ahmadu Bello University, Zaria Research policy.

Acute Toxicity Study

Acute toxicity study was carried out in mice and chicks via the oral route using the Up and Down Procedure (OECD 425, 2001).

Anticonvulsant Screening: Pentylenetetrazole-induced Seizure in Mice

The method as previously described by Swinyard *et al.,* (1989) was employed. Thirty (30) mice were randomly divided into five groups of 6 mice per group. The first group was treated with distilled water (10 ml/kg). The second, third and fourth groups were treated with the ethanol leaf extract of *Clerodendrum capitatum* at doses of 100, 200 and 400 mg/kg via oral route respectively. The fifth group received 200 mg/kg sodium valproate, and served as positive control. One hour after pre-treatment, the animals in all groups received PTZ (85mg/kg) subcutaneously. Mice were observed over a period of 30 minutes. Absence of an episode of clonic spasm of at least 5 sec duration indicated the extracts ability to protect the mice from PTZ-induced seizures.

Strychnine-induced Seizure in Mice

Thirty (30) mice were divided into five groups of 6 mice each. The first group received 10 ml/kg distilled water. The second, third and fourth groups received 100, 200 and 400 mg/kg of the ethanol leaf extract of *Clerodendrum capitatum* via oral route respectively. The fifth group received

phenobarbitone (30 mg/kg, po). After one hour of treatment, mice in all the groups received strychnine at a dose of 1.2 mg/kg subcutaneously. The ability of the extract to provide protection against tonic convulsions and death shows the anticonvulsant activity of the extract (Porter *et al.,* 1984).

Maximal Electroshock Test (MEST) in Chicks

The method of Swinyard and Kupferberg (1985) was adopted. Thirty (30) day old chicks were divided into five groups of ten chicks as follows: Distilled water (10ml/kg), 100 mg/kg, 200 mg/kg, 400 mg/kg of the extract and phenytoin (20 mg/kg, ip). The administration was done orally except for positive control which was given intraperitoneally. Maximal electric shock was induced to each of the chicks in all the various groups using the upper eyelid corneal electrodes after 1 hour of treatment. The machine parameters for seizure induction were set and maintained at current (80mA), pulse width (0.6ms), frequency pulse (150 /sec) and shock duration (0.8 sec). Hind limb tonic extension was considered as seizure and the lack of it as protection.

Statistical Analysis

Results were expressed as mean ± standard error of mean (SEM) and presented as tables. Data were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's post-hoc test. Results were considered as statistically significant at $p<0.05$.

RESULTS

Phytochemical Screening of Ethanol Leaf Extract of *Clerodendrum capitatum*

Phytochemical screening of ethanol leaf extract of *Clerodendrum capitatum* revealed the presence of various phytochemical constituents such as alkaloids, flavonoids, tannins, carbohydrates, cardiac glycosides, anthraquinones and steroids (Table 1).

Table 1: Phytochemical Constituents Present in the Ethanol Leaf Extract of *Clerodendrum capitatum*

Phytochemical	Inference
Alkaloid	+
Tannins	+
Cardiac glycosides	+
Steroids	+
Flavonoids	+
Saponins	-
Carbohydrate	+
Anthraquinones	+

Key: + = Present - = Absent

Acute Toxicity Study

The median lethal dose was estimated to be greater than 5000mg/kg in both mice and chicks.

Pentylenetetrazole-Induced Convulsion in Mice

The ethanol leaf extract of *Clerodendrum capitatum* produced a significant ($p<0.05$) increase in mean onset of seizures at all extract doses compared to the negative control. However, only the 100 and 200 mg/kg extract doses produced 33.3%

protection. The standard anticonvulsant (sodium valporate, 200 mg/kg) produced 100% protection against PTZ-induced convulsion (Table 2).

Table 2: Effect of Ethanol Leaf Extract of *Clerodendrum capitatum* in Pentylenetetrazole-induced convulsion in Mice

Treatment (mg/kg)	Mean onset of seizures (min)	Percentage protection (%)	Percentage mortality (%)
DW (10 ml/kg)	2.40±0.68	0	100
ELEC 100	4.80±0.07*	33.33	66.7
ELEC 200	6.60±0.40*	33.33	66.7
ELEC 400	10.80±0.86*	0	100
SAV 200	0.00±0.00	100	0

Values are presented as Mean ± SEM; Data analyzed using one-way ANOVA followed by Dunnett's post hoc test, DW = Distilled water, ELEC = Ethanol leaf extract of *Clerodendrum capitatum,* SAV = Sodium valproate; n = 6; * p<0.05 compared to distilled water.

Strychnine-induced Convulsion in Mice

The ethanol leaf extract of *Clerodendrum capitatum* at 200 and 400 mg/kg significantly (p<0.05) delayed the mean onset of convulsion induced by strychnine in mice compared to the distilled water treated group. Phenobarbitone (20 mg/kg) the standard drug, however produced 100% protection against convulsion with no observed mortality (Table 3).

Table 3: Effect of Ethanol Leaf Extract of *Clerodendrum capitatum* on Strychnine-induced Convulsion in Mice

Treatment (mg/kg)	Mean onset of seizures (min)	Percentage protection (%)	Percentage mortality (%)
DW (10 ml/kg)	3.60±0.92	0	100
ELEC 100	5.60±0.68	0	100
ELEC 200	6.80±0.58*	0	100
ELEC 400	6.20±0.58*	16.7	83.3
PHN 200	0.00±0.00	100	0

Values are presented as Mean ± SEM; Data analyzed using one-way ANOVA followed by Dunnett's post hoc test, DW = Distilled water, ELEC = Ethanol leaf extract of *Clerodendrum capitatum,* PHN = Phenytoin; n = 6, * p < 0.05 compared to distilled water.

Maximal Electric Shock Test in Chicks

Administration of the ethanol leaf extract of *Clerodendrum capitatatum* at all tested doses did not protect the chicks against maximal electroshock induced convulsion. However, the extract at doses of 200 and 400 mg/kg produced significant (p<0.05) decrease in seizure duration compared to the distilled water treated group. The standard drug phenytoin (20 mg/kg protected all the chicks from tonic hind limb extensions induced by maximal electroshock (Table 4).

Values are presented as Mean ± SEM; Data analyzed using one-way ANOVA followed by Dunnett's post hoc test, DW = Distilled water, ELEC = Ethanol leaf extract of *Clerodendrum capitatum,* PHN = Phenytoin; n = 10, * p < 0.05 compared to distilled water.

Table 4: Effect of Ethanol Leaf Extract of *Clerodendrum capitatum* on MEST-induced convulsion in Chicks

Treatment (mg/kg)	Mean duration of seizures (min)	Percentage protection (%)
DW (10 ml/kg)	14.40±0.14	0
ELEC 100	10.60±0.68	0
ELEC 200	5.20±0.58*	0
ELEC 400	7.80±0.58*	0
PHN 200	0.00±0.00	100

DISCUSSION

Clerodendrum species have been used traditionally for the treatment of many ailments including bacterial infections, tuberculosis, erectile dysfunction, diarrhea, malaria, hypertension, epilepsy and diabetes (Wang *et al.,* 2018). This study evaluated the acute toxicity effects and the anticonvulsant action of the ethanol leaf extract of the plant *Clerodendrum capitatum* using chemical and electrical-induced seizure models in mice and chicks.

Phytochemical screening revealed the presence of several phytochemicals such as alkaloids, flavonoids, tannins, carbohydrates, cardiac glycosides, anthraquinones and steroids. Some of these phytochemicals including flavonoids, cardiac glycosides, anthraquinones and steroids have been reported to be major bioactive principles of the genus Clerodendrum; responsible for many observed biological activities (Wang *et al*., 2018).

The oral median lethal dose of the ethanol leaf extract of *Clerodendrum capitatum* was estimated to be greater than 5,000 mg/kg in mice and chicks, suggesting that the extract was practically non-toxic according to classification of LD_{50} values by Lorke (1983) and Matsmura (1975).

Pentylenetetrazole is a chemical that has been used to induce convulsion by diminishing the GABAergic tone through inhibition of benzodiazepine site of the GABA receptor channel complex (De Deyn *et al*., 1992). The main inhibitory neurotransmitter in the brain is gamma amino butyric acid and the inhibition GABAergic neurotransmission has been thought to be one of the fundamental factors responsible for epilepsy (Amabeoku *et al*., 1998). When GABAergic neurotransmission is increased this leads to a decrease in seizures and thus the inhibition of PTZ-induced seizures suggests effect on GABAergic neurotransmission (Leonard, 2003).

The pentylenetetrazole-induced seizure model is used to identify compounds that have the ability to raise seizure threshold in the brain (Raza *et al.,* 2001). Drugs such as sodium valproate and phenobarbitone used in the treatment of absence seizures, have been found to suppress PTZ-induced seizures (McNamara, 2010). The ethanol leaf extract of *Clerodendrum capitatum* showed a dose dependent prolongation in the mean onset of seizures in the PTZ model. This result suggests that the extract could be effective in the treatment of absence seizures.

In the strychnine-induced seizure test, only the highest dose (400 mg/kg) moderately protected the animals against seizure. Strychnine is a competitive antagonist of glycine in the central nervous system (Ngo *et al*., 2004). Compounds that are effective in seizures induced by strychnine, act by enhancing the inhibitory action of glycine. The ethanol leaf extract of *Clerodendrum*

capitatum moderately prevented strychnine-induced seizures. This suggests that the anticonvulsant effect of the extract may partially be mediated via enhancing the action of the glycine receptors.

The maximum electroshock test model evaluates the ability of a compound to protect against hind limb extensions (White *et al*., 1998). It is a model for generalized tonic clonic seizures and protection against hind limb tonic extension, indicates the ability of a compound to inhibit or prevent seizure discharge within the brain as shown by drugs such as phenytoin (Stables and Kupferberg, 1997). The ethanol leaf extract of *Clerodendrum capitatum* did not protect the chicks from seizures induced by maximal electroshock. This suggests that the extract does not have any activity against generalized tonic clonic and partial seizures.

Numerous phytochemicals including flavonoids, alkaloids, glycosides and triterpenes have been previously reported to possess anticonvulsant activity (Barua *et al.,* 2013, Rapacz *et al.,* 2016). Thus, the presence of the above secondary metabolites in the extract may be singly or in combination be responsible for the reported anticonvulsant property.

CONCLUSION

The ethanol leaf extract of *Clerodendrum capitatum* produced marked activity against PTZ-induced seizures, thus supporting the ethnomedicinal application of the plant as an anticonvulsant agent.

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