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Methanol leaf extract of *Albizia chevalieri* Harms possesses anticonvulsant activity in acute and chronic models of epilepsy

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ABSTRACT

Background & Aim: *Albizia chevalieri* Harms (Mimosaceae) is widely used in traditional medicine to treat various kinds of diseases such as epilepsy, diabetes mellitus, hemorrhoids, asthma, leprosy and gonorrhoea. The effectiveness of its leaf extract in the management of epilepsy is widely acclaimed among communities in northern Nigeria. This study aimed at evaluating the anticonvulsant effects of methanol leaf extract of *A. chevalieri* using acute and chronic models of epilepsy.

Experimental: Median lethal dose (LD_{50}) of the extract was determined in chicks, mice and rats via intraperitoneal route. Anticonvulsant screening of the extract was performed using maximal electroshock-induced seizure test in day-old chicks; Pentylenetetrazole (PTZ)-, picrotoxin- and 4-aminopyridine-induced seizure models in mice. Similarly, its effects on pentylenetetrazole-induce kindling in rats was evaluated.

Results: Intraperitoneal LD_{50} values of the extract were estimated to be 1200, 1130 and 2150 mg/kg in chicks, mice and rats, respectively. The extract provided a dose dependent protection and significantly ($P<0.01$) increased in the mean onset of seizures induced by PTZ. At 300 mg/kg, it also offered 66.67 and 50% protection against picrotoxin- and 4-aminopyridine-induced seizures, respectively. The extract reduced the severity of seizure episodes induced by sub-convulsive doses of PTZ. The reduction was significant ($P<0.01$) at 75 and 300 mg/kg on day 11 when seizure score 5 was reached. These findings suggest that *A. chevalieri* leaf extract possesses anticonvulsant and antiepileptogenic properties.

Recommended applications/industries: The anticonvulsant properties of *A. chevalieri* can be applied in the treatment of epilepsy.

1. Introduction

Epilepsy is one of the oldest recognized conditions known to mankind that affects individuals of all ages. It is estimated that 50 million individuals have epilepsy, making it one of the most common neurological diseases (WHO, 2018). About 80% of the people who have epilepsy live in developing countries, and high burden of the disease in these countries could be due to poor knowledge, high cost of effective drugs, lack of diagnostic facilities and human resources (Neni *et al.*, 2010; Wagner *et al.*, 2015; Megiddo *et al.*, 2016). For these reasons and more, people in developing parts of

the world largely utilize herbal medicines to manage this debilitating condition (Zhu *et al.*, 2014). The use of medicinal plants in ethno-medicine have a long history and these plants have been shownto be effective in the management of epilepsy for centuries (Sahranavard *et al.*, 2014). Studies conducted on these plants corroborate their value as sources of lead compounds in the management of epilepsy (Zhu *et al.*, 2014; Tambe *et al.*, 2016). *Albizia chevalieri* is an important plant that is also used in herbal medicine in the management of epilepsy.

Albizia chevalieri Harms (Mimosaceae) is either a tree or shrub of acacia type that grows up to 6-12 meters high, native to tropical and subtropical regions including Nigeria. It has loose balls of whitish fragrant flowers and flat brown pods (Burkill, 1995). The leaf extract of the plant is used either as cold water decoction or as powder mixed with pap, for the management of diabetes mellitus by traditional medical practitioners in some parts of Niger Republic and north-west Nigeria (Saidu *et al.*, 2007). The bark extract is used in the treatment of diarrhoea, heaemorroids/pile, bronchitis, asthma, leprosy and gonorrhoea (Ronald, 2013). The leaf is also used as an antihelminthic and antiprotozoal drug (Iwu, 1993). In the same vein, traditional medical practitioners in Zaria, claim that the aqueous leaf decoction of *A.chevalieri* is effective in the management of convulsions (Personal Communication, May, 2014).

The leaf and bark extracts of *A. chevalieri* have been reported to have significant hypoglycemic (Saidu *et al.*, 2007) and hypolipidemic activities (Saidu *et al*., 2010). The leaf extract has also been reported to possess antioxidant properties (Aliyu *et al.*, 2009). According to Noté *et al*. (2017), triterpenoid saponins isolated from stem bark extract of *A. Chevalieri* possess pro-apoptotic activity. Silver nanoparticles isolated from the bark extract of *A. Chevalieri* were also found to possess anticancer and antibacterial activities (Khan *et al.*, 2018). To our knowledge, reports on the anticonvulsant activity of *A. Chevalieri* leaf extract are scarce despite its well acclaimedeffectiveness and acceptability in the management of epilepsy. This study therefore, was aimed at evaluating the anticonvulsant properties of methanol leaf extract of *A. Chevalieri* in laboratory animals.

2. Materials and Methods

2.1. Experimental animals

Three species of animals were employed for this study: mice, rats and cockerels. Adult Swiss Albino mice of both sexes (18-22 g) and Wistar rats of both sexes (180-200 g) were obtained from the Animal Facility, Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria. The animals were kept in clean plastic cages with saw dust beddings and metal covers. They were fed with standard rodent feed (Feeds Master, Ilorin) and water *ad libitum* and maintained in a well-ventilated room under normal atmospheric conditions. Day old cockerels (30-40 g) were obtained from the National Animal Production and Research Institute (NAPRI), Ahmadu Bello University, Shika, Zaria. Experimental protocols for the use of animals was approved by the Institutional Animal Ethics Committee (ABUCAUC/2017/059).

2.2. Chemicals and Drugs

The chemicals used include Methanol, Pentylenetetrazole (PTZ), Picrotoxin and 4-aminopyridine (Sigma-Aldrich Co., USA), while the standard drugs used were Phenobarbitone (Lab Renaudin, France), Phenytoin sodium (Parker-Davis and Co. Ltd, Detroit), Sodium valproate (Sanofi-aventis, UK) and Diazepam (Valium Roche Ltd).

2.3. Plant material

Fresh leaves of *Albizia chevalieri* were collected from Kakeyi village, in Zaria local Government area of Kaduna state, Nigeria. The sample was taken to the Herbarium section of the Department of Botany, Ahmadu Bello University, Zaria, where it was identified and authenticated by a taxonomist, Sanusi Namadi. A voucher specimen number 900247 was assigned by comparing with a voucher specimen previously deposited in the herbarium.

2.4. Preparation of the plant extract

The powdered leaf (640 g) was extracted by cold maceration using 70% $^{v}/_{v}$ methanol with occasional mixing for 72 hours. The resultant mixture was filtered using Whatman filter paper (No. 1) and the filtrate concentrated and dried using water bath maintained at

temperature of 40-50°C. The extract was kept in a desiccator until required for use.

2.5. Phytochemical screening

The methanol leaf extract of *Albizia chevalieri* was subjected to standard phytochemical screening to test for the presence or absence of alkaloids, saponins, flavanoids, tannins, glycosides, anthraquinones and steroids (Evans, 2009).

2.6. Acute toxicity studies

The median lethal dose (LD_{50}) of the extract was determined in mice, chicks and rats through intraperitoneal (*i.p.*) route according to Lorke's method (1983). The method employs two phases, phase I and II. In phase I, three groups of three animals were administered 10, 100 and 1000 mg/kg doses of the extract, respectively, to ascertain extent of toxicity of the extract. The animals were observed for signs of toxicity and death within 24 h period. In phase II which depended on the outcome of phase I, other specific graded doses of the extract were administered to four different groups of mice, chicks and rats as the case apply and observed for sign of toxicity and death within another 24 h period. From the outcome of phase II, LD_{50} value was determined by calculating the geometric mean of the lowest dose that caused death and the highest dose for which the animals survived.

2.7. Acute anticonvulsant studies

2.7.1. Maximal electroshock test (MEST)

The methods of Swinyard and Kupferberg (1985) was employed. Fifty day old chicks weighing between were randomly divided into five groups of ten chicks each. The first group were treated with normal saline 10 ml/kg, *i.p*. (negative control); while the second, third and fourth groups were treated with 75, 150 and 300 mg/kg doses of the extract *i.p*, respectively. The fifth group was treated with phenytoin 20 mg/kg *i.p* and served as positive control. Thirty minutes later, maximal electroshock was administered to induce seizure in the chicks using Ugo Basile electroconvulsive machine (Model 7801) with corneal electrodes placed on the upper eyelids of the chicks. The current, shock duration, frequency and pulse width was maintained at 80 mA, 0.8 s, 100 pulse/s. and 0.6 ms respectively. The chicks were observed for hind limb tonic extension and recovery.

2.7.2. Pentylenetetrazole (PTZ)-induced seizure test

The method of Swinyard *et al*. (1989) was employed using five groups of six mice each. Mice in group I were treated with normal saline 10 ml/kg *i.p*. The second, third and fourth groups were treated with 75, 150 and 300 mg/kg doses of the extract *i.p*, respectively, while the fifth group was treated with 200 mg/kg valproic acid. Thirty minutes later, mice in all groups were treated with 85 mg/kg body weight of freshly prepared PTZ subcutaneously (*s.c*). The mice were then observed for 30 minutes for the presence or absence of clonic spasm.

2.7.3. Picrotoxin-induced seizure test

The method described by Vogel, (2008) was employed. Thirty mice were divided into five groups of six mice each. The first group served as control and was treated with 10 ml/kg normal saline *i.p*. The second, third and fourth groups were treated with 75, 150 and 300 mg/kg doses of the extract *i.p*, respectively. The fifth group was treated with 30 mg/kg phenobarbitone *i.p.* Thirty minutes later, mice in all groups were treated with 4 mg/kg of picrotoxin *s.c*. and then observed for clonic and or tonic seizures for thirty minutes.

2.7.4. 4-aminopyridine-induced seizure test

The method described by Yamaguchi and Rogawski, (1992) was employed. Thirty mice of either sex were randomly divided into five groups of six each. The first group were treated with 10 ml/kg normal saline *i.p*. Mice in the second, third and fourth groups were treated with 75, 150 and 300mg/kg doses of the extract *i.p*, respectively. The fifth group was treated with 30 mg/kg body weight phenobarbitone *i.p*. Thirty minutes later, mice in all groups were administered a dose of 14mg/kg body weight of freshly prepared 4-aminopyridine *s.c*. The mice were observed for 30 minutes for presence or absence of convulsions.

2.8. Chronic pentylenetetrazole-induced kindling test

The method described by Gupta *et al.*, (2003) as modified by Amoateng *et al*., (2012) was employed. Forty Wistar rats were randomly divided into five groups of eight rats each. The first group was pretreated with normal saline (1 ml/kg) and served as the negative control. The second, third and fourth groups were pretreated with 75, 150 and 300 mg/kg

doses of the extract *i.p*, respectively, while the fifth group (positive control) was pretreated with diazepam (1 mg/kg *i.p*). After 30 minutes of treatments, sub-convulsive dose of PTZ (35mg/kg *i.p*.) was administered to all groups and then observed over another 30 minutes for convulsive behaviors. The resultant seizures were scored as follows: stage 0 (no response), stage 1 (ear and facial twitching), stage 2 (convulsive waves throughout the body), stage 3 (myoclonic jerks, rearing), stage 4 (turning onto one side, forelimb clonic seizures) and stage 5 (turning over onto the back, generalized clonic seizures with falling). The PTZ administration was stopped when the negative control group showed seizure score of 5 (injection 6) and the subsequent high death rate that occurred in such group.

2.9. Statistical analysis

Data analysis was carried out using Statistical Package for Social Sciences (SPSS, Version 20). The differences between means were analyzed using one-way analysis of variance (ANOVA) followed by Tukey *post hoc* test. Non parametric Kruskal-Wallis test was used to analyze the seizures scores in the kindling test. Values of $P<0.05$ were considered statistically significant. Data obtained were presented in figures, tables and plates where appropriate.

3. Results and discussion

The increasing demand for effective and safer drugs against epilepsy have led to continuous research on medicinal plants as alternative sources of lead compounds with therapeutic potentials. The outcome of this study provides evidence that the methanol leaf extract of *Albizia chevalieri* possesses anticonvulsant activity in acute and chronic experimental models of epilepsy.

The biological actions produced by plant extracts are mostly attributed to their secondary metabolites (Noté *et al.*, 2017). Preliminary phytochemical screening of methanol leaf extract of *A.chevalieri* revealed the presence of alkaloids, flavonoids, saponins, steroids, tannins, triterpenes, glycosides and cardiac glycosides. These phyto-constituents were largely corroborative of the findings of Aliyu *et al*. (2009). Some of these constituents such as alkaloids, flavonoids and saponins have been reported to possess anticonvulsant properties (Zhu *et al.*, 2014). Vitexin and Quarcetin are flavonoids reported to possess antiepileptic activities (Rabiei, 2017). Indeed, the anticonvulsant properties of *Ficus religiosa* and *Ficus platyphylla* have were also attributed to their saponins (Chindo *et al.*, 2009; Singh and Goel, 2016). Therefore, the anticonvulsant activities observed with *A. chevalieri* in this study could also possibly be attributed to its phytochemical constituents.

The intraperitoneal median lethal doses of the rmined inemethanol leaf extract of *A. chevalieri* was det mice, rats and chicks (Table 1). Based on the estimated LD_{50}, the extract was considered as slightly toxicin mice, chicks and rats following intraperitoneal administration (Loomis and Hayes, 1996).

Table 1: Median lethal doses of methanol leaf extract of *Albizia chevalieri*

Species	Route of administration	LD_{50} Values (mg/kg)
Mice	Intraperitoneal	1130
Rats	Intraperitoneal	2150
Chicks	Intraperitoneal	1200

The methanol leaf extract of *A. chevalieri* did not protect the chicks against maximal electroshock induced seizures at all doses tested. There was no significant difference ($P>0.05$) in the mean recovery periods when compared to the normal saline control group (Table 2).

Table 2: Effect of methanol leaf extract of *Albizia chevalieri* on maximal electroshock induced convulsion in chicks

Treatment (mg/kg)	Mean recovery period (Min.)	Quantal Protection	% Protection against seizure
NS 10 ml/kg	7.00±1.21	0/10	0.00
ACE 75	5.60±0.91	0/10	0.00
ACE 150	13.40±2.13	0/10	0.00
ACE 300	6.50±1.89	0/10	0.00
PTY 20	17.00±0.00	9/10	90.00

Values are presented as Mean ± SEM, No significant difference compared to normal saline control group - One way ANOVA, n=10, NS = Normal saline, ACE = Methanol leaf extract of *Albizia chevalieri*, PTY = Phenytoin

MEST is employed for pre-clinical evaluation of compounds effective against generalized seizures of the tonic-clonic and partial seizures (Mares and Kubova; 2006; Malami *et al*., 2017; Velisek, 2017). Drugs that act on sodium channels e.g. carbamazepine, phenytoin, oxcarbazepine and lamotrigine are also known to suppress hind limb tonic extension induced by maximal electroshock (Banach and Borowicz, 2015; Yuen and Troconiz, 2015). Therefore, the results obtained in MEST suggests that *A. chevalieri* extract may not be effective against generalized tonic-clonic seizures.

In the PTZ-induced seizure test, *A. chevalieri* extract provided a dose dependent protection (16.67, 66.67 and 83.33%) as well as a significant (P<0.01, P<0.001 and P<0.001) increase in the mean onset of seizures at doses of 75, 150 and 300 mg/kg, respectively (Table 3).

Table 3: Effect of methanol leaf extract of *Albizia chevalieri* on PTZ-inducedconvulsion in mice

Treatment (mg/kg)	Mean Onset of Seizures (min.)	Quantal protection	% Protection against seizure	% Mortality
NS 10 ml/kg	6.50±0.43	0/6	0.00	100.00
ACE 75	10.60±0.87**	1/6	16.67	66.67
ACE 150	15.00±0.58***	4/6	66.67	33.33
ACE 300	14.00±0.00***	5/6	83.33	16.67
SV 200	-	6/6	100.00	0.00

Onset of seizures presented as Mean ± SEM, ** = P<0.01, *** = P<0.001 as compared to normal saline group – One-way ANOVA followed by Tukey *post hoc* test, n=6, NS - Normal saline, ACE = Methanol leaf extract of *Albizia chevalieri*, SV = Sodium Valproate.

PTZ-induced seizures test represents a valid model for human absence seizures (Löscher, 2017), and has been employed experimentally to study seizure phenomenon and to identify pharmaceuticals that may raise seizure threshold (Rang *et al*., 2016). PTZ has been shown to be an antagonist at gamma-amino butyric acid (GABA) pathways in the central nervous system (CNS), resulting in an imbalance between the ionic concentrations of the membrane. It induces seizures by blocking the major inhibitory pathways mediated by GABA in the CNS (DeSarro *et al.*, 2003; Li *et al.*, 2014). The inhibition of GABAergic neurotransmission is known to facilitate seizures, while its enhancement has been shown to inhibit seizures (Rang *et al*., 2016). Accordingly, anticonvulsants such as phenobarbitone, valproic acid, gabapentin and clonazepam inhibit PTZ-induced seizure by enhancing the action of GABA-receptors, thus facilitating the GABA-mediated opening of chloride channels (Czuczwar and Patsalos, 2001; Greenfield Jr., 2013). Postsynaptic $GABA_A$receptors are multi-unit complexes with binding sites for the endogenous ligand GABA, benzodiazepines, barbiturates and other ligands with a central chloride ion channel (Czuczwar and Patsalos, 2001). Thus, the inhibition of PTZ-induced seizures by *A.chevalieri* leaf extract may suggests an enhancement of GABAergic neurotransmission.

A. chevalieri extract offered 66.67% protection against picrotoxin-induced seizures at doses of 75 and 300 mg/kg. It also significantly (*P*<0.05) increased the mean onset of seizures at 75 mg/kg when compared to normal saline control group. The standard drug used (phenobarbitone, 20 mg/kg) protected 100% of the mice (Table 4).

Table 4: Effect of methanol leaf extract of *Albizia chevalieri* on Picrotoxin-induced seizure in mice

Treatment (mg/kg)	Mean onset of seizures (min.)	Quantal protection	% Protection against seizure	% Mortality
NS 10 ml/kg	8.83 ±0.48	0/6	0.00	83.33
ACE 75	12.50 ± 0.50*	4/6	66.67	0.00
ACE 150	9.40 ± 0.93	1/6	16.67	16.67
ACE 300	9.00 ± 0.00	4/6	66.67	16.67
PHB 20	-	6/6	100.00	0.00

Onset of seizures presented as Mean ± SEM, * = *P*<0.05 compared to normal saline control group – One-way ANOVA followed by Tukey *post hoc* test, n=6, NS - Normal saline, ACE = Methanol leaf extract of *Albizia chevalieri*, PHB = Phenobarbitone.

Picrotoxin, a non-competitive $GABA_A$-receptor antagonist, produces seizures by blocking the chloride-ion channels linked to $GABA_A$ receptors, thus preventing the entry of chloride ions into neurons. This leads to decreased GABA transmission and activity in the brain (Lason *et al.*, 2013). The ability of *A. chevalieri* extract to attenuate seizures induced by picrotoxin further supports the possible interaction of its phyto-constituents with $GABA_A$-receptors and or GABA neurotransmission. Phenobarbitone, the standard anticonvulsant, is known to enhance GABAergic neurotransmission by increasing chloride ion flux through the chloride channels of $GABA_A$-receptors (Waller and Sampson, 2018). Since *A.chevalieri* extract mimicked, to a large extent, the anticonvulsant actions of phenobarbitone, it is possible the extract antagonizes picrotoxin-induced seizures by opening the chloride channels associated with $GABA_A$-receptors.

Considerable genetic, molecular, physiological and pharmacological evidence support the role of K^+ channels in the control of neuronal excitability and epileptogenesis (Kobayashi *et al.*, 2008).Inhibition of K^+ channels in rat hippocampal slices also causes epileptiform activity. Consequently, K^+ channel activators enhance potassium currents and reduce neuronal excitability; therefore, K^+ channel openers may have potential as anti-epileptic drugs (Rogawski and Loscher, 2004). 4-aminopyridine, a non-selective potassium channel antagonist is a powerful pro-convulsant in animals and in man (Kobayashi *et al.*, 2008; Heuzeroth *et al*., 2019). It inducesseizure activity by enhancing spontaneous and evoked neurotransmitter release (Kobayashi *et al.*, 2008). In this study, *A. chevalieri* extract did not produce a significant increase ($P>0.05$) in the mean onset of seizures induced by 4-aminopyridine at all the doses tested when compared to the negative control. However, it provided 50% protection against 4-aminopyridine-induced seizures at 300 mg/kg (Table 5). The ability of *A. chevalieri* extract to inhibit 4-aminopyridine-induced seizures demonstrates additional anticonvulsant activity mediated through the potassium channels.

Table 5: Effect of methanol leaf extract of *Albizia chevalieri* on 4-aminopyridine-Induced Seizure in Mice

Treatment (mg/kg)	Mean Onset of Seizures (min.)	Quantal protection	% Protection against seizure	% Mortality
NS 10 ml/kg	5.00 ±0.58	0/6	0.00	100.00
ACE 75	5.50 ± 0.43	0/6	0.00	100.00
ACE 150	4.40 ± 0.51	1/6	16.67	33.33
ACE 300	6.25 ± 0.50	3/6	50.00	50.00
PHB 20	9.00 ±0.00***	4/6	66.67	16.67

Onset of seizures presented as Mean ± SEM, *** = $P<0.001$ compared to normal saline control group – One-way ANOVA followed by Tukey*post hoc* test, n=6, NS - Normal saline, ACE = Methanol leaf extract of *Albizia chevalieri*, PHB = Phenobarbitone

In the kindling test, *A. chevalieri* extract at all doses tested reduced the severity of seizure episodes induced by the sub-convulsive administration of PTZ. The reduction was significant ($P<0.01$) at 75 and 300 mg/kg of the extract on day 11 (when seizure score 5 was reached). Similarly, the standard drug, diazepam (1 mg/kg) significantly reduced the severity of seizures. The activity of diazepam was comparable to the extract at 300 mg/kg (Figures 1 and 2).

The PTZ-induced kindling is an established animal model for identifying antiepileptic drugs and may also detect disease-modifying epileptogenic effects (Fischer *et al.*, 2016). Several reports have shown that the progression of seizures in kindling is associated with decreased numbers of $GABA_A$ receptor binding sites in hippocampus, amplification in glutamate release and elevated nitricoxide levels (Riazi *et al*., 2006; Cocoran and Tesky, 2009). Standard anticonvulsants like diazepam and carbamazepine have been shown to inhibit tonic-clonic seizures induced by sub-convulsive doses of PTZ and thus, effective against chronic form of epilepsy (Arora *et al.*, 2010; Rathor *et al.*, 2013, Malami *et al.*, 2016; Wapa *et al.*, 2018). The administration of *A. chevalieri* extract at all tested

doses was able to decrease the severity of seizures by preventing the seizures from reaching the classical seizure stage. This suggests that the extract could prevent epileptogenesis.

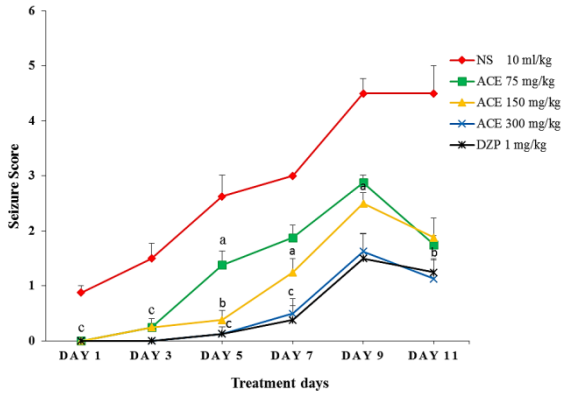

Figure1: Effect of Methanol Leaf Extract of *Albizia chevalieri* on PTZ-Induced Kindling in Rats. Seizure score presented as Mean ± SEM, the superscripts a, b and c represent P<0.05, P<0.01 and P<0.001 compared to normal saline control group, respectively – Non parametric Kruskal-Wallis test, n=8, NS=Normal saline, ACE=Methanol leaf extract of *Albizia chevalieri*, DZP =Diazepam.

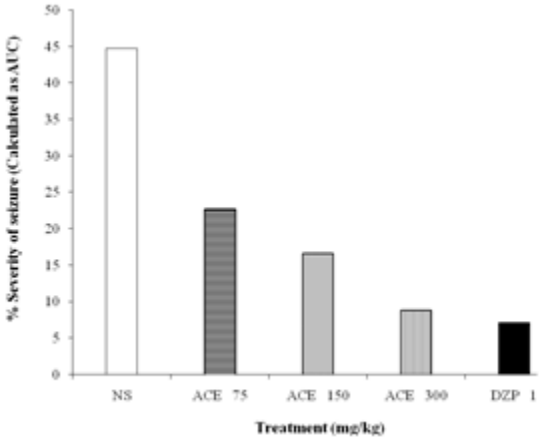

Figure 2: Effect of methanol leaf extract of Albizia chevalieri on severity of seizure in PTZ-induced kindling in rats. Percentage severity of seizures calculated as area under the curves (AUCs) for the test duration. n=8, NS = Normal saline, ACE = Methanol leaf extract of Albizia chevalieri, DZP = Diazepam

4. Conclusion

The methanol leaf extract of *Albizia chevalieri* possesses anticonvulsant and antiepileptogenic properties. This provides scientific basis for the ethnomedical use of the plant extract in the management of epilepsy.

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