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Preliminary phytochemical and anticonvulsant studies on the root extracts of *Ficus capensis* Thunb. (Moraceae)

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Abstract
Ficus capensis Thunb. (Moraceae) is used in West Africa to manage different ailments including epilepsy, leprosy, neuralgia, weakness, stiffness, oedema, amenorrhoea and difficult childbirth. The aim of the study was to carry out preliminary phytochemical screening, acute toxicity and anti-convulsant studies of the methanol root extract (MRE) and hexane fraction of *Ficus capensis*. The preliminary phytochemical screening of the MRE and its fractions were carried out using standard procedures. Anticonvulsant activity was studied using Maximum electro-shock induced seizure test (MEST) in chicks and Pentylenetetrazole (PTZ)-induced seizure in mice. Preliminary phytochemical screening of the MRE and its fractions revealed the presence of various secondary metabolites. The intraperitoneal median lethal doses of MRE and WHF in mice were found to be 1,131 and 1,264 mg/kg respectively. No protection was recorded for MRE and WHF against maximal electro-shock induced convulsion; the standard drug, Phenytoin (20 mg/kg) had 100 % protection. The MRE (300 mg/kg) and WHF (100, 200 and 400 mg/kg) produced a significant ($P<0.05$, $P<0.001$) dose independent anticonvulsant activity in the PTZ-induced seizure in mice; the standard drug, sodium valproate (200 mg/kg) had 100 % protection. The finding of the study suggests that the root extracts of *Ficus capensis* possess significant anticonvulsant activity validating the ethno-medicinal use of the plant in management of epilepsy.

Keywords: *Ficus capensis*; Phytochemical screening; Acute toxicity study; Anticonvulsant studies

INTRODUCTION

Epilepsy is a chronic neurologic disorder of periodic and unpredictable seizures (provoked and unprovoked) which results from abnormal electrical activity in the brain [1,2]. Epilepsy could also be due to abnormal recurrent and spontaneous electrical discharge of a group of neurons in the brain and exhibits itself as a seizure occurrence in the patients [3]. Epilepsy is one of the most prevalent neurological disorders with about 0.5 to 1% of world population [4,5]. Medicinal plants are those plants that are used in treating and preventing specific ailments and diseases that affect human beings [6]. Medicinal plants have many biological

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activities such as anti-neoplastic, anticonvulsant, antiviral, anti-inflammatory, anti-pyretic, analgesic and anti-malarial [7]. Several hundreds of plants are good sources of medicinal plants that are used in traditional medicine for many different purposes [8]. Traditional plants are used for the treatment of diseases in different parts of the world [9]. About 80% (3.5 to 4 billion) of people in developing countries depend on plants as source of drugs [10]. Herbal remedies used in traditional folk medicine provide an interesting and still largely unexplored source for the development of potentially new drugs for the treatment of diseases [11]. Medicinal plants are known to contain some bioactive secondary metabolites (compounds) such as tannins, alkaloids, flavonoids, carbohydrates, terpenoids and steroids which produce definite physiological action on human body [12,13].

The plant, *Ficus capensis* belongs to the family Moraceae, a large family of about 40 genera and over 1000 species [14]. The plant is also known as *Ficus sur* (Forssk) [15]. *Ficus capensis* is distributed in North-Eastern and Western Nigeria as well as tropical Africa and Islands [14]. The English name is *fig cape*. It is commonly called *Opoto*, in Yoruba, *Girka (*Shira), *Haguguwa* (Hadaija), *Farin baure* (Zaria) in Hausa, *Okwe in* Igbo [14]. The plant is *Rima bichehi* in Fulani and *Obada* in Edo language [16,17]. The plant *Ficus capensis* is a deciduous tree with spreading roots and branches and broad green leaves [18]**.** *Ficus capensis* is a sacred tree with medico-magic and magico-religion uses. The root of *Ficus capensis* is used in treatment of cancer. The root is also use for the treatment of epilepsy, leprosy, neuralgia, weakness, stiffness, edema, amenorrhea and difficult childbirth [14].

Ficus capensis has been reported to have antimicrobial activity [18,19]. *Ficus capensis* have also been reported to have effect on gastrointestinal motility properties [17]. The leaves and stem bark of *Ficus capensis* have been reported to have antibacterial activity [20]. The leave has also been reported to be useful in controlling diarrhea [17]. *F. capensis* leaves extract have been reported to have clinical relevance in the management of anemia and immunity-dependent disorders [21]. *F. capensis* leaves extract at a very low concentration have been reported to favour spermatogenesis, thus demonstrating a potential to treat azoospermia [22]. Antiabortifacient [23], immune-stimulatory [24], antidiarrhoea [25], antioxidant [26], pro-fertility in treating azoospermia [27] and anti-sickling effect of red blood cells [28]. Leaves of *F. capensis* have been a potential source of natural antioxidant, antimicrobial and anti-inflammatory drugs [29]. Epilepsy is a neurological disorder, which could be as a result of damage, injury, chemical or metabolic assault [30]. About 50 million people in the world have epilepsy [31] out of which one-third of them are not being adequately managed with the currently available antiepileptic drugs because of non-compliance as a result of long-term therapy, unwanted side effects, high cost and even unavailability of the drugs [1]. Epilepsy (also known as the falling sickness) is one of the most prevalent neurological disorders in many communities in Nigeria [32]. We report herein the preliminary phytochemical screening, acute toxicity and anti-convulsant studies of the methanol root extract and hexane fraction of *Ficus capensis*.

EXPERIMENTAL

Collection, identification and preparation of plant material. The root of *Ficus capensis* was collected in July 2016 at Sakaru village, Zaria Local Government Area of Kaduna State. It was identified by U.S. Gallah at the point of collection and further authenticated by Namadi Sanusi at the Herbarium unit, Department of Biological Sciences, Ahmadu

Bello University, Zaria by comparing with herbarium reference voucher specimen (No. 900153). The root was shade dried, size reduced to powder, labelled and stored at room temperature for use.

Extraction procedures. The powdered root (4.162 g) was extracted with 70% methanol (20 L) using cold maceration method for 10 days. The extract was evaporated *in-vacuo* using rotary evaporator to yield a dark-brown residue (396 g) subsequently referred to as the methanol root extract (MRE). MRE (250 g) was suspended in distilled water and filtered. The water insoluble portion of the methanol root extract was partitioned successively with n-hexane (3.5 L), chloroform (2 L), ethylacetate (2.5 L) and n-butanol (2.5 L) to obtain water insoluble hexane fraction (WHF), water insoluble chloroform fraction (WCF), water insoluble ethylacetate fraction (WEF), water insoluble n-butanol fraction (WBF) and the water insoluble residual fraction (WF) respectively. The extract and fractions were sbjected to thin-layer chromatography using different solvent systems.

Preliminary phytochemical screening. Different chemical tests were carried out on the Methanol Root Extract (MRE), hexane (WHF), chloroform (WCF), ethylacetate (WEF) and n-butanol fractions (WBF) to identify the presence of various phytochemical constituents using standard operating procedure.

Acute toxicity studies. The method described by Lorke [33] was employed. The route of administration was intra-peritoneal. In the first phase, nine mice of either sex were divided into three groups containing three mice each. The first, second and third groups received 10, 100 and 1000 mg/kg of extract respectively. In the second phase, four animals were used. Each of the four animals received different doses of the extract, which are: 200, 400, 800 and 1600 mg/kg as a result of the outcome of phase I study. The median lethal dose was calculated using the following formula

$$LD_{50} = \sqrt{Minimal\ lethal\ dose\ X\ Maximal\ survival\ dose}$$

The hexane fraction was similarly studied.

Maximum electro-shock induced seizure test in chicks. The method described by Swinyard & Kupferberg [34] was employed in this study. The anticonvulsant study of MRE involves fifty chicks divided into five groups (n=10). Group 1 (Negative control) received normal saline intraperitoneally (i.p). Groups 2, 3 and 4 (treatment groups) received graded doses of the methanol root extract 75, 150 and 300 mg/kg respectively. Group 5 (positive control) received 20 mg/kg of Phenytoin. The route of administration was intraperitoneal. The animals were observed for 30 minutes after which they were subjected to maximum electro-shock induced seizure in all the groups. The lack of tonic extension of the hind limb and an episode of HLTE was regarded as protection and full convulsion respectively. In unprotected animals, the recovery time was recorded. UGO Basile electroconvulsive unit ECT 800 fitted with ear clip electrode with shock duration of 0.8 sec, current 80 mA, pulse width 0.6 ms and frequency pulse of 100 Hz was used. The hexane fraction was similarly treated as above with doses of 100, 200 and 400 mg/kg.

Pentylenetetrazole (PTZ) induced seizure in mice. The method described by Swinyard & Kupferberg [34] was also employed in this protocol. Thirty mice were divided into five groups (n=6). Group 1 (Negative control) received normal saline intraperitoneally (*i.p.*). Groups 2, 3 and 4 (treatment groups) received graded doses of the methanol root extract 75, 150 and 300 mg/kg respectively. Group 5 (positive control) received 200 mg/kg of sodium valproate. The route of administration was intraperitoneally. After thirty minutes, all the groups were administered 20 mg/kg of the

freshly prepared PTZ subcutaneously. All the mice were observed for a period of thirty minutes after the sc. PTZ administration for the onset of HLTE and death, which were recorded for statistical analysis. The hexane fraction was similarly treated with the doses of 100, 200 and 400 mg/kg.

Statistical analysis. Data were presented as Mean ± SEM as well as percentages. Data were analyzed using one-way Analysis of Variance (ANOVA) followed by post hoc Dunnett test for multiple comparisons. Differences were considered significant at $p< 0.05$.

RESULTS

Preliminary phytochemical screening conducted on the methanol root extract (MRE) of *F. capensis* revealed the presence of carbohydrates, glycosides, steroids, triterpenes, tannins, flavonoids, alkaloids and saponins. WEF and WBF contain similar constituents as MRE except steroids and triterpenes. WHF revealed the presence of steroids, triterpenes and tannins while WCF indicated the presence of steroids, triterpenes, alkaloids, flavoinoids and saponins (Table 1). The MRE (75, 150 and 300 mg/kg) and WHF (100, 200 and 400 mg/kg) did not protect the chicks in MEST model. Phenytoin, the standard drug gave maximum (100 %) protection to chicks (Table 2 and 3) respectively. There was a significant (P<0.05, P<0.001) dose independent anticonvulsant activity in the PTZ-induced seizure in mice. MRE at 300 mg/kg had 33.3 % protection to mice against seizure while WHF exhibited 33.3, 50 and 33.3 % protection at 100, 200 and 300 mg/kg (Table 4 and 5) respectively.

Table 1: Phytochemical screening of the MRE, WHF, WCF, WEF and WBF

Constituent	Test	MRE	WHF	WCF	WEF	WBF
Carbohydrates	Molisch	+	-	-	+	+
	Fehling's	+	-	-	+	+
Anthraquinones	Bontrager	-	-	-	-	-
Glycosides	Keller-Killiani	+	-	-	+	+
Steroids/Terpenes	Liebermann-Burchard	+	+	+	-	-
	Salkowski	+	+	+	-	-
Tannins	Lead acetate	+	+	-	+	+
Flavonoids	Sodium hydroxide	+	-	+	+	+
	Shinoda	+	-	+	+	+
	Ferric chloride	+	-	+	+	+
Alkaloids	Dragendorff	+	-	+	+	+
	Mayer	+	-	-	+	+
	Wagner	+	-	+	+	+
Saponin	Frothing	+	-	+	+	+

+ =present, - = absent MRE = methanol root extract, WHF = Water insoluble hexane fraction, WCF = Water insoluble chloroform fraction, WEF = Water insoluble ethyl acetate fraction, WBF = Water insoluble butanol fraction.

Table 2: Effect of MRE and PHT on maximal electro shock induced seizure in chick

Treatment (mg/kg)	Mean recovery seizure (min)	Quantal protection	Protection against seizure (%)
NS	8.33±0.69	0/10	0.0
MRE 75	7.50±1.66	0/10	0.0
MRE 150	14.83±0.83	0/10	0.0
MRE 300	16.17±0.72	0/10	0.0
PHT 20	-	10/10	100.0

Values are presented as Mean ± SEM, One way ANOVA followed by Dunnett's Post hoc test, n=10, NS = Normal saline, MRE = Methanol Root Extract of *Ficus capensis*, PHT = Phenytoin

Table 3: Effect WHF and PHT on maximal electro shock induced seizure in chick

Treatment (mg/kg)	Mean recovery seizure (min)	Quantal protection	Protection against seizure (%)
NS	8.33±0.69	0/10	0.0
WHF 100	9.83±2.53	0/10	0.0
WHF 200	10.33±2.44	0/10	0.0
WHF 400	6.67±0.90	0/10	0.0
PHT 20	-	10/10	100.0

Values are presented as Mean ± SEM, One way ANOVA followed by Dunnett's Post hoc test, n=10, NS = Normal saline, WHF = Hexane fraction of *Ficus capensis*, PHT = Phenytoin

Table 4: Effect MRE and SV on pentylenetetrazole induced seizure in mice

Treatment (mg/kg)	Mean onset of seizure (min)	Quantal protection	Protection against seizure (%)
NS	9.17±1.55	0/6	0.0
MRE 75	16.00±4.06	2/6	33.3
MRE 150	17.83±3.54	2/6	33.3
MRE 300	21.00±2.62*	2/6	33.3
SV 200	-	6/6	100.0

Protection against seizure and mortality expressed as percentages; Mean onset of seizures presented as Mean ± SEM, * = $p< 0.05$ compared to normal saline group - One way ANOVA followed by Dunnett's post hoc test of multiple comparison, n=6, NS - Normal Saline, MRE = Methanol Root Extract of *Ficus capensis*, SV = Sodium valproate.

Table 5: Effect WHF and SV on pentylenetetrazole induced seizure in mice

Treatment (mg/kg)	Mean onset of seizure (min)	Quantal protection	Protection against seizure (%)
NS	9.17±1.55	0/6	0.0
WHF 100	20.17±4.31*	2/6	33.3
WHF 200	23.33±2.78**	3/6	50.0
WHF 400	19.67±3.13*	2/6	33.3
SV 200	-	6/6	100.0

Protection against seizure and mortality expressed as percentages; Mean onset of seizures presented as Mean ± SEM, ** = $p< 0.001$ compared to normal saline group - One way ANOVA followed by Dunnett's post hoc test of multiple comparison, n=6, NS - Normal Saline, WHF = Hexane fraction of *Ficus capensis*, SV = Sodium valproate.

DISCUSSION

The preliminary phytochemical screening of the methanol root extract of *Ficus capensis* revealed the presence of saponins, tannins, glycosides, steroids, terpenoids, alkaloids and flavonoids while the hexane fraction contained steroids/terpenes and tannins. These phytochemical constituents have been reported to possess different kinds of pharmacological properties [35]. This include anti-oxidative [36], anti-cancer [37] and anti-malarial [38]. Triterpenes and steroids, among other phytochemicals have been reported to possess anticonvulsant activity [39].

Determination of median lethal dose value of plants used by traditional medicine practitioners using acute toxicity study is of paramount importance because it provides information regarding the margin of safety of the plant. The i.p median lethal dose (LD_{50}) value of the methanol root extract was found to be greater than 1000 mg/kg body weight in Swiss albino mice. This LD_{50} value implies that the methanol root extract is relatively safe [40]. Doses of less than or equal to 30% of the LD_{50} which have been demonstrated to be relatively safe for ethno-pharmacological research were used throughout the research procedure [41].

The outcome of the study provides evidence that MRE possess significant anticonvulsant activity. The effectiveness of the plant extract in the experimental

convulsion paradigm used probably suggests that the herb could be used to manage epilepsy especially *petit mal* seizures and human generalized absence seizures.

MRE failed to alter MES thresholds at all doses tested in contrast to the positive control agent phenytoin. MEST is a standard AEDs test that evaluates the test material's ability to protect against hind limb tonic extension (HLTE) phase of the MEST [42]. It is a model for generalized tonic-clonic seizure, which is highly reproducible with consistent end- point [43].

MEST is used to validate pre-clinical test that predicts drug effectiveness in generalized seizures of the tonic-clonic (grand mal) type [44]. Drugs that act on sodium channels e.g. carbamazepine, phenytoin, oxcarbazepine and lamotrigine are known to suppress hind limb tonic extension induced by maximal electroshock [45] thus the study suggests that MRE does not interfere with the sodium channels to elicit its anticonvulsant effect.

The study revealed that MRE, WHF and valproic acid inhibited pentylenetetrazole (PTZ)-induced seizures. MRE and WHF dose independently suppressed the onset and latency of seizure induced by PTZ. The pentylenetetrazole (PTZ) test represents a valid model for human generalized and absence seizures [46]. Anticonvulsant activity in PTZ test identifies compounds that can raise the seizure threshold in the brain [47,48]. PTZ has been shown to interfere with GABA neurotransmitter and the GABA receptor complex [49].

Pentylenetetrazole has been used experimentally to study seizure phenomenon and to identify pharmaceuticals that may control seizure susceptibility. The exact mechanism of the epileptogenic action of PTZ at the cellular neuronal level is still unclear but it has been generally reported to produce seizures by inhibiting gamma-amino butyric acid (GABA) neurotransmission [50].

Enhancement of GABAergic neurotransmission has been shown to inhibit or attenuate seizures while inhibition of GABAergic neurotransmission activity is known to promote and facilitate seizure. Anticonvulsant agents such as diazepam, valproic acid and phenobarbitone inhibit PTZ-induced seizure by enhancing the action of GABA-receptors thus facilitating the GABA-mediated opening of chloride channels [51, 52]. Postsynaptic $GABA_A$-receptors are multi-unit complexes with binding sites for the endogenous ligands such as GABA, benzodiazepines, barbiturates and other ligands with a central chloride ion channel [53]. Thus, the inhibition of PTZ-induced seizures by the MRE and WHF suggests that their effects may be by enhancing GABAergic neurotransmission although it is also possible that it could also be via depressing glutamate-mediated excitation [54].

Conclusion

The methanol root extract and water insoluble n-hexane fraction of *F. capensis* had demonstrated significant anticonvulsant activity with moderate toxicity validating the ethno-medicinal claim of the use of the plant in the management of epilepsy.

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